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Start-ups – Spin-offs New Enterprises

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CHIMIA 2000, 54, No. 4

EDITORIAL

Surprise! Surprise?

How great was my astonishment when I heard from our editor that no less than 50 start-up and spin-off companies related to chemistry shall be presented in CHIMIA. Why astonishment? Because I, like so many others, have been led to believe that it is especially difficult to start a company in Switzerland. To be sure, there are difficulties (you will read about them), some serious like the prevailing mood to shy away from risk, some others like the bureaucratic hurdles which have to be overcome. Independent thinking as in Einstein's or Le Corbusier's Swiss days is still rarely welcome. Therefore, those who start-up companies need courage. As this issue of CHIMIA shows, there is a remarkable number of new entrepreneurs who had this courage. Let's congratulate them and hope more young people will follow their example.

It is most encouraging to read that financial succor exists for young enterprises. A helping hand to master the start-up mechanics also exists, mostly from our two Federal Institutes of Technology. Last but not least, as Dr. Glutz mentions, the New Swiss Chemical Society is useful for networking.

Some of these young enterprises may no longer exist in the distant future. To maintain our standard of living it is necessary to create a climate hospitable to new ventures. Therefore, we appeal to our political representatives to ease the legal conditions and to remove barriers hindering new start-ups. The New Swiss Chemical Society wishes all these young companies success, knowing full well how important they are to the future of our country and to chemistry.

H. Luzius Senti Ph. D.
President
New Swiss Chemical Society

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New Enterprises Emerging from Industry and Universities: Their Importance for the Swiss Economy

François L'Eplattenier*, President Novartis Venture Fund

Abstract: It is vital for the Swiss economy to stimulate the emergence of new businesses from industry and universities. This will enable the creation of attractive jobs, the attenuation of the negative consequences of the restructuring of established companies and an improved valorisation of academic research results. Although, in the last few years, a lot of progress has been made in fostering entrepreneurship in Switzerland, a change of our attitude toward risk and above all failure is still needed. A special emphasis must made to find ways which promote a risk-taking instead of risk-avoiding attitude in the education of our youth.

Keywords: Failure tolerance · Job creation · Learning by doing · Spin-offs · Start-ups

Technological breakthroughs and the globalisation of the economy force numerous corporations to restructure, with the consequence that thousands of jobs and job opportunities are eliminated. The wave of mergers, also in our country, is primarily a consequence of the economical constraints of this structural change, although me-too effects and ego-trips of CEOs must not be neglected. The main challenge we have to face in Europe and in Switzerland particularly, is that we are not able to create enough new jobs in order to compensate for those lost due to the restructuring of established companies. This represents the great difference with the United States. It is, therefore, of great importance to restore the dynamics of job creation thanks to new small businesses.

What big companies, while restructuring, can do in this perspective, is to offer financial help to their collaborators responsible for activities which are no longer needed or no longer considered as core activities in the new corporation, to create their own enterprise. Such a procedure offers the following advantages:

1) An opportunity is given to collaborators to develop and unfold their entrepreneurial talents.
2) It supports the parent company in its restructuring programs, without eliminating working places.
3) The parent company can furthermore retain access to required services from these spin-off companies – outsourcing – and this for a competitive price.

Such financial support cannot, of course, be considered as a measure of a social program to save jobs. Projects for the creation of companies must only be taken into consideration if the applicants can submit a promising business plan, based on realistic assumptions and business objectives. Severe criteria concerning success prospects for the selection of proposals also serve the interests of business creators. This is of particular importance in a country like Switzerland, for we live in an environment with a very low failure tolerance. One shot is all you get!

Beside rigorous standards in the selection of projects, it is also critical to allocate financial resources in a restrictive way. The comfort level must be kept as low as possible. Too many financial means lead to complacency, to a lack of sense of urgency, and to investment in not absolutely necessary infrastructure, all fatal errors for the future success of a new company.

To help its collaborators to create their own business allows the parent company not only to economically outsource services, but also favours the formation of technology boutiques. These became essential partners for the insourcing activities, in particular of big pharma companies, for the following two main reasons:

1) In order to increase R&D productivity, most pharmaceutical companies have implemented so-called 'faster time to market' programs, with the aim to reduce the development time required to bring new drugs to the market. 'Faster time to market' is, however, no longer a way to distinguish a company from its competitors; it has become the state of the art, every company must master this issue to survive.
'Faster time to development' is nowadays the way to differentiate, namely the ability to reduce the discovery time. This means that the discovery potential of big pharma must be improved and for that purpose many new technologies and scientific approaches will be insourced from biotech boutiques. Pluri-disciplinarity of R&D activities as well as the speed with which new knowledge is generated do not allow even companies with big R&D budgets to be up-to-date in all disciplines in a timely fashion, and time is of the essence. Insourcing knowledge from such biotech boutiques has not only the advantage of providing the flexibility to respond rapidly to changes in technology and the ability to access new expertise but also allows big pharma companies to overcome inward focus.
2) Mergers and acquisitions produce huge and heavy organisations. Success or failure of such big companies will strongly depend on the capability of management to lead them in an efficient and dynamic way. For this purpose large corporations are verticalized, split in numerous fully integrated business units. This is of course efficient to manage existing business activities, but not appropriate for the management of technological innovations which cut

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across the franchise of existing business units or which lie outside their franchise. For such projects there is a great risk that they won't receive enough attention or that they will be cut off because they do not match the current objectives of existing business units. Corporations, which due to their strong verticalized organisational structure, are no longer able to manage this type of technological innovation successfully are better off going the venture route, to externalise these activities and financially help the involved project champions to create their own company. If this spin-off process is well managed, the mother company will remain the preferred partner for future corporate deals.

Not only big companies can be the source of new enterprises, but also universities, as demonstrated by the United States. A great number of American biotech-boutiques have indeed emerged from universities and have been founded by professors. The creation of these start-ups is one of the most efficient ways to valorise economically the results of academic basic research. They can be considered as the driving belt between the universities, with all its knowledge and expertise accumulated in the frame of basic research programs and the economy. In our country such a valorisation process is still rather rare. Switzerland is in fact the country in the world with the highest concentration of Nobel prize winners. But we don't belong to the best when it is a question of transferring research results rapidly and efficiently from the laboratory to the market place. To overcome this ivory tower syndrome, a certain pressure is put on universities by some politicians and representatives of industry, to give a stronger emphasis to applied research with an economical finality. In my view this is the wrong approach. University must remain focused on its two traditional missions, namely:

1) Education of an elite, who can be successfully integrated in the practical world.
2) Perform basic research of high quality and originality, also as a vehicle to educate top scientists and engineers.

The usefulness of academic research must not be judged according to the potential of the practical application of its results. Universities must not substitute themselves to industry in taking over tasks industry must and can fulfil better. What, however, has to be done is to improve the efficiency of the knowledge- and technology-transfer mechanisms, particularly through the following measures:

1) First intensify the personal contacts and the quality of the dialogue between representatives from universities and industry. This will enable university to know the long-term needs of industry better, in order to integrate them in their education and basic research programs. People from industry must, however, be able to formulate their long-term needs in a consistent and coherent way based on a vision of the future.
2) Secondly, as mentioned above, foster the creation of new businesses emerging from universities. And, as illustrated by Route 128 near Boston and by Silicon Valley, this particular type of knowledge and technology transfer has allowed the academic world to maintain its integrity and objectivity while participating in the creation of high-tech boutiques.

The benefits of such a valorisation process for those involved are quite obvious:

- For the universities, additional financial resources. This in a time of zero-growth of budgets and an increasing number of students should be rather welcome.
- For members of academic institutions, the satisfaction of having their research results valorised practically and of being recognised by a much broader class of society than just their peers.
- For graduates leaving universities, attractive job opportunities. In the USA the creation of university start-ups has substantially contributed to counterbalance the negative effects of restructuring in the economy.
- For society at large and taxpayers in particular, a better valorisation of basic research results brings an improved return on investments put into academic institutions.

The advantages for all those involved seem so obvious that it is somewhat strange that such a practice is not more widespread in our country. What are in fact the reasons for this reserve towards entrepreneurial initiative in Switzerland? What are the obstacles and how can they be overcome?

The biggest obstacle is of course our attitude toward change, risk and above all failure. We have the privilege to live in a wealthy society. However, success acts as a soporific and maintaining the *status quo* becomes the first priority. Change is perceived as a threat and not as a challenge which opens new opportunities. We, therefore, are inclined to stay in safe positions with stable employment rather than to head out into the entrepreneurial unknown. Such an attitude is also reflected in our legislation, which is conceived to prevent and not to promote, penalising those with a doing mentality. This generates a bureaucracy which is a heavy burden to the management of small companies.

The fact that so few start-ups are emerging from our Swiss universities is another illustration of our mentality, which of course strongly influences the way we educate our youth. Teaching in our schools is still too much focused on learning by listening, instead of learning by doing, which would foster a risk-taking instead of risk-avoiding attitude. Furthermore, most of our professors do not see it as their task and responsibility to participate in the creation of new businesses and to develop an entrepreneurial spirit among their students. To do business is not always well perceived by the faculty. It is, therefore, not surprising that to become an entrepreneur is rarely what our students are dreaming about.

Money is often mentioned as a major obstacle for the creation of a company. I believe, however, that for projects with a convincing business plan and management team, financing does not represent a major issue, with the exception of the kick-off phase. Seed money is still lacking. Thanks to the Commission for Technology and Innovation as well as European and National research programs, some financial resources for the seed phase of company creation are available. But the state should do more and must do more. The financial participation of the state at this stage of business creation is totally legitimate. It is a phase involving many risks, in which, for example, the feasibility of a new technology must be definitively proven and during which the young entrepreneurs are learning their job by practising it. On top of this, new working places are generated.

I am not of the opinion that we should try to reproduce *tel quel* what is going on in the United States. We can learn many things from the Americans, but if we want to stimulate business creation in Switzerland in a sustainable way, we must not neglect the rather soft factors, related to our environment, history and culture.

In conclusion I would like to point out that in the last few years a lot of progress has been realised in our country to foster entrepreneurial initiatives and to improve conditions for business creation. We also have a lot of talented people, money and an efficient infrastructure. What we still need is more self-confidence and less fear to be stigmatised for failure.

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Technology Parks: Breeding Places for Tomorrow's Stars at the Stock Exchange

Thomas von Waldkirch*
Director Technopark Zürich Foundation

Abstract: Technology parks play an important role in the improvement of entrepreneurial culture and offer an ideal environment for technological start-up companies. Thorough selection of candidates, good coaching, close networking between carriers of different competencies and with external partners in R&D, finance, and industry are the basis for the high success rates of start-ups, for example in the Technopark® Zürich. Technology parks give the start-up tenants a high credibility and trustworthiness.

Keywords: Science Parks · Start-ups · Technology Parks · Technology Transfer

New Enterprises – Vitamins of Political Economy

Political economies like the Swiss economy which has been accustomed to high wealth for decades are not proof against the danger of catching a cold in globalised competition – just like a human body in a draught. Established enterprises react by focussing on core competencies and by fusions. In the same way we humans pull in our extremities and move closer together when the air becomes cold. But in addition we take vitamins as a preventive measure against influenza. The analogue in public economies are start-up and new enterprises. They create new employment and introduce – with exceptions – innovations with their high added value into the market place. It is pleasant to see that the awareness for the value of pioneering enterprises in this context has increased dramatically in the last decade. What were the driving forces for this cultural change?

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Promotion of a Culture for New Enterprises

Cultures can be changed, although not in a short timeframe. Therefore it pays to stand up for a change of culture, and because this will take time, this process must start today. The best means is to take good examples and to make them publicly visible. Fifteen years ago good examples of new enterprises did exist, but they were not known as examples worthy of imitation.

ETH Zürich, the Swiss Federal Institute of Technology, Zürich, one of the two Technical Universities of Switzerland, owes its international reputation mainly to its outstanding results in basic research. A number of Nobel laureates like Wolfgang Pauli, Vladimir Prelog, Richard Ernst and others show proof of this. ETH's attractiveness for the world's best scientists and professors, however, was also due to its high financial background in international comparison. In my former position as head of the ETHZ President's Office for Research, I felt responsible to contribute to a comparable level of financial support reaching into the future. This meant the valorisation of research results with chances for commercial exploitation within Switzerland and hence the creation of tax income for the State. The magic term for this process is *technology transfer*. Therefore fostering technology transfer does not mean killing basic research, on the contrary. For this purpose we organised – in cooperation with Dr. Branco Weiss – the first Seminar in 1983 on the topic: 'University and Industry – a fruitful contrast?' Nobody would put a question mark today! One of the most prominent lecturers was Richard Ernst on his excellent collaboration with Spectrospin.

But neither such collaborations between ETHZ and industry nor start-up companies from academia were known to the public or to the majority of the professors of ETHZ at that time. This had to be improved. Thanks to the active support of the ETH management, the topic 'technology transfer' could be put on a professional basis by founding ETH-TRANSFER in Zürich and EPFL-CAST (Centre d'appui scientifique et technologique) in Lausanne (1986). Teaching mandates at ETHZ on 'Foundation and management of new enterprises' and 'Technology transfer' were additional measures. At the same time my plans for a Technology Park as an operative and visible centre for technology transfer were progressing. Recently, Dr. Branco Weiss funded a Chair of Entrepreneurship in Lausanne.

The Characteristics of Modern Key Technologies

Analysing key technologies over the decades shows clearly that they emerge mostly from the combination of existing, but not yet combined know-how. A good example is mechatronics as a combination between mechanics, microelectron-

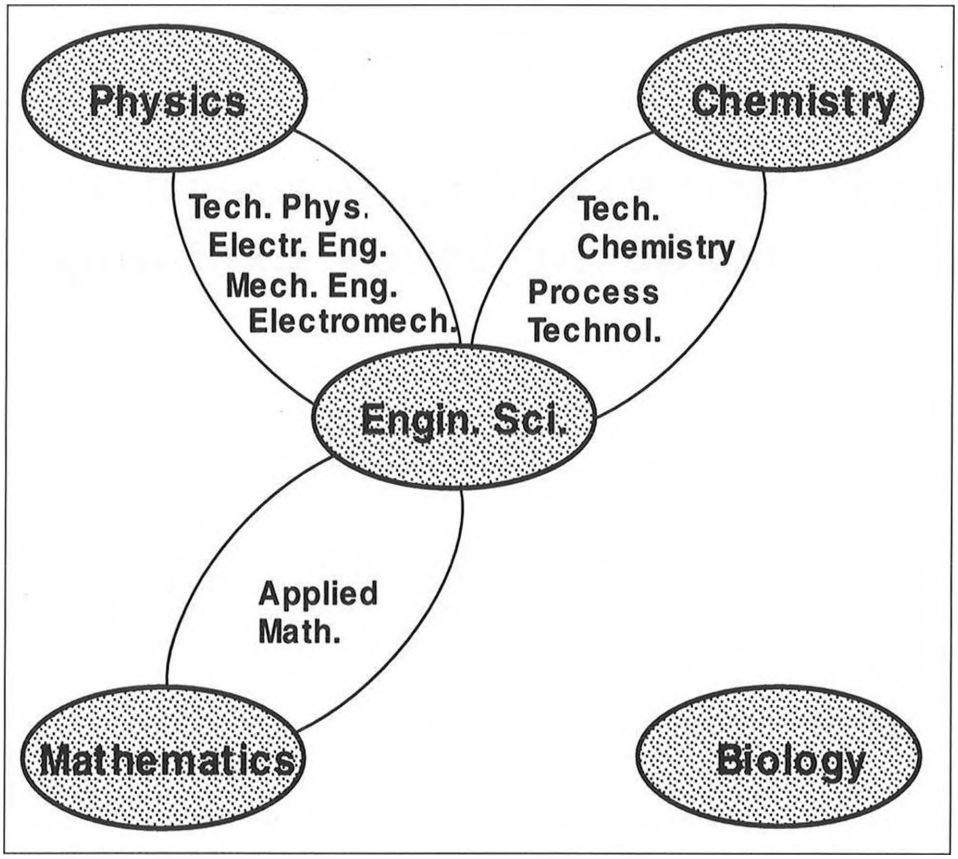

Fig. 1: System of pacemaker and key technologies around 1950.

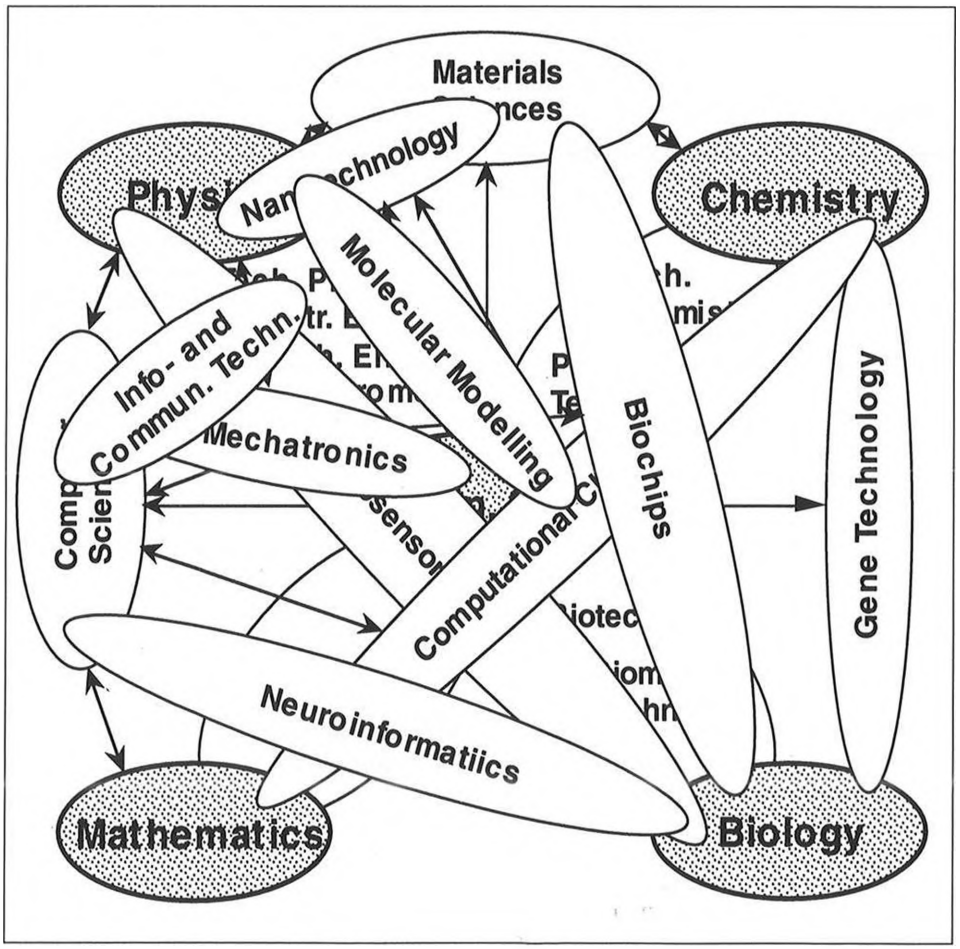

Fig. 2: System of pacemaker and key technologies in the near future.

ics and computer science. Fig. 1 and 2 may illustrate this. As a conclusion it turns out that, in order to encourage successful innovations, it is important to create an environment where people with different know-how can meet and collaborate. Additionally, we see that academic education should develop the ability and the will to cooperate with specialists of other domains.

Structure of Technology Transfer

Traditionally, graduates from universities transfer new results and technologies from academic research to the economy. This classical way, however, has often become too slow in view of the high rate of change. Therefore new axes are necessary. These are intensified continuing education (transfer of knowledge), collaborative research between academia and enterprises (possible with existing companies only; transfer of knowledge and know-how) and in particular new technology-oriented enterprises (transfer of know-how).

The Role of Technology Parks

Technology Parks like the Technopark® Zürich are visible and operative centres for the above-mentioned three modern axes of technology transfer. They support the encouragement of technology-oriented start-ups in two specific ways: on one side they offer an ideal environment for start-ups, which for Technopark® Zürich comprises primarily the following elements:

1) Quality address: Due to thorough selection according to chances for success on the basis of business plans (including, of course, help to optimise them) and by assessing the founding person(s), the rate of failure could be drastically lowered. In the Technopark® Zürich the failure rate lies for the innovation-oriented start-ups – *i.e.* the ones with the highest risk – below 10% within eight years. For this purpose the Technopark® Zürich Foundation (responsible within Technopark® Zürich for the support of technology transfer and of start-ups; the infrastructure is handled by the Technopark® Real Estate Co. Inc.) has a specialised advisory board. It is sponsored by UBS AG and consists of specialists of all relevant entrepreneurial aspects such as technology, management, financing,

marketing, law *etc.* As a consequence, (potential) customers can trust young enterprises in the Technopark® Zürich to continue to exist in the future and to remain a reliable partner. For the start-ups this means a direct advantage.

2) The close vicinity to numerous other start-ups of different ages: This allows for a daily and informal exchange of experience: not to be alone and to profit from the experience of others.
3) Comprehensive mix of competencies: the Technopark® Zürich combines developers and users of know-how and technology under one roof. Hence, these two groups of people with completely different sets of values get to know each other by daily contact, start to understand and to trust each other, and lay the necessary basis for a real collaboration. No technological topic is preferred, giving rise to the optimal basis for the above-mentioned combination of know-how. The activity mix in the Technopark® Zürich comprises three areas: INNOVATION (*i.e.* tenants active on the market with products and know-how based on their own intellectual property), TRANSFER (*i.e.* services to support market entry and business, such as patent attorneys, marketing, PR, advertisement, industrial design, financing, head hunting, translations *etc.*), and PRODUCTION (*i.e.* market supply by application of existing technologies or real manufacturing). This allows partners to be found for particular competencies in-house and in an informal way – according to Technopark Zürich's motto: 'We net competencies' – without, of course, any obligation to choose a partner in-house. In addition, personal networks of the park managers and other tenants on the national and international level can be used.
4) Close connections to universities such as ETH Zürich (Swiss Federal Institute of Technology) or the Zürich University of Applied Sciences, both of which are active in the park with collaborative projects with industry and with spin-off-companies. This results in advantages with respect to know-how exchange and to finding specialists.
5) A number of central services such as a copy centre, telephone service, restaurant, bancomat, meeting and seminar rooms *etc.*
6) Staggered rents.
7) Support in bridging bottlenecks in financial liquidity.
8) In-house seminars concerning entrepreneurial aspects.
9) PR advantage by the general PR activity of the park and by numerous events with tens of thousands of external participants over the year.
10) Flexible space allocation according to changing demand.
11) Support of expansion into the international market. The Technopark Zürich Foundation edited a book [1] on the topic: 'Boundless business' with detailed information on how to open up foreign markets, including tables for decision support. In addition, seminars based on this book are organised.

On the other side, technology parks have the role to make start-ups visible and 'tangible'. As Switzerland's largest technology park, the Technopark® Zürich houses no fewer than 120 young enterprises out of 190 tenants. Hence, media, potential founders, students, professors, business angels, investors *etc.* can find interesting young enterprises very easily. This again promotes start-up-entrepreneurs in large circles and contributes significantly to improving entrepreneurial culture.

Additional Factors to Promote Entrepreneurial Culture

Beside the nine Swiss technology parks (organised in the Club of Swiss Technology Parks, see *www.swisstechparks.ch*) founded in the early nineties, it was paradoxically the recession which contributed to today's high valuation of pioneering entrepreneurs. It shook up a Switzerland spoilt by high wealth and used to unemployment rates below 1% for decades. Job security melted both for graduates from universities and for employees in large companies. The career was no longer the only criterion for success, but searching and catching opportunities in an entirely altered labour market as well. As a consequence ETH Zürich started courses on the topic 'In the mood for my own enterprise!' and competitions in business plan development for undergraduates and graduates of Swiss universities. In addition, other universities started offers of education for future entrepreneurs, and in St. Gallen an Institute for Young Enterprises was founded. These activities have contributed a lot to today's entrepreneurial verve.

Supporting Instruments for Start-ups

In order to stand a good chance of success a start-up company needs four ingredients:

1) A convincing business idea that shows a clear 'Unique Selling Proposition' compared with the existing situation. For technology companies this often means a technically 'better' or cheaper solution for a known need or, in the ideal case, a solution for a still unsolved problem.
2) A positive echo from the market: potential clients have to be as fond of the business idea as the future entrepreneurs are. The needs of the market is the most important and strongest motivator for a genuine innovation. But as the great innovations that are triggers of Kondratieff cycles (*e.g.* computers and biotechnology) repeatedly show, the market is often not aware of its needs at the beginning.
3) Management. This comprises numerous elements such as patent application (or other protection of Intellectual Property), business planning, marketing, fast and specific international coverage of the market, contracts with subcontractors and sales partners, financing and controlling, human resource management, continuous further development of the technological supply, increase of productivity, strategic alliances *etc.*
4) Sufficient start-up financing (equity above all) to cover the initially expected negative balance without problems.

The first requirement is **courage**, which in spite of his descent from William Tell is not exactly Homo Helveticus' strong point. Courage for something new, courage to act and courage to take on a thorny and risky task. To have courage means to take the risk and not to shrink from it.

We Swiss tend to look for and emphasise risks in changes and new suggestions, in order to reject innovative ideas and approaches at a very early stage. The only way not to prevent a true opportunity-threat analysis is to track down the **opportunities** first. Let's acquire a little more of the American positive attitude: 'Let's give it a chance!' instead of judging according to the Helvetic motto: 'Yes, but...'. Young people have to be motivated to courageous actions and kept away from the insurance mentality and perfecting an idea before its realisation. With today's enormously short innova-

tion cycles, the right time to market is much more important than a perfect clarification and elimination of risks: to be too late is the greatest risk of all!

It is interesting to observe how the topics 'technology transfer' and 'start-up' have increasingly become the subjects of studies, reports and articles in the past ten years. In the multicoloured brochure 'Wirtschaftsstandort Zürich: Wettbewerbsfähigkeit heute und morgen' from 1995 [2] the conclusion of 'Thesis 9: Factor Knowledge' is: 'A comprehensive network has to be created .... between universities or technical colleges and industry.' Due to its passive phrasing this kind of statement doesn't get anything going – '*...has to be created..*' doesn't commit to anything and doesn't place the responsibility on anyone. How should such a network look like? Isn't there one yet? Who builds it? Who pays for its creation? How do you motivate people to join the network?

The topics 'technology transfer' and 'support of start-ups' became (and are often still today) catchwords. An idea is not yet an innovation, and a catchword-demand is not an action. Only in the accomplished act of innovation is an innovative achievement, not to mention its necessity. Negative decisions to concrete action-oriented suggestions, which on the one side acknowledge a need, but explicitly refuse a contribution on the other are particularly cheap. Within this category falls a proposal for the creation of a Swiss Seed Money Fund in 1994 which was turned down by the banks although they explicitly 'acknowledge(d) the difficulties of start-up companies to get start capital for innovative projects'. In such cases the following Indian proverb applies: 'Who recognises a problem and does not contribute anything to its solution, is part of the problem himself.' Maybe the proposal was a little too premature at the time.

Seed Money

Seed money stands for the earliest financing round of companies mostly still in the planning phase (prototyping, feasibility study, screening tests *etc.*).

Initiative Start-ups

In spite of the refusal of the Seed Money Fund in 1994, I wanted to find a solution for the undisputed need for seed money. At that time only the W.A. de Vigier Foundation offered seed money by prizes of CHF 100000 to start-ups. Due to its enormous private wealth I recognised that Switzerland should well dispose of the species 'Business Angels' who could provide young companies with finances, know-how and contacts during their build-up phase. Therefore we founded, with a few idealists in the environment of the Foundation Technopark Zürich, the project '**Initiative Start-ups**' (sponsors: the Ernst Göhner Foundation and the Hans Eggenberger Foundation). The aim of it was and is to give selected promising young companies the opportunity to present their business ideas to Business Angels invited *ad personam* and interested in laying the basis for bilateral engagements and agreements. Eight meetings have been taken place so far with increasing success and in the meantime the instrument has found strong imitators on the EU level. This is why we plan to extend it within Switzerland with meetings in different places, a systematic recording of Business Angels and enabling contacts on the Internet.

Volkswirtschaftsstiftung

Since 1997, the privately financed Stiftung zur Förderung Schweizerischer Volkswirtschaft durch wissenschaftliche Forschung, which was originally aimed at supporting research projects after World War I, offers loans without interest from CHF 100000 to 150000 available to technology start-ups in the seed money phase.

KTI Start-up!

The Federal Office for Education and Science BBT has organised the program KTI (Commission for Technology and Innovation), which enables the co-financing (50% each) of co-operation projects between SMEs and universities/research institutes by tax money. A few years ago the program KTI Start-up was added. After evaluation, it awards technology start-ups with a KTI-Start-up! label as a proof of quality. These companies get also the opportunity to solve seed money tasks with KTI financing in collaboration with universities.

ETeCH AG

In analogy to the highly successful examples in the US, a project is being created that gives researchers the opportunity to present their results with no risk to the company. ETeCH will analyse the market chances and take them over with rights and duties. Then they will be transferred into Intellectual Property Rights (*e.g.* a patent) and launched *via* an existing or new company. The researcher gets a proportion of the profit, but carries no risks.

Venture Capital

After years of virtual non-existence of Venture Capital in our wealthy country, this aspect has boomed since 1997. Today more than 40 Institutions fight for the best projects and even banks that are traditionally not specialists for equity but borrowed capital have engaged actively in this new, very important field. This is a very positive development and will largely influence the new founder age.

Management

Comprehensive management qualities become more and more important for the success of a company. The quick penetration of well-defined market segments on an international basis becomes a vital factor in the era of globalisation with its enormously fast reaction time. The experience shows, however, that engineers often present a splendid idea, but lack the necessary educational basis for demanding management. This way, financing by venture capital will stay away, because the prerequisites for success are not assured enough.

On the other side, there are a lot of bright young people in this country, who have management skills and would like to build up a firm, but don't have a business idea.

That is why we plan – in analogy with 'Initiative Start-ups' (see above) and in co-operation with various partner organisations – to create a 'market place' for engineers with a business idea and young managers, where they can meet and when applicable start their own business and succeed. The launch is scheduled for fall.

Once more as our slogan says: 'We net competencies'.

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Promotion of Start-ups at the Swiss Federal Institutes of Technology: The Right Time to Start-up

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Abstract: In the past few years 'Entrepreneurship' has taken over more and more space in the minds of students and researchers, especially at the Swiss Federal Institutes of Technology in Zürich and Lausanne. Also various initiatives by the Institutions, by the Federal Government and by private sponsors have been created to support start-ups. One of the most broadly established is Venture 2000 – Companies for Tomorrow, the nationwide business plan competition run by ETH Zürich and McKinsey & Company in collaboration with about 40 other universities, research institutions and so-called 'Fachhochschulen'. The Offices for Technology play an important role in the promotion of start-ups. This article describes their services and goals and the Venture 2000 competition.

Keywords: Business plan competition · EPF Lausanne · ETH Zürich · Start-up · Technology transfer · Venture 2000

At present entrepreneurship is very popular at the Swiss Federal Institutes of Technology in Zürich and Lausanne. In the last years the number of spin-off firms has significantly increased. This is due to a large part to the wide variety of supportive measures that the Institutes' management has made available. A selection of these is described below.

At the Swiss Federal Institutes of Technology, the recognition that encouraging start-ups is one of the most important means of applying research to the benefit of society has grown even stronger over the last few years. Not only are new products realized with spin-offs but also attractive new jobs are created. Consequently, efforts in technology transfer in general and the encouragement of spin-off firms in particular were reinforced. One of the first initiatives in this area was the course, 'Lust auf eine eigene Firma!' launched by Verena Steiner of the ETH Zürich through ETH tools.

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Brilliant Start

ETH tools had a brilliant start with 'Lust auf eine eigene Firma!'. Within a brief period, it became the best attended series of courses on founding a firm in Switzerland: over 10000 people have participated in the program up till now. The results from the first three years of the course: hundreds of newly founded firms and over 930 jobs were created by participants.

In 1997, together with the management consulting firm McKinsey & Company, Switzerland, the first country-wide business plan competition 'Venture 98 – Companies for Tomorrow' was launched with great success, and led to similar initiatives in several countries. Now, the second generation of this competition, Venture 2000, is underway, organized by ETH transfer and McKinsey.

From Great Ideas to Companies for Tomorrow

On February 21 this year, 13 teams from Swiss universities, technical colleges, research institutions and other specialized colleges were rewarded for their compelling entrepreneurial ideas. Lukas Mühlemann (CEO of the Credit Suisse Group) presented the prizes for the first round of Venture 2000.

About 400 people from all over Switzerland participated in the first round, with 120 business ideas from various fields: according to actual trends e-business ideas were very well represented – about every fourth idea came from this area. Ideas from biotechnology, chemistry and material sciences were equally well represented, at 10% each. Software, healthcare and electronics accounted for 7% each.

Venture 2000 Continues

The first-round prizes represented just the first stage in the business plan competition: for the second round (submission deadline is May 2, 2000) complete business plans must be drawn up. For those

interested, about 150 coaches, a hotline (0800 880 120) and a variety of additional assistance is available on the Venture 2000 website (*www.venture.ethz.ch*). Participation in Round 1 is not a prerequisite for participation in Round 2; indeed, new teams are very welcome.

The special offer of input and guidance from experienced entrepreneurs, experts and venture capitalists, available at no cost, is unique to Venture 2000. In the second round, the ten best business plans will be awarded CHF 2500 each. Finally, in the third round in June, presentation of the business plans will be in the foreground – and then the Advisory Board will award the main prizes of CHF 60 000, CHF 40 000 and CHF 20 000.

Successful Role Models

The experience of the first business plan competition two years ago demonstrates that participation in it contributes significantly to the founding of firms: of the 87 business plans submitted, 27 firms have been founded, and others are in the process of being founded. The winner of Venture 98, a company called Sensirion AG, Zürich, currently has 17 employees and plans to build up the number to about 30 by the end of this year. Sensirion is active in the sensor technology area.

A unique feature of Venture 2000 is the non-bureaucratic cooperation between the different institutions: last year the starting event was organized jointly by the ETH Zürich, the ETH Lausanne and the University of Basel. About 40 institutions, large and small, are actively involved in Venture 2000. And the participants are also much more widely spread than in Venture 98.

ETH transfer – the Hub

The offices of the two federal institutes involved in the support of spin-offs work very closely together and regularly exchange experience in this area, one that is still novel for Switzerland. In Zürich, ETH transfer coordinates the activities. This office expanded significantly during the last year. Infrastructure for start-ups is made available at reasonable cost and loans are available, as is advice from a wide range of experts. It is ideal that the ETH has space in the Technopark Zürich and that its use is coordinated by ETH transfer.

Currently, the KTI Start-up initiative aspires a close cooperation with the ETH. ETH transfer is planning to act as a local reception office for innovation and start-ups. A new web site (*www.transfer.ethz.ch*) will be continuously extended and support this strategy. These efforts have also produced results: in the last years the number of firms founded out of the ETH has grown dramatically, 16 in 1999 compared to 3 or 4 at the beginning of the 90s.

Special Chair at Lausanne

Last year a chair for entrepreneurship was established at the Swiss Federal Institute of Technology in Lausanne: CREATE under the direction of Prof. Jane Roystone is active along three axes: a 14-week basic course for students, thirty seminars, oriented to high-tech entrepreneurs and the offer is rounded off with workshops by and for entrepreneurs.

Lausanne also offers opportunities similar to Zürich for spin-offs to be gradually developed out of the Institutes. The ideal basis for this is represented by the 'Parc scientifique' in the grounds of the EPFL. In Lausanne, as in Zürich, potential entrepreneurs receive thorough advice, from clarification of the necessary resources, to working out the actual business plan all the way to support in financing negotiations.

As a result, in the past three years, 37 firms have been founded in Lausanne. The program 'Envie d'Entreprendre' contributed to this result, a program already in its fourth series.

More Venture Capital Available

In the last two years, the interest of venture capital firms in high-tech start-ups in Switzerland has grown significantly. Together with the above-mentioned support activities and a global perspective, they comprise one of the bases for the successful founding of firms.

In summary: it's the right time to start-up.

Contacts and Links

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The Contributions of the Swiss Priority Programme Biotechnology and Partner Organisations to the Rapid Development of the Biotechnology Sector in Switzerland

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Abstract: Biotechnology is now a rapidly growing sector in Switzerland, both in the academic and in the industrial environments. The creation of biotech research and industry networks and the creation of specific biotech agencies by the Swiss Priority Programme Biotechnology have significantly contributed to this very positive development. In the academic sector, important structural and institutional improvements have been achieved and promoted. In addition, technology transfer activities – including the creation of new biotech spin-offs and start-ups – have been successfully promoted by the SPP. This review also presents some of the most important biotech-relevant activities and contributions by partner organisations and gives a short outlook on the funding situation after 2001, when the SPP BioTech will be terminated. The Commission for Technology and Innovation (CTI) will then have a key function for the further development of biotechnology in Switzerland.

Keywords: Creation of spin-off companies · Funding of biotech R&D · SPP BioTech agencies BATS, BICS, Unitectra · Swiss Priority Programme Biotechnology · Technology transfer

The SPP BioTech as a Concerted National Activity in Support of Modern Biotechnology

The 1980s were a turning point for Swiss biotechnology. Prior to 1980, biotechnology applications in Switzerland were limited to the industrial sector and a few pioneering academic institutions such as the Swiss Federal Institutes of Technology in Zürich and Lausanne. In the 1980s, more and more leading Swiss institutions and small and medium-sized enterprises (SMEs) began using molecular biology and genetic engineering techniques for all types of applications in the life sciences. It soon became clear that the potential of biotechnology to benefit society was immense, if provided with the proper environment for its development.

Various groups and organisations in Switzerland, such as the Swiss Academy of Technical Sciences, the Swiss Coordination Committee for Biotechnology, the Board of the Swiss Federal Institutes of Technology, and the State Secretary for Science and Education launched several proposals in order to induce national efforts for the promotion and development of biotechnology. In 1989, the Swiss Science Council mandated the Swiss Coordination Committee for Biotechnology to perform a comparative study on national and international biotechnology R&D programmes, their goals and development strategies. Swiss science policy makers used this document [1] to lay the foundations for the first nationwide biotechnology programme, subsequently approved by the Swiss parliament and initiated in 1992. This was the beginning of the Swiss Priority Programme Biotechnology.

Organisation, Strategies, and Goals of the SPP BioTech

The Swiss Priority Programme Biotechnology (SPP BioTech, 1992–2001), financed and administrated through the Swiss National Science Foundation (SNSF), aims at ensuring the international competitiveness of Swiss biotechnological research and development [2][3]. It is application- and/or problem-oriented and sets out to bring research closer to technology transfer and development activities, by encouraging synergistic collaborations between universities, institutes and partners from the private industry. Fields of biotechnology where Switzerland already holds a strong position are strengthened, while fields that need encouragement are given a chance, through the setting of relevant research priorities that ease technology transfer in Switzerland.

Based on a thorough assessment of the national research capacity, a number of modules were created in order to con-

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solidate the applied biotechnology research in Switzerland as listed below (for more details see refs [2][3]).

The Research Modules of the SPP BioTech

- Processes for the Production and Purification of Proteins for Medical Applications
- Biotechnology: Bioengineering and Biocatalysis
- Food Biotechnology (started in 1996)
- Bioelectronics and Neuro-Informatics
- Biosafety Research and Development of Biotechnology
  - Biotechnology Information and Communication (Agency BICS)
  - Biosafety Research and Technology Assessment (Agency BATS)
  - Technology Transfer (Unitectra, formerly Biotectra))
- Biotechnology of Higher Plants
- SPP BioTech Education Programme

The strategy of the SPP BioTech is to strengthen biotechnology research in Switzerland, without neglecting the peripheral activities necessary for bringing technological innovation into society. The SPP BioTech supports scientific activities that use modern biotechnology to help achieve sustainable development and efficient use of resources in industrial processes and agricultural systems. The programme also recognises the important role of continuing education in biotechnology for young researchers, and funds were accordingly allocated for Ph.D. students, postdocs, visiting scholars and junior group leaders. In addition, the programme includes a module for the study of biotech-related issues that are of significant concern for the public.

Addressing public concerns regarding applications in biotechnology in a timely and informative manner is of utmost priority in the SPP BioTech. The level of public acceptance for technology applications can determine the speed at which development proceeds in certain critical research areas. It is for this reason that the agencies BATS (Biosafety Research and Assessment of Technology Impacts), BICS (Biotechnology Information Centre) and UNITECTRA (formerly Biotectra, Technology Transfer) were created under the auspices of the SPP BioTech.

The research activities within the SPP BioTech gradually proceeded from ideas and goal-oriented basic research approaches to practical application of the achieved results. The programme comprises three distinct phases with a total budget (public funding) of approximately 100 million Swiss francs:

• *Build Up Phase 1992–1995:*
Main focus on application-oriented research (and development); initiation of efficient collaboration between universities, research institutions and industries; creation of nationwide scientific networks, start of technology transfer activities → transfer of products, methods, services.

• *Consolidation and Extension of Collaboration with Industry 1996–1999:*
Continued application-oriented research and concentration on successful strategies; extension and intensification of contacts with industry; motivate the SMEs to join; speed-up technology transfer (including creation of new SMEs).

• *Harvest and Termination (Outphasing) 2000–2001:*
Continuation of the most successful and productive projects; focus on development aspects and technology transfer in order to exploit the achievements. In this last phase all the remaining projects are co-funded by one or more transfer partners (big companies, SMEs, Federal Offices, Federal Research Stations, *etc.*) → principle of matching funds.

The participation in SPP BioTech has also helped a significant number of research teams to find easier access to EU Framework IV Programmes. The success rate for Swiss applicants (36% for the first call in 1995) was far above the European average (26%).

Some of the major achievements and impacts of the SPP BioTech are listed below:

- Creation of centres of competence and nationwide networks for biotechnology research.
- Strengthening biotechnology activities at the Swiss Federal Institutes of Technology in Zürich and Lausanne.
- Creation of the Institute for Neuro-Informatics, which is jointly operated by the University of Zürich and the Federal Institute of Technology, Zürich.
- Support for bioelectronics research and applications of this technology for the development of biomedical equipment.
- Creation of a nationwide network for Swiss biosafety research on recombinant and 'naturally' occurring organisms.
- Close collaboration between universities and government institutions in the field of plant biotechnology, for the development of a more sustainable agriculture.
- Innovative research in food biotechnology for healthier and safer dairy products (since 1996).
- Technology transfer between academia and industry and also among industry was facilitated, from a heightened awareness of the necessity.
- As a result a significant number of spin-off companies were created, see below.

At the end of the second programme period (1999), the company participation as transfer partners in the SPP BioTech projects was already very significant, both in numbers of companies (more than 100!) and in terms of financial contributions (18.8 million CHF on top of the public funding). Companies can be involved as main applicants, co-applicants, active partner in R&D, licensees, or interested discussion partners (to perform technology transfer later). Many companies are involved in more than one project or research module! In 1999 we counted: 9 big national/international companies, 71 Swiss SMEs, and 23 foreign companies. In the outphasing period the contributions by the transfer partners amount to about 40% of the total budget of approx. 15 million CHF.

The Creation of Agencies in Support of Swiss BioTech

With the creation of the three SPP BioTech Agencies (BATS, BICS and Unitectra (formerly Biotectra)) important issues of public concern were addressed and the desired development of biotechnology in Switzerland was structurally supported. All these agencies are located in Basel (Clarastrasse 13) with support of the Canton Basel Stadt.

Access to reliable information is fundamental for good decision-making on the personal and governmental level. Members of the public require an adequate understanding of the meaning of new discoveries in order to make personal choices. Officials on all administrative levels need easily accessible knowledge and resources for the preparation of new legislation or for regulatory oversight. The agencies BATS (Biosafety Research and Assessment of Technology Impacts of the SPP BioTech) and BICS (Biotechnology Information and Communication of the SPP BioTech) provide information on all aspects of biotechnology. They are

both non-profit and non-lobby organisations.

The safety of technological applications is a prerequisite to their introduction into society. A special module 'Biosafety Research and Development of Biotechnology' was created by the SPP BioTech to address the safety aspects of biotechnology applications. The agency BATS is in charge of initiating and co-ordinating research projects on the biosafety of transgenic organisms, as well as hazardous, naturally occurring organisms. The research in the module is organised as a Swiss network, involving scientists from Universities, Federal Institutes of Technology, Agricultural Research Stations, and Industry.

The objectives of the Internet site: *http://www.bioweb.ch* developed by BATS are to 1) offer value-added knowledge on biotechnology impacts, and 2) pool and organise digital information for easy access. Contributors of information are national and international research institutions, government agencies and non-governmental institutions, as well as international organisations. At this site, the visitor can find information on a range of biotechnology applications. The information for the site is carefully gathered and checked for the quality of the source. In addition, the retrieval of information is facilitated through a full-text retrieval system. Links are also given to other relevant sites. These sites are constantly being improved in order to serve the public better. A new feature of the *bioweb* site is an interactive discussion podium. Visitors to the site can discuss issues related to biotechnology with other citizens and a panel of scientists knowledgeable in the field. BATS plays an important and widely recognised role in the world of biosafety research and biotechnology assessment, both on the national and on the international level. The work of BATS is well documented by a large number of publications, status reports, TA studies, biosafety guides, and handbooks.

BICS publishes the unique Swiss quarterly review on biotechnology, *BioTeCH forum*, available in a bilingual French/German edition. Other publications of BICS include facts sheets (*e.g.* on biosafety projects and AgroBiotech) and brochures which are also available online and are a source of useful information not found in the media. The home page of the agency BICS *http://bics.ch* allows the visitor an easy access to a vast selection of links covering all aspects of this field.

BICS has established an extensive documentation and library on biotechnology and biotechnology development worldwide, which is open to the public. The agency communicates to a wider public the results achieved within the framework of SPP Biotech and informs about national and international trends and activities in biotechnology, with special focus on the interface between Science/Technology and Society. BICS is an active partner in trans-disciplinary science communication networks.

The SPP BioTech agency Biotectra (now Unitectra) was created in 1996 in order to professionally assist and instruct the members of the SPP Biotech and other customers in Swiss biotechnology beyond the SPP in all issues of technology transfer, ranging from patenting/licensing/contract negotiation to the creation of new companies.

In order to efficiently organise biotech transfer in Switzerland and to optimally conduct scientific matchmaking a 'structural analysis' of the Swiss environment was essential. Unitectra established the necessary inventories and connections:

- In 1996 the first 'Swiss Biotechnology Industry Guide' was published (180 entries). The compilation of the data comprised a thorough analysis of the specific R&D and partnering needs of the biotech SMEs. This served as a rational base for the establishment of a transfer network.
- The analysis was complemented by the compilation (1997) of the 'Biotechnology Research Compendium Switzerland' (313 entries) [4].
- In 1998, Unitectra catalysed the formation of the 'Association of Swiss Biotech Companies' VSBU/ASBC (now approx. 110 member companies).

Spin-off companies established by former SPP BioTech participants and others based on results from SPP BioTech projects:

Cistronics Cell Technology GmbH, Zürich (founded 1998, ETH Zürich):
A company focussing on the development of novel multicistronic expression concepts; mammalian gene regulation systems and novel strategies for the detection of human therapeutic antibiotics.

Cytos Biotechnology AG, Schlieren (1996, ETH Zürich):
The company is active in various fields such as novel tools for drug discovery, serum-free protein expression systems, and vaccine production.

Metabolic Concepts GmbH, Zürich (1998, ETH Zürich):
The company provides consulting services for fermentation process development.

Prionics AG, Zürich (1997, University of Zürich):
A company specialising in the detection of prions which cause various diseases in humans and animals. It also aims at developing novel approaches for prevention and therapy of these diseases.

Tenaxis AG, Zürich (1999, ETH Zürich):
The company develops tailor-made (bio)catalytic processes involving liquid stream-driven processes.

TransSense GmbH, Ecublens/Basel (1998, EPF Lausanne):
TransSens develops novel planar patch clamp devices and systems.

Unitectra AG, Zürich, Bern and Basel (1999):
A recent spin-off which is built on Biotectra, the former technology transfer office of the SPP BioTech. Unitectra acts as the technology transfer organisation of the Universities of Bern and Zürich and of the SPP BioTech. Services are also provided for other organisations.

ZeptoSens AG, Witterswil (1998):
The main focus of this Novartis spin-off is the development of analytical platforms based on its competencies in the areas of advanced optical sensor and array technologies, biointeraction analysis and bioassay design and development.

- In 1999, the second, significantly enlarged edition of the 'Swiss Biotechnology Industry Guide' was published (now 234 entries) [5].
- In 1999, Biotectra was transformed into Unitectra AG, a non-profit-making limited company. Unitectra acts as the transfer organisation of the Universities of Zürich and Bern and the SPP BioTech. At the same time, the transfer spectrum was enlarged and now comprise the areas: life sciences, medicinal technologies, informatics, chemistry, physics, *etc.*

In parallel, an efficient biotech transfer network with universities, federal institutions and regional economic development boards was established.

Research Projects of SPP BioTech Have Led to Several Spin-off Companies

An intense interaction between academia and private industry in order to ensure the transformation of research results into products and services was one of the key aspects for the SPP BioTech from its outset. Alternatively, SPP BioTech participants were motivated to transfer their research results themselves through the creation of spin-off companies. In the eight years since the start of the programme, eight companies were founded by participants of the SPP BioTech and others based on technology and results developed in the scope of the programme.

These companies are listed in the box. They resulted from different modules of the SPP BioTech and are active in different fields. In addition, a number of other recent start-up companies participated in the programme and could significantly profit either directly through the funding of projects or from results developed in the context of the SPP BioTech.

A common issue for many spin-off and start-up companies in the high-tech sector is the necessity to develop proprietary technology and to establish a strong patent position on their intellectual property (IP). This is of particular importance for venture capital based companies because a strong patent portfolio reduces the risk for the investor to fully lose the invested capital if the company itself should fail. Until recently, Swiss universities had no active IP policy and rarely protected inventions themselves by filing patent applications. Since formal support on technology transfer issues was lacking in general, scientists in academia had to take care of all transfer issues themselves. Although there are some past success stories, the lack of effective technology transfer mechanisms represented a clear weakness of Swiss universities. As a result, IP frequently was not protected nor transferred to private industry because of lack of time, interest and understanding of business-related aspects by faculty members.

Four years ago, only the two Swiss Federal Institutes of Technology in Lausanne and Zürich had a technology transfer office to provide support for their faculties. In order to improve the situation, the programme direction of the SPP BioTech set aside money to support the protection of IP such as the filing of patents. Moreover, a technology transfer office was established in 1996 (Unitectra, formerly Biotectra) which provides services on technology transfer issues to all participants of the programme, including IP protection. This approach enabled several of the spin-offs mentioned above to protect their IP early on and to start building a patent portfolio. In return, this helped later on to attract investors to fund the company.

The SPP BioTech is now in the outphasing period until the end of 2001. In this final stage of the programme, several further spin-off companies are expected to result from different research projects of the programme. Adding all these spin-off activities to the many successes in technology transfer among academia and small, medium and large companies, a very positive summary of the SPP BioTech can now be made.

Biotech Spin-off Activities Beyond the SPP BioTech

The number of spin-off projects at universities is rapidly increasing. Unitectra together with SPP BioTech recently published the second edition of the 'Biotechnology Industry Guide Switzerland' [5]. The survey revealed that more than 40 new companies which are active in the field of biotechnology were established in the past four years. Many of the new companies have their roots either in one of the Swiss universities or in one of the multinational companies.

Whereas the two federal institutes of technology in Lausanne (EPFL) and Zürich (ETHZ) have a longer tradition in spinning-off new companies, the cantonal universities have, in the past, not been very active in this regard. This can mainly be explained by the fact that research performed at the federal institutes of technology, such as in the engineering sciences, frequently is more closely related to concrete applications. However, the past few years have seen a strong increase in the number of spin-off projects and actual spin-off companies from the cantonal universities. Unitectra, now also the technology transfer organisation of the Universities of Bern and Zürich, currently has more than 10 spin-off projects on-going at these two universities. This increased interest for spin-offs can be attributed to a number of different reasons:

- Awareness and education: A number of different programmes at the academic institutions increased the awareness that the creation of a spin-off company presents an attractive alternative for career planning and also provided some insight into entrepreneurial start-up companies for students. A good example is the start-up programme of ETH tools which started several years ago and has provided training for thousands of students. Since its beginning, it has been copied at several other universities. The business plan competition of ETHZ and the McKinsey company is another example. First organised in 1998, it attracted more than 500 participants from different universities. A similar number is expected in the second edition of this competition which was launched a few months ago. A third, more recent example are the programmes offered by the newly formed Chair for Entrepreneurship and Innovation at EPF Lausanne (CREATE) which is sponsored by Dr. Branco Weiss.
- Positive attitude of universities towards technology transfer: Universities in the past few years have become more conscious about their responsibility to actively care about the transfer of research results into products and services in collaboration with the private sector. Initiatives for collaborations with companies and also for the creation of spin-off companies are actively and openly supported. In addition, scientists can get active support at many of the universities from their local technology transfer offices, most of them established only recently.
- Practical support provided for spin-off projects varies between different universities and can include one or more of the following elements: consulting services in defining a business concept and writing of a business

plan; help in identifying and contacting appropriate coaches, business partners and investors; loans; renting of space and other infrastructure, either on campus or in nearby incubators. The technologies which are the property of the universities are usually licensed to the spin-off companies. Compensation of the universities occurs either in the form of licensing payments such as royalties on net sales or in the form of an equity position of the university in the spin-off. Equity models have become popular in different countries, *e.g.* USA and UK, whereas they are still rare in Switzerland.

- Role models: One of the most powerful motivators at universities are successful spin-offs which act as role models. In the biotech field such examples are the companies Modex Therapeutiques in the French part and Prionics and Cytos Biotechnology in the German part of Switzerland. They all enjoyed a strong media coverage and stimulated many scientists at their home universities to consider setting-up their own enterprise.

However, successful managers with hands-on experience in start-up companies are today in our experience one of the main bottlenecks. Since academics rarely have the necessary business skills to run a company, they usually require appropriate coaches and partners to help them.

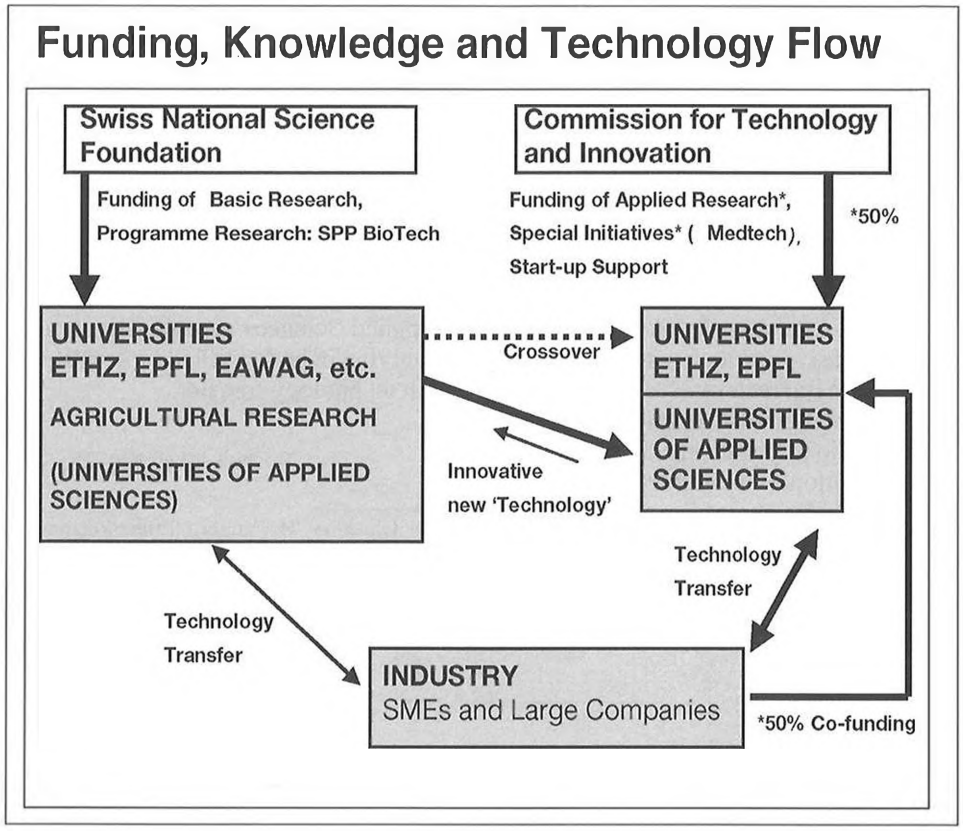
- Small and medium sized enterprises (SME) as a real opportunity: SME nowadays play an important role as sources for innovation in particular in the fields of information technology and life sciences. Many life sciences multinationals spend an increasing percentage of their R&D budgets externally for collaborations and alliances with SME. This provides new opportunities for entrepreneurs in academia, a trend which could be observed in the USA already during the past 10 years.

At the same time, society is no longer built on life-long employment by one company, a situation which in Switzerland only changed in the past years mainly due to the effects of globalisation. Whereas in the past industry attracted most of the young academics leaving university, self-employment today offers a real alternative with only moderately increased risk.

- The Association of Swiss Biotech Companies (VSBU): The VSBU with more than 100 member companies provides a contact network for young entrepreneurs. Since its foundation in the spring of 1998 numerous formal and informal contacts between experienced entrepreneurs and representatives from start-up companies have helped the latter to overcome many of the daily problems arising typically in young companies.
- Better developed venture capital market: Due to the increased spin-off and start-up activities, Switzerland has become an attractive location for venture capital funds and companies despite some existing legal limitations. This has led to an increased number of venture capital organisations and has improved the situation for entrepreneurs looking for venture capital financing. One such fund in particular, the Novartis Venture Fund, has played a very active role in the past few years. It not only co-funded a wide range of companies in the life sciences field but also acted for many entrepreneurs as a 'door opener' to receive more funding by other venture capitalists.

SPP BioTech together with Unitectra edited two brochures with stories about biotech entrepreneurs in the USA and Switzerland [6][7]. In these stories the founders describe their experiences in setting-up the company, and they talk about the successes and problems they had. The overall 21 stories of start-up companies give an excellent impression of the attitudes of Swiss and US entrepreneurs and the environment they are living in.

Scheme



Transitions and Collaborations – Future Developments

At present, there are three types of public funding for biotechnology research in Switzerland (see Scheme):

- Funding of basic research projects (individual projects) *via* the Swiss National Science Foundation (Division III).
- Funding of target-oriented programme research (projects co-ordinated in modules) *via* the SPP BioTech of the Swiss National Science Foundation (Division IV); strong emphasis on technology transfer, at the pre-competitive level. This programme is now complete. New projects cannot be submitted.
- Funding of application-oriented research and development projects *via* the Commission for Technology and Innovation (CTI). Industry co-finances 50% of these projects.

For the future development of Swiss biotechnology, the Commission for Technology and Innovation (CTI) will play a very important role, especially after

2001, as the SPP BioTech will be terminated at this time. Although it can be assumed that a significant part of the SPP BioTech research teams will find new SNSF funding within the framework of newly established 'National Centres of Competence in Research, NCCR' (now in the evaluation phase), it is crucial to organise and facilitate smooth transitions between SNSF and CTI. At present, many of the researchers in the SPP BioTech teams have already taken advantage of the extensive research network created by the SPP BioTech to access additional CTI and/or industrial funding. Some of the 'SPP BioTech start-ups' have also obtained additional funding from CTI and/or have found support from the CTI Start-up Programme. As a general trend, the number of young biotech companies (mainly spin-offs from Universities and Federal Institutes of Technology) applying for CTI-support or for the 'CTI Start-up Label' is steadily increasing.

In addition, also in the context of the CTI funding system, the establishment of a 'Biotech-Network' comprising several Universities of Applied Sciences (Fachhochschulen) is currently under discussion. If properly integrated into the Swiss Biotech scenery and brought to efficient interaction with Universities and Federal Institutes of Technology, the Universities of Applied Sciences can play a very important role in both applied biotech R&D and in technology transfer.

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START biotech

STARTbiotech
Students Seize Their Opportunities in Biotechnology Ventures: STARTbiotech

Philipp S. Angerer*

Abstract: Biotechnology is developing into a business sector of global scale and interest. STARTbiotech took place at the ETH Zürich to promote biotechnology venturing and to make people in Switzerland aware of the issues involved. At this one-day event, organised by students, all the major problems and advantages of founding a biotech venture were addressed in a series of lectures, a contact lunch and a plenary discussion featuring experts and experienced bioentrepreneurs. The resonance was very promising.

Keywords: Biotechnology · ETH Zürich · Forum · Foundation · STARTbiotech · Students · Ventures

Recently, many initiatives focussing on the issue of business foundation have arisen, sponsored and set up by big concerns and public and private organisations. Much attention is paid to information technology and Internet issues. People tend to underestimate the potential of another promising sector: biotechnology; in the eyes of some investors, the 'dot-com industry' of the new millennium.

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Switzerland is not considered to be at the epicentre of this evolving trend, standing in the shadow of other protagonists like the USA, UK or Germany. Yet it has all the prospects to serve as an incubator for biotechnology and develop its own mature industry: low tax, availability of capital, excellent infrastructure and a history of outstanding research in fields in and around biotechnology. A vast potential lies in the universities and in the heads of their students. But the classic career in biotechnology and related fields at university is low paid and demands a lot of dedication on behalf of highly qualified people. As an alternative, they could use their ideas and turn them into products.

A group of biochemistry students at the Swiss Federal Institute of Technology in Zürich (ETHZ) were aware of these facts and of the resulting opportunities that could give their future another direction. Out of this conviction, they founded STARTbiotech.

STARTbiotech, entirely run by students, is a long-term project. The organisation promotes entrepreneurship and the link between universities and the biotechnology industry. Last but not least, STARTbiotech aims to motivate students and promote entrepreneurial thinking.

To attain these goals, STARTbiotech organised the 1st Biotechnology Venture Founding Forum, which took place on Friday February 4th, 2000, at the ETHZ. It was a one-day event, and concerned the foundation of biotechnology ventures.

About 200 students and professors involved in different subjects from science to economics, and other interested persons attended, making up an interdisciplinary and international audience. Some participants already had ideas and aimed to realise their founding plans.

They eagerly followed the introduction by Prof. Dr. Olaf Kübler, President of the ETH, in which he supported the students' action and initiative. He was followed by Arnd Baetzner, President of the Student Union of the ETH (VSETH), who emphasised the importance of the multidisciplinary link at student level between the ETH and the University of St. Gallen, called 'Achse ETH/HSG'. The Achse ETH/HSG should lead to promising joint projects between science and economics at student level, in the style of STARTbiotech.

The issues of biotechnology venture founding and success were then addressed by two of the most prominent bioentrepreneurs in Switzerland, Dr. Bruno Oesch of Prionics AG and Dr. Wolfgang Renner of Cytos AG. They both complemented their entrepreneurial stories with advice and tips for the audience.

After the break Prof. Dr. Bernard Witholt, ETH Institute of Biotechnology, focussed on the future of biotechnology: he covered the prospects and gave an outlook on possible developments in his field, giving the audience an idea of which part of applied biotechnology would be the most successful in the years ahead. The last speaker, Dr. Branco Weiss, who is a key figure in current initiatives in founding ventures, shared some of his valuable experience in venturing and commented on the dos and don'ts of founding and running a business.

The two-hour lunch was an excellent opportunity to chat with the speakers or explore the contact fair in the Semper Aula of the ETH, at which an interesting array of organisations, biotech firms and even global concerns had their representatives, *e.g.* Ares Serono, UBS, Association of Swiss Biotechnology firms (VSBU), m-phasys from Germany.

The afternoon was filled with a panel discussion, which bore the title: 'How to found a biotech venture'. The panel consisted of Dr. Ernst Thomke, Chairman of BBBiotech, Dr. Bruno Dalle Carbonare, president of BioValley Switzerland, Dr. Hans Peter Rutz from NEKKO Research, Dr. Rolf Studer, New Medical Technologies, Bernhard Waxenberger from the University of St Gallen and Dr. Verena Steiner from ETH tools. The discussion, which became an open, informative and constructive dialogue between the audience and the panel, was moderated by Christian Dettwiler from the 'NZZ Format' TV show.

The closing speech was held by Bruno Rosset, Regional Vice President of Ares Serono, representing the Association of Swiss Biotechnology Firms (VSBU), taking an active position in giving special emphasis to the importance of networks like the VSBU for start-ups and small biotech companies.

The feedback of the participants after the forum was positive all down the line. Vital questions were answered, important contacts made and new viewpoints were acquired. Also the prospective founders came closer to realising their plans. This positive resonance confirmed the view that biotechnology is indeed to be considered a serious business. The forum STARTbiotech will take place again soon, as an important catalyst in the contact between research and business.

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Financing an Early Stage Venture

Alfred Scheidegger*

Abstract: In early stage start-ups or spin-off companies the strong financial backing and expertise brought in from the beginning is crucial to bring innovative ideas to the market. Venture capital funds have a clear investment focus and investment criteria with regard to industry/technology focus, geographical region, size of market, team with leadership, secured intellectual property rights, common vision and values, favorable exit/return. The numerous initiatives at universities promoting entrepreneurship and the spin-off of scientific discoveries and the changing attitude of academics regarding risk taking is presently creating a vivid venture capital scene.

Keywords: Early stage · Investment criteria · Technology · University · Venture capital

Venture Capital for Start-ups and Spin-offs in Switzerland

In the USA venture capital was the basis of the fast commercial success of businesses in the field of high-technology and of biotechnology in particular in the past decades. In Switzerland, venture capital is establishing itself as a key instrument allowing for the fast growth of such enterprises.

In early stage or spin-off companies the strong financial backing from the beginning is crucial to bring innovative ideas to the market. The money for the venture capital comes from institutional investors such as pension funds, insurance companies and banks as well as from private investors.

Successful venture capital funds have profound technological and scientific expertise as well as marketing and managerial experience in their respective fields of investment. In addition they have a professional network at their disposal. This is especially valid when investing in start-up companies. Due to the early stage of such projects, risk to be taken is considerably higher by nature. In fact, only few projects will develop their potential and reach the expected extraordinary high return. Because of the demanding expertise for early stage investments and the high risk involved, only few venture capital funds are specializing on such investments in Europe.

How to Attract Investors

The first step on the way to project financing is to raise the interest of the venture capitalists with a sound business plan backed by a competent team. Professional investors pay attention to some critical issues that should be elaborated in the business plan.

- Why will your idea become a market leader
- What is the exact target market
- What are the rules of these markets and what are the specific buying criteria of these customers
- How does the proposed product/service address these criteria
- How does your product compare with competing products or approaches against these criteria
- What makes your technology unique, and how is it protected
- Why is your team the winning team
- How much investment is needed and what does the investor get for it

How Investors Decide

Investors take considerable risks in supporting a new business that wants to penetrate an existing market or create a new one. Venture capital funds have a clear investment focus and investment criteria. Common criteria found among most venture capital funds are:

- Industry / technology focus
- Geographical region
- Large / growing market
- Team with leadership
- Secured intellectual property rights
- Lead function of investor or co-investment
- Common vision and values
- Favorable exit / return
- Stage of financing

Factors Supporting Venture Capital Financing

A successful venture capital system is dependent on possibilities to exit the investments by an initial public offering (IPO) or a trade sale to another usually larger company. Therefore, robust stock markets for fast growing companies seeking fresh capital are crucial. The newly established New Market at the SWX Swiss Exchange now allows for an early public offering in Switzerland too. In Europe, 40% of the companies going to a new Stock Exchange market have been financed with venture capital.

The growing number of venture capital funds in Switzerland is dependent on a qualitative and quantitative deal flow. Basic technology platforms and revolutionary innovations very often originate from universities and research institutes which are financed by public money. Also thanks to the numerous initiatives at universities promoting entrepreneurship and the spin-off of scientific discoveries, venture capital funds are able to find attractive investment targets.

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ACTELION
Creative Science for Advanced Medicine

Actelion Ltd.: An Emerging Biopharmaceutical Company

Walter Fischli* (Head, Drug Discovery) and Thomas Weller (Head, Chemistry)

Abstract: Actelion is an emerging R&D biopharmaceutical company focusing on the discovery and development of innovative drugs to treat and prevent diseases related to the endothelium. Actelion was founded two years ago and has its headquarters and research facilities in the new Innovation Center Allschwil, in the region of Basel/Switzerland. Its initial public offering is foreseen in first half of 2000.
Actelion has two clinical products, *bosentan* and *tezosentan*, two endothelin antagonists directed to the management of severe vascular disorders. Bosentan is in Phase III trials for chronic heart failure and for pulmonary hypertension whereas tezosentan is in Phase III trials for acute heart failure. Both products were discovered by members of the current management team during their employment at F. Hoffmann-La Roche, and Actelion licensed the exclusive rights to these compounds from F. Hoffmann-La Roche. Very recently, Actelion entered into a license agreement with Genentech Inc. to co-promote tezosentan in the US.
Actelion's drug discovery involves a multidisciplinary approach, which applies state-of-art technologies such as combinatorial chemistry, X-ray analysis and computer modeling. In pre-clinical development, a cross-therapeutic evaluation of novel compounds is performed. The research is focused on the endothelium and covers therapeutic areas affected by the endothelium such as cardiovascular disorders, inflammation and cancer. Based on its expertise, Actelion has entered into a research collaboration with Johnson & Johnson Inc.

Keywords: Actelion · Bosentan · Endothelium · Medicinal chemistry · Tezosentan

Introduction

The pharmaceutical landscape is changing rapidly as health care costs escalate and pressure for cost containment intensifies. Industry is faced with a new mandate to provide drugs that are not solely innovative but also affordable and provide add-on value over existing therapy. Consequently, pharmaceutical companies are responding with organizational and structural changes to streamline and reduce their tremendous R&D costs. In order to maintain an acceptable launch of new drugs each year, there is an increasing need to license-in more drugs. In parallel, smaller companies are discovering and/or developing an increasing number of innovative molecules and serve as an important source of innovation for the large pharmaceutical companies.

Actelion Ltd is one of these new small R&D pharmaceutical companies concentrating on the discovery and development of small molecular weight novel drugs for largely unmet medical needs. The company represents the integration of unique industry experience and leading scientific expertise that concentrates on one organ, the endothelium, rather than on specific indications. By this 'organ' approach, technical and scientific opportunities can be better exploited and should lead to a larger flow of new chemical entities.

History of Actelion

Actelion was founded in December 1997 by three former executives of F. Hoffmann-La Roche and was financed in April 1998 and March 1999 by two financing rounds gathering 70 million SFr. Since its foundation, Actelion has

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achieved major milestones:

- It completed the recruitment of an experienced management team.
- It moved into its own new laboratories in December 1998 and recruited the scientific staff of close to 50 people to run its own research.
- It has established three full drug discovery projects and discovered interesting new compounds which have led to several patent applications so far.
- It obtained the license of two new, innovative drugs from F. Hoffmann-La Roche:
  - *tezosentan* which was licensed in the preclinical phase and which Actelion has brought so far to phase III of worldwide clinical development for acute heart failure,
  - *bosentan* which Actelion develops in phase III for the chronic treatment of congestive heart failure and for pulmonary hypertension.
- It entered in July 1999 into a research collaboration with Johnson & Johnson Inc.
- It entered in February 2000 into a license agreement with Genentech Inc. to co-promote tezosentan.

Thus, within two years, Actelion has created the infrastructure of a company able to discover its own drugs and to develop them. Actelion has also succeeded in building a balanced portfolio, ranging from research projects to compounds in advanced clinical development. At present, the initial public offering is prepared for the first half of 2000.

Scientific Approach to Drug Discovery: Focus on the Endothelium

The endothelium is a thin layer of cells constituting the interface between blood and the vessel wall. This strategic location makes it well available for drugs or molecular bio-material engineering such as transfection or transplantation of transfected cells. Furthermore, it is accessible for diagnostic procedures.

Recent discoveries showed that the vascular endothelium serves as a biochemical filter and regulator of many vascular phenomena. There is also an intimate cross-talk to the underlying smooth muscle cells. One main function of endothelial cells is the maintenance of vascular tone which is achieved by the balanced release of constricting (*i.e.* prostaglandin, endothelin) and relaxing factors (*i.e.* prostacyclin). Another major function is to provide a non-thrombogenic surface that does not allow platelets or other blood cells (*i.e.* monocytes, leukocytes) to adhere.

In addition to this involvement in cardiovascular disorders, the endothelium is involved in other important pathophysiologic reactions such as inflammation (leading to adhesion and infiltration of inflammatory cells or graft rejection), and angiogenesis (important factor in cancer metastasis or in diabetes) (Fig. 1). To exploit its expertise on the endothelium, Actelion has entered in July 1999 into a research collaboration with Johnson & Johnson Inc.

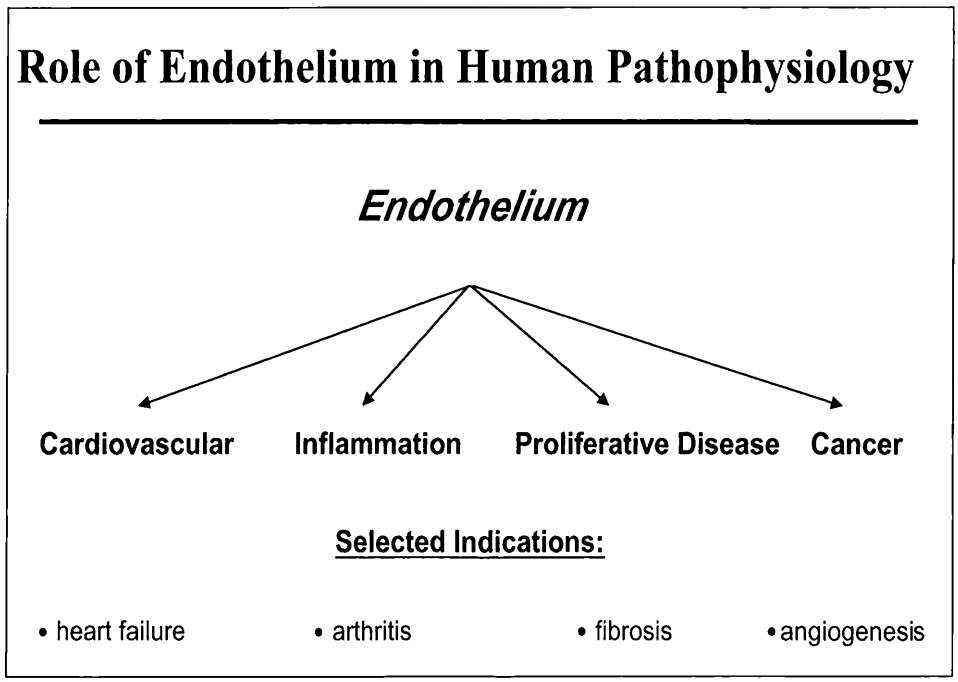

Fig. 1

Strategic Approach to Drug Discovery

Actelion's drug discovery and development consists of iterative processes between different scientific disciplines which have all been integrated such as molecular biology, biochemistry, medicinal chemistry, pharmacology and clinical pharmacology. However, the integration of individual technologies is, indeed, not a guarantee for finding better drugs faster. Actelion's answer is to put these state-of-art technologies in an integrated approach which includes the deep understanding of epidemiology and pathophysiology of the diseases as well as the process of discovery and development of innovative compounds. Actelion has gathered an experienced and successful team and the necessary know-how from molecular biology to clinical development.

A central part of Actelion's research consists of *medicinal chemistry* taking about 50% of the overall research effort. At present, 40% in chemistry are Ph.D. collaborators including postdoctoral fellows, 60% experienced technicians. One third of the chemistry manpower is dedicated to parallel and combinatorial chemistry, technologies which are applied whenever possible in every project. Actelion has identified several lead compounds in their projects by screening approaches which led to several patent applications after further synthetic work. Also, computer modeling has been implemented for rational molecular drug design. At present, modeling studies are done using non-proprietary protein templates complexed to Actelion's novel lead compounds. Crystallography and X-ray studies are being integrated to analyze our proprietary protein-ligand co-complexes (Fig. 2).

Actelion has invested in a proprietary *research information management system* centered on Oracle 8.0.4. It can handle chemistry such as the web-based registration of chemical structures with immediate assignment of Actelion numbers. Also, searches for substructures can be done as well as searches in an in-house reaction database containing two million reactions. For biology, the system can estimate inhibition values from raw data, display and store approved results. Most importantly, it can interconnect the chemical with the biological information to allow structure–activity relationship studies.

In *molecular biology*, a gene array system (ActArray I) is being designed to measure mRNA expression levels of

Actelion-related targets in human tissues and cells (Fig. 3). The array will help to define novel drug targets and will identify changes in gene expression patterns in pathophysiological conditions or under drug treatment. The current goal is set to simultaneously measure the expression levels of up to 300 genes. Besides, about 15 new targets are being cloned and expressed and will be integrated into the drug discovery process.

First Clinical Candidates

The first products intrinsically linked with the endothelium are Actelion's first two clinical products, bosentan and tezosentan, two endothelin receptor antagonists directed to the management of severe vascular disorders. The endothelin isopeptides are substances secreted from endothelial cells functioning through two endothelin receptors, ET_A and ET_B, belonging to the G-protein coupled receptor family. Actelion's two antagonists are mixed ones blocking both receptor subtypes. Bosentan is in Phase III trials for chronic heart failure and for pulmonary hypertension whereas tezosentan is in Phase III trials for acute heart failure. Both products were discovered by members of the current management team during their employment at F. Hoffmann-La Roche, and Actelion licensed the exclusive rights to these compounds from F. Hoffmann-La Roche. Very recently, Actelion entered into a license agreement with Genentech Inc. to co-promote tezosentan in the US.

Actelion's Location

Actelion is situated in Allschwil, a suburb of Basel/Switzerland, a city which offers significant benefits such as:

- Availability of highly qualified personnel in chemistry and the pharmaceutical field,
- Loyalty, dedication and motivation of people with a tradition of quality work,
- Stability of political, economic and working environment,
- Proximity of top universities, private institutes and engineering schools,
- Entrepreneur-friendly employment laws.

Actelion is located in the stimulating environment of the newly formed Innovation Center of Northwestern Switzerland which represents with 25 000 m^2 the second biggest TechnoPark in Switzerland. The participating companies are from the natural sciences, mostly biomedicine and, synergistic to Actelion, involved in combinatorial chemistry, liquid crystal chemistry, high-throughput screening, software for life science research or clinical research and drug development.

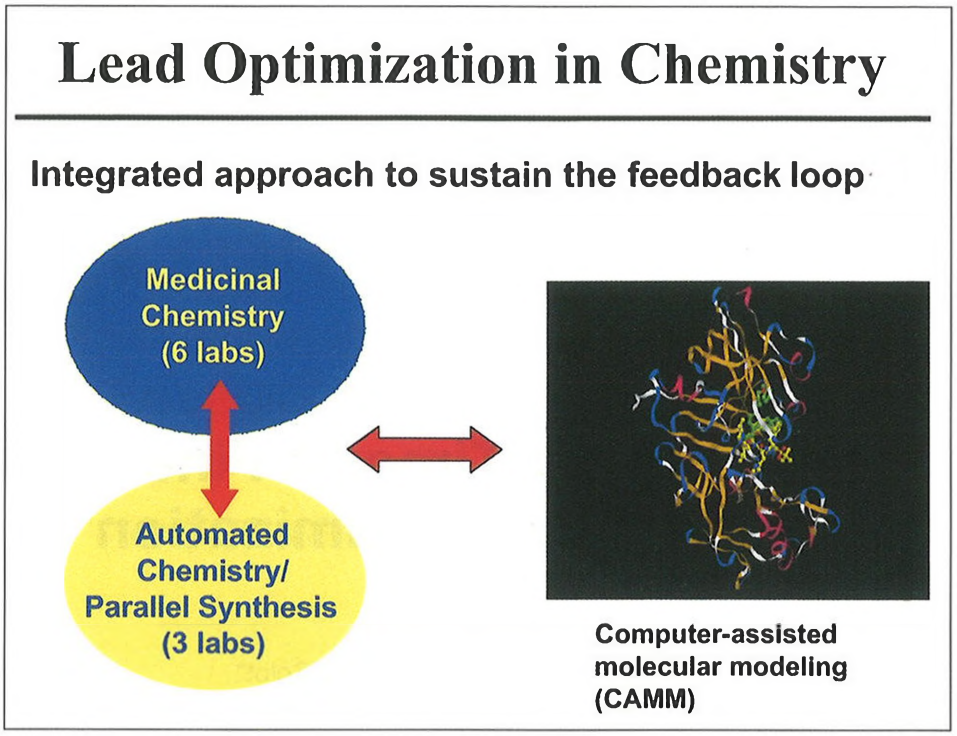

Fig. 2

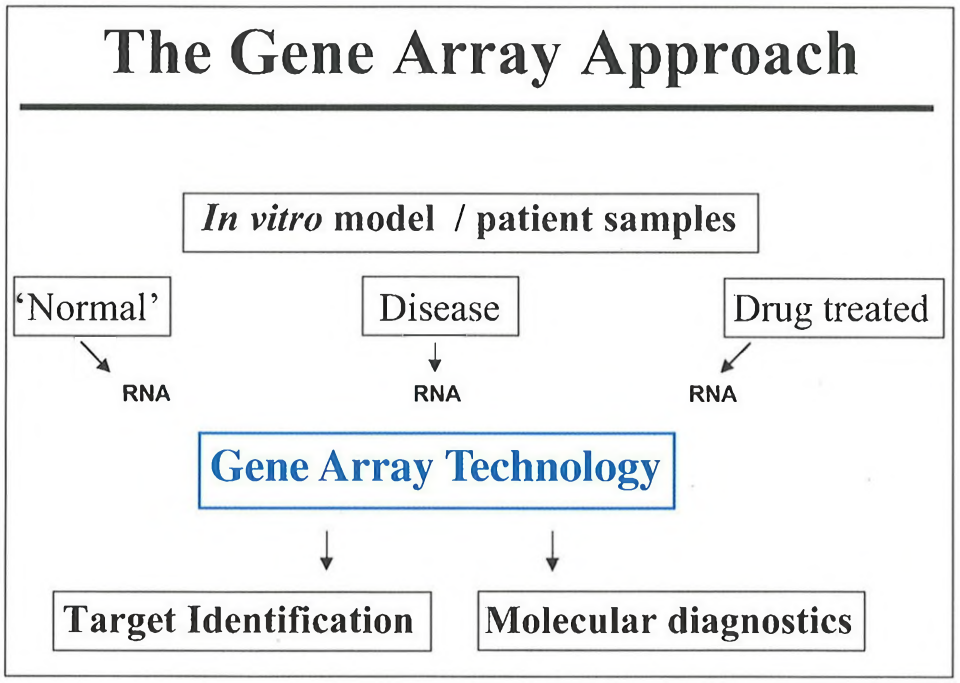

Fig. 3

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AICOS Technologies AG
Saving Time: A Fine Art – Quality & Process Optimization

Yves-Laurent Grize and Philippe Solot*

Abstract: TIME IS MONEY. So saving time is essential for enterprises who want to improve their productivity. This paper presents how researchers as well as development and production people can profit from the advantages offered by statistical tools and simulation methods to increase significantly the efficiency of their working processes. Several case studies are briefly discussed.

Keywords: Material flow simulation · Multipurpose plant optimization · Process optimization · Production logistics · Statistical experimental design

In the current era of market globalization, the saying 'time is money' applies more than ever. Process industries, especially the chemical-pharmaceutical industries, need to constantly increase their efficiency in order to remain competitive. An appropriate way to achieve this ambitious objective is to save time wherever it can be saved, thus freeing resources for other purposes. This holds true throughout the company departments, from research to marketing over development and production.

AICOS Technologies, a Basel-based spin-off of the central information systems department of the former Ciba-Geigy, specializes in supporting process industry companies in this time-saving process. The enterprise was founded in early 1997 by four applied mathematicians who, at that time, dealt almost exclusively with production optimization and data analysis problems of their employer. The share capital of CHF 100 000 was financed from their own means. A venture capital loan enabled the necessary telephone and computer infrastructure to be financed.

Today, about three years later, some hundred companies – including BASF, Clariant, Ems-Chemie, Lonza, Merck, Nestlé, Roche, Sanofi-Synthélabo,... – are accessing the scientific expertise and the long-term practical experience of AICOS Technologies – which adds up to more than 40 person-years in the process industries. A large diversification of the customer portfolio could be achieved: in 1999, more than two thirds of the turnover was gained from projects originating from companies other than Novartis and Ciba Specialty Chemicals. Geographically, AICOS Technologies looked over the borders and could quickly establish new customer relationships in Europe, especially in France and Germany.

Finally, the small structure that resulted from the outsourcing has led to an extended flexibility and generated a better working atmosphere, resulting in a higher motivation for the collaborators and, in the end, profit for the customers.

A Panel of Products and Services for Time Saving

AICOS Technologies services are tailored to the needs of R&D and production people and divided into the three application areas: Quality Engineering, Production Logistics and Data Analysis. It includes specialized software packages, consulting services and a full catalogue of training programs for chemists, engineers and lab collaborators.

The three software packages STAVEX (expert system for the design and analysis of experiments), SIMBAX (logistic simulation of production processes and plants) and EasyStat (Excel add-in for fast data analysis) have been developed with user-friendliness as an essential feature: 'The methods used internally should be transparent for the user; he or she should be able to profit from their performance without needing to understand their details' was part of the specifications. Moreover, the needs of the process industries were taken into account, hence the users are able to cope with the specificity of this branch with no difficulty. However, most of the tools can also be used in other branches of industry.

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Besides specialized software packages, the portfolio of AICOS Technologies also includes consulting services. Its consultants use their knowledge of the practical world, especially within the process industries, to realistically comprehend problems described by their customers and to define accordingly the problem limits. Then, suitable models are developed in order to be able to understand thoroughly the situation and to work out improvement measures. In more software-oriented projects, consultants determine which software packages are the most appropriate for a given problem setting and may develop a specific software solution if no package fulfills the customer requirements.

AICOS Technologies services are completed by training sessions. Courses on the use of the software packages mentioned above are provided and also general courses in applied statistics. Nearly all courses are taught on PCs, to make it possible for the participants to be able to understand more easily the software functions or methods. Training sessions tailored to the needs of a company are also offered by AICOS Technologies as in-house variants. Finally, courses can be taught in English, French and German as desired.

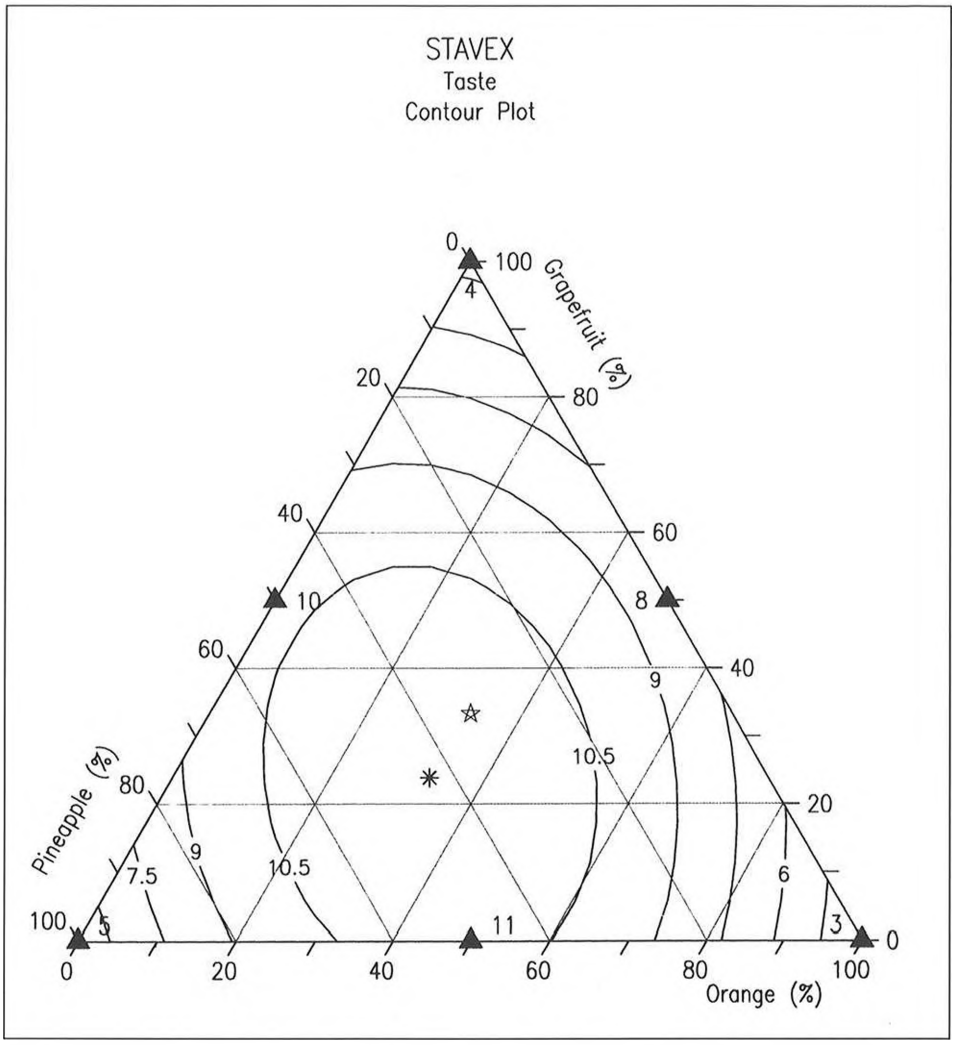

Fig. 1 Example of a STAVEX model for the optimization of a complex fruit juice mixture involving four components and a large number of parameter restrictions.

Saving Time Through Efficient Experimentation

Experimentation and interpretation of the collected data is the basis for scientific decision-making. However, experiments are often costly in time and money. And which chemist today is not faced with the task of optimizing a chemical reaction or a process within a tight schedule and at the lowest possible cost? Under these constraints the traditional approach to study a system by varying its different parameters 'one-at-a-time' is no longer applicable: this usually leads to a large number of often redundant experiments and to an ambiguous interpretation of the results. This is simply too costly. Because they exactly address these issues, the methods of statistically designed experiments (DoE) have recently regained great interest in many R&D departments.

Namely they allow scientists to obtain a maximum of reliable and useful information with a minimum experimental effort. By using sophisticated mathematical combinatorial and statistical theory, it is possible to identify which is the best series of experiments to be conducted, given a fixed experimental budget and some specified optimization questions. For example, a complex dyestuff process involving over ten different parameters could be optimized in this fashion. Three experimental plans with a total of only 29 experiments were used to achieve satisfactory production conditions involving new settings for temperature and concentration. Although the final optimization was done with two factors only, five other factors were found to be important during the course of experimentation and were set subsequently at their optimum level.

Although not all of the DoE tools are new, it is only since the emergence of user-friendly software and graphics-oriented techniques that they can be used by a large number of non-statisticians on a routine basis. Because of the importance of these methods, Ciba-Geigy decided in the early 90s to develop in-house an expert system, named STAVEX, to encourage chemists and engineers to apply DoE tools without the help of statisticians (Fig. 1). Today, the developers of STAVEX are amongst the founders of AICOS Technologies and further develop this system which is successfully used in many chemical, pharmaceutical and food sciences companies throughout Europe. A partnership agreement between AICOS Technologies and Mettler-Toledo was sealed in 1998 according to which Mettler-Toledo distributes STAVEX as a support tool to its powerful automatic labor reactors worldwide.

Saving Time Through Efficient Production Logistics

In the production environment, increasing productivity is the usual objective. But in which ways can it be achieved? One often thinks first of technical measures, because they may enable considerable progress: a temperature increase accelerating a reaction or the use of a new high-technology device guaranteeing a higher performance *etc.* can for instance be quoted. The organizational level, at which especially logistic aspects

hide significant optimization possibilities, constitutes a second important action level.

As a first practical application, the development of a chemical process for the production of a new product can be mentioned. Productivity objectives are often expressed in form of the desired cycle time, say, a batch should be ready every five hours. With which process variant can this be achieved in the most economic way? For the simplest processes, answers can easily be given, since the slowest process stage – the so-called bottleneck – determines the rhythm of the whole production. Nevertheless, reality is much more complex. It is often the case that a given reaction can be performed in several different devices, that batches are grouped before further processing, that semicontinuous processes are controlled by tank level conditions or that recycling takes place. Then the answers to the questions mentioned above cannot be found any more in one's head. The sophisticated material flow simulation methodology of AICOS Technologies, which uses the language of chemical engineering, then offers process engineers valuable support, enabling them to evaluate very easily the process variants considered and to visualize their differences graphically. In this way, the development department can compare a greater number of variants, concentrate on the most promising ones *via* the systematic elimination of the bottlenecks and finally determine the best production process.

In multipurpose plants, conflicts between products requiring shared devices are more likely, which leads to time losses (see, for example, Fig. 2). In such cases, the production capacity can be considerably increased by eliminating unnecessary waiting times. For this purpose, AICOS Technologies offers detailed analyses of the plant production logistics which prevent inappropriate decisions about plant-redesign investments being made. If needed, the issues of operational production planning and scheduling can also be dealt with.

This methodology has been successfully applied to a variety of production settings. Examples include the synthesis of optical brighteners, dyestuffs, the formulation of pigments, the synthesis of pharmaceuticals, the biotechnological production of a drug and the packaging of fine chemicals. The savings achieved in a large multipurpose plant amounted to as much as three million Swiss francs. In general, such process and plant optimization studies often lead to *production capacity increases of more than 20%*.

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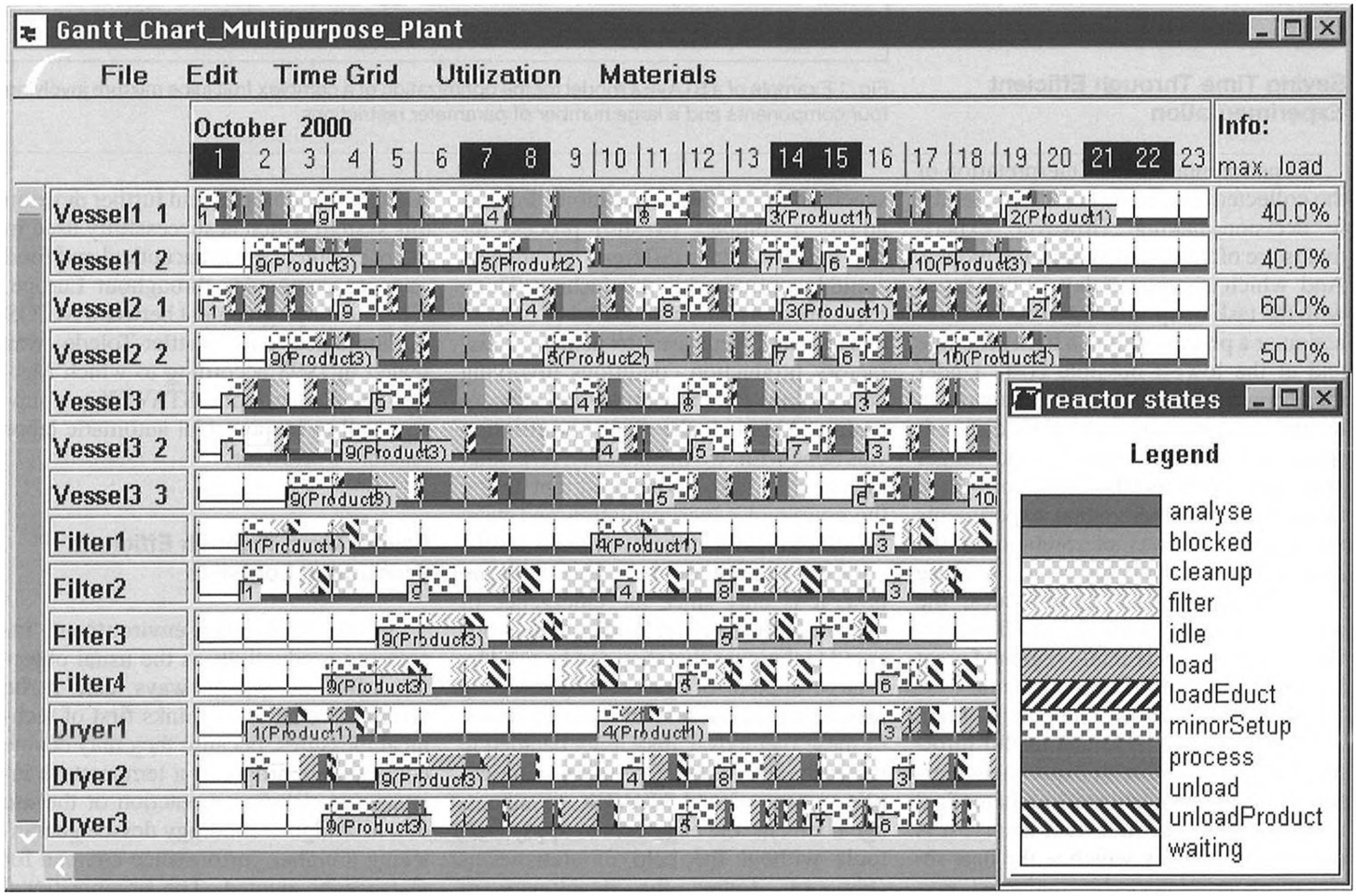

Fig. 2 Example of a Gantt chart obtained with the simulation tool SIMBAX for the optimization of a multipurpose plant.

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ARGONAUT TECHNOLOGIES

Argonaut Technologies AG
Reaping the Benefits of Parallel Synthesis: Meeting Challenges from Discovery to Development

Kara Andrews*

Abstract: Parallel synthesis provides a fundamentally more efficient way for chemists to work. The key is to design parallel synthesis tools that are suited to the specific requirements of each area of research and development.

Keywords: Automation · Combinatorial chemistry · Organic synthesis · Parallel synthesis · Process development

Until recently, the majority of synthetic organic chemistry has remained a painstakingly slow, manual process. From discovery to compound optimization to process development, synthesis can often be a limiting factor in getting a product to market quickly.

Certainly combinatorial chemistry, automation, miniaturization and other technological and scientific advances have accelerated the synthesis of large libraries of compounds destined for high-throughput screening. But these techniques have been used predominantly by specialists early in the discovery cycle. Now chemists later in the cycle are also under pressure to adopt new techniques that will enable them to work faster.

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Parallel synthesis – running multiple independent reactions simultaneously – provides a fundamentally more efficient way for chemists to work. The key is to design parallel synthesis tools that are suited to the specific requirements of each area of research and development. For example, compare the needs of a combinatorial chemist making targeted libraries for lead discovery; with the needs of a bench chemist synthesizing a small series of compounds in order to study structure–activity relationships; with the needs of a process chemist optimizing reaction parameters for use in a pilot plant.

At Argonaut Technologies, understanding these different requirements is the first step in developing new parallel synthesis instrumentation. Teams of chemists and engineers work with industry leaders to identify the goals, scale, range of reaction conditions, need for automation and other factors that will be critical in the laboratory. Then these teams work together to design and validate the instrument by using it in our own laboratories.

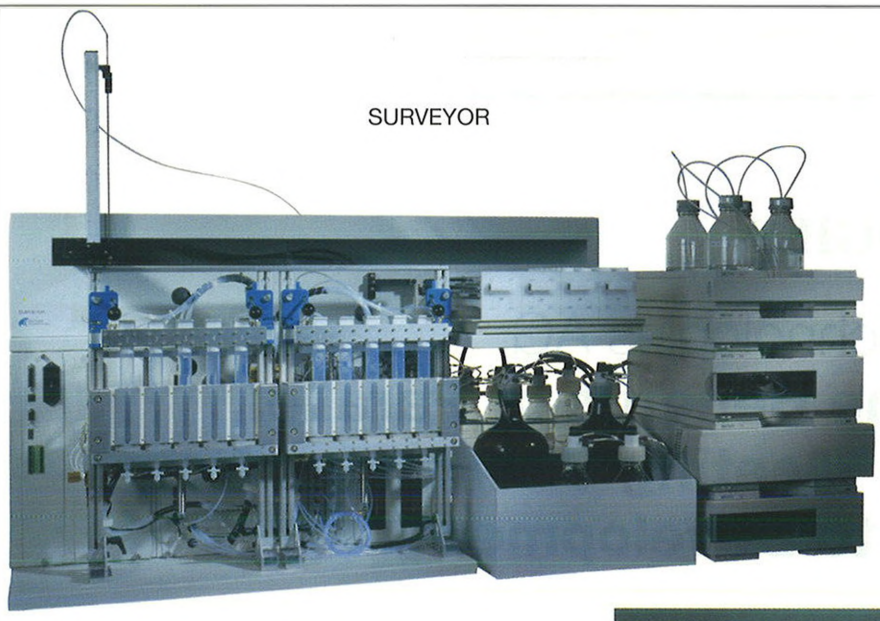
Argonaut Technologies was founded in 1994 with the mission of developing innovative tools to help chemists reap the benefits of parallel synthesis. Argonaut's headquarters in San Carlos, California includes chemistry laboratories, engineering and manufacturing facilities and administrative offices. In 1997, the European headquarters and technical center was established in Muttenz, Switzerland to assist customers and our network of distributors throughout Europe.

Supporting Changes in Library Synthesis

With increasing knowledge of molecular targets and more powerful computational tools for library design, there is growing interest in synthesizing smaller, focused libraries of more novel compounds. This trend has ramifications for library synthesizer design. More difficult chemistries are often required in order to make these libraries. This means that the synthesizer must be capable of maintaining a completely inert environment and handling air- and moisture-sensitive reagents with precision while producing reliable and reproducible results.

When dealing with a large number of reactions, a high degree of automation helps to avoid potential human error, plus

SURVEYOR



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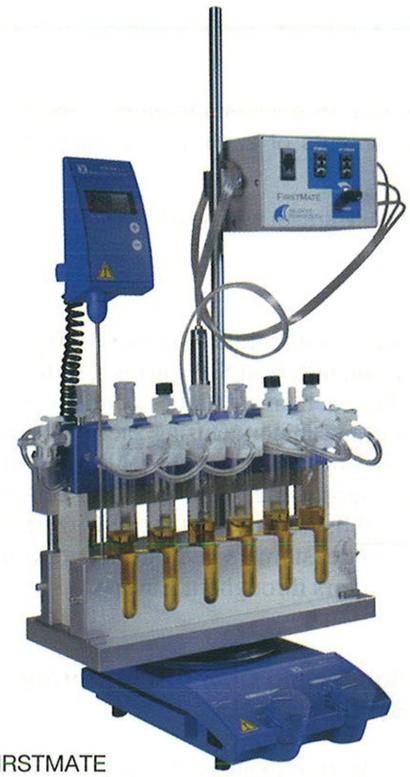

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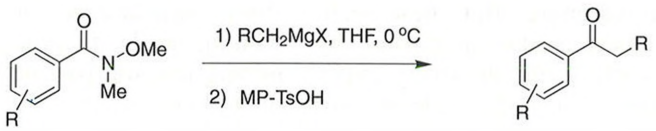
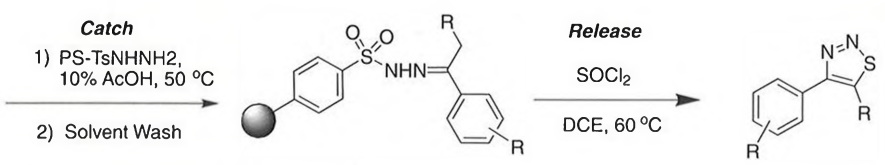
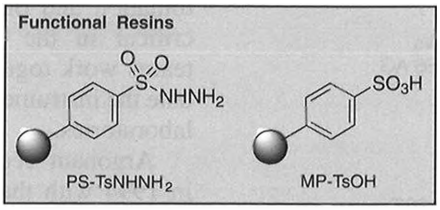




Using a 'catch and release' strategy, 1,2,3-thiadiazoles were synthesized in parallel using a polymer sulfonyl hydrazide resin (PS-$TsNHNH_2$). Resin capture of ketones synthesized from Weinreb amides and Grignard reagents afforded resin-bound sulfonylhydrazones, which underwent cyclizative cleavage with thionyl chloride to afford 1,2,3-thiadiazoles.

CATCH & RELEASE



it frees valuable time to perform other tasks. But automation needs to be combined with the flexibility to visually monitor the reactions and intervene if necessary.

These capabilities have been built into Argonaut's Trident™ system, a modular synthesis platform that consists of the Trident Automated Synthesizer for both solution and solid phase synthesis; the Trident Workstation, for semi-automated synthesis; and the Trident Sample Processing Station, for automated liquid–liquid extraction and other workup, purification and sample processing functions.

Accelerating Traditional Benchtop Synthesis

When applying parallel synthesis techniques to traditional, lower-throughput applications, the most important factor is to not limit the flexibility, hands-on control or wide-range of synthetic methods that are used to craft individual molecules. Straightforward equipment that is simple to use and fits smoothly into the existing workflow makes it convenient for chemists to perform parallel reactions.

The Quest™ synthesizer is used in hundreds of laboratories around the world to perform synthesis, including gaseous reactions, plus concentration workup and purification of up to 20 compounds on one simple instrument. The new FirstMate™ is a good option for those who want a compact set of modules that works with standard glassware, yet provides both heating and cooling with robust agitation and an inert environment.

New Options for Hydrogenations and Catalyst Optimization

Performing parallel gaseous reactions at higher pressures and temperatures requires a different technology to reproduce the environment within large autoclave reactors. Reactors designed with magnetically coupled, overhead impeller stirring, individual control of the temperature and pressure in each vessel and the monitoring of gas uptake allow chemists to track and compare the course of reactions under different conditions.

Argonaut Technologies turned to industry pioneer Symyx Technologies for the reactor design used in Endeavor™ to perform eight parallel gaseous reactions. This technology has been validated in Symyx' own laboratories. Endeavor can be used to perform hyrdrogenations and carbonylations, or for accelerating the optimization of homogeneous catalysts.

Faster Process Development Reduces Time to Market

By the time a compound reaches the process development stage, the pressure to quickly identify an efficient synthetic process is enormous. The speed of performing parallel reactions can significantly accelerate this work. In order to optimize reaction conditions for manufacturing, process chemists need the ability to control and vary multiple reaction parameters across a number of reactions and collect as much data as possible. Frequent sampling and HPLC analysis are critical, but can be an onerous task, especially if a reaction must run overnight.

With a consortium of six companies, Argonaut has developed a platform that gives process chemists unprecedented control over ten simultaneous reactions. Automated sampling and HPLC injection and analysis are integrated into the platform. Surveyor™ uses simple, graphical software to set up experiments and control temperature, temperature ramp rates, reagent and solvent addition, agitation, sampling and analysis.

The Importance of Resins and Reagents

For both solution-phase and solid-phase synthesis, polymer resins are an important consideration. Scavenger resins and polymer-bound reagents can facilitate parallel synthesis and help to eliminate the purification bottleneck associated with solution-phase synthesis. Scavenger resins are added after the reaction is complete to trap impurities, allowing their removal by simple filtration.

For solid-phase chemistry, different base resins with unique properties and a variety of linkers give more flexibility in the choice of solvents and reaction methodology. Argonaut is known for producing consistent, high-quality resins, along with extensive technical information to help chemists use them effectively.

Summary

Accelerating organic synthesis presents different challenges throughout research and development. Argonaut Technologies is addressing these challenges with both the innovative tools and the expertise that help chemists meet the new demands to work faster and more efficiently. Argonaut's mission is to focus on parallel synthesis and provide a complete solution – from understanding our customers' needs to providing reliable products to following up with service, training and ongoing support.

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ARPIDA LTD
A Second Generation Start-up for the Research and Development of Anti-infectives

Seema Mukhija, Thomas Hesterkamp, Andreas Haldimann, Peter Sperisen, Jürgen Jäger, Johannes Hoffner, Sorana Greiveldinger-Poenaru, Laurent Schmitt, Isabelle Hampele, Harald Winteler, Artur Jezewski, Kaspar Burri, Ivan Kompis, Dieter Gillessen, and Khalid Islam*

Abstract: Arpida Ltd was founded in July 1997 as a 'second generation' start-up company dedicated to the discovery and development of novel drugs for the treatment of infectious diseases. The company has a total staff of 23 (16 Ph.D.s), an international scientific advisory board composed of opinion leaders in infectious diseases, and a network of drug-development companies. Arpida has an internal infrastructure for drug discovery – employing genomics-assisted selection of targets, screening for novel leads, and parallel synthesis for rapid lead optimisation – and leverages partners for drug development and clinical trials.

Keywords: Combinatorial chemistry · Drug development · Genomics · Infectious diseases · Lead screening

1. Introduction

There is an increasing need for new anti-infective molecules to overcome the developing resistance to current clinical drugs (Fig. 1). The recent technological advances such as the sequencing of several genomes, ability to generate large combinatorial chemistry libraries and increase in the understanding of protein structure have revolutionised the research for new compounds. The anti-infective market is a highly dynamic market that offers diversified opportunities with space for both small biotechnological companies and large global pharmaceutical companies. For example, global pharmaceutical companies are particularly strong in areas of chemistry, production and marketing, while small biotechnological companies have innovative technologies in areas of genomics and proteomics, *e.g.* Incyte, Genome Therapeutics, GPC (Genome Pharmaceuticals Corporation), Oxford Glycosciences, *etc.*, or combinatorial chemistry, *e.g.* Oxford Assymetry, Morphochem *etc.* The need to combine innovation and the ability to take drugs to market has fostered the need to establish strategic alliances that can result in synergistic partnerships and reduce development times from research to market to 6–9 years compared with the current 10–13 years. Unlike the technology-based first-generation start-ups there are several more broad-based 'second-generation' start-ups, *e.g.* Versicor, Cubist, Microcide, *etc.*, that can progress compounds from exploratory research phases to late clinical phases. Such 'second-generation' start-ups combine the best of two worlds with the innovation and speed of a start-up and the know-how and focus of a true drug-development company.

Arpida is one of a handful of European companies operating as a 'second-generation' start-up (Fig. 2). Since the start of operations in 1998, Arpida has developed a 'lean and mean' internal infrastructure for drug discovery and devel-

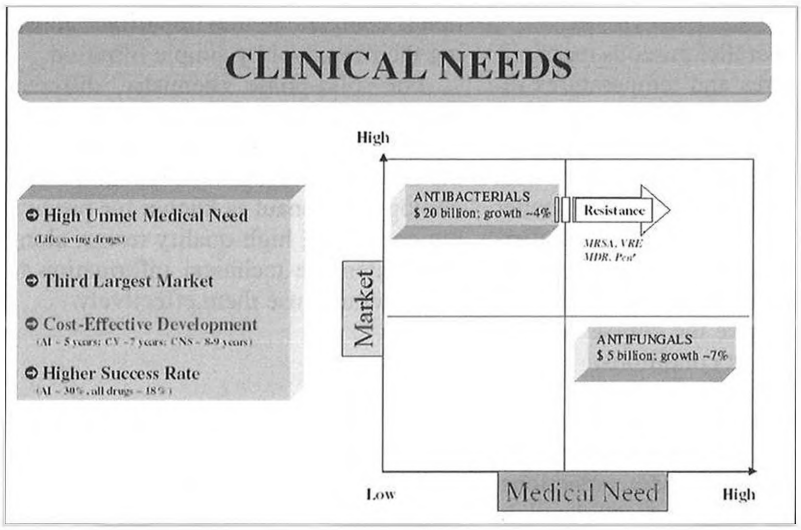

Fig. 1

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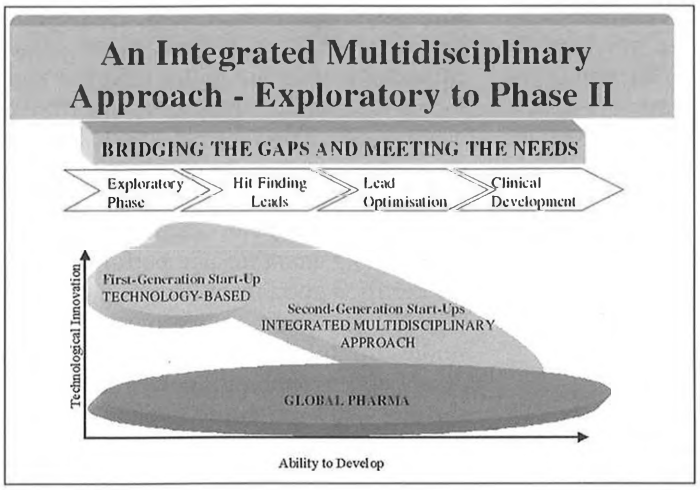

Fig. 2

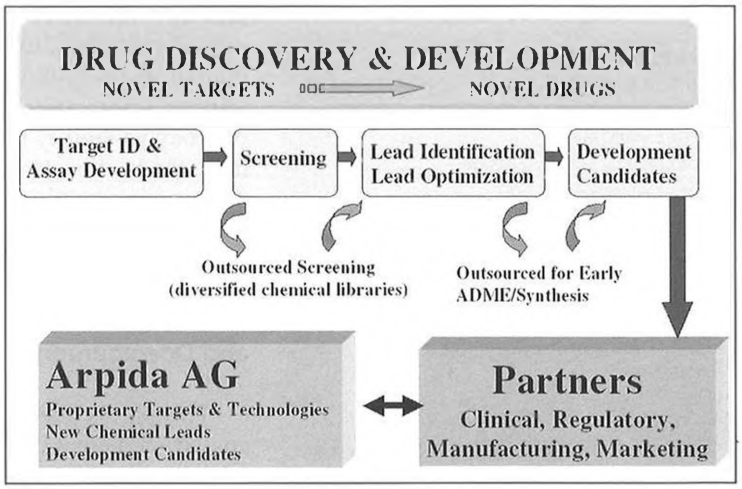

Fig. 3

opment of anti-infectives. Its management team is composed of highly experienced managers from Roche and its scientific staff is comprised of young talented and highly motivated scientists with Ph.D.s and postdoctoral studies from top-notch universities around the world. Arpida has established scientific collaborations with leading experts in the US (Harvard, Boston, Iowa, Buffalo, Princeton), Switzerland (Basel, Zürich, Bern, Lausanne, Geneva), Germany (Halle, Würzburg, Tübingen), Italy (Milan, Rome) and The Netherlands (Groningen). Several of these experts are also founding members as well as members of the scientific advisory board providing advice on cutting-edge science and technology. Finally, Arpida exploits its unique location in the BioValley area to leverage a powerful network of companies specialised in various aspects of drug development (Fig. 3).

The drug discovery and development process can be simplified and schematised into essentially five areas (see Table):

- Exploratory research
- Hit-finding & Lead Generation
- Lead optimisation
- Development candidates
- Clinical Trials

2. Exploratory Research

Arpida, like most other drug companies, uses a target-oriented approach for discovering drugs with novel mechanisms of action to find more efficacious clinical treatment of infections caused by drug-resistant micro-organisms. Genomics-assisted selection of targets allows efforts to be concentrated on those targets that exhibit high homology within the pathogens but that have no or low homology to mammalian proteins. As the human genome has not been fully sequenced there is a risk that eventually a human homologue may exist and to reduce such a risk, comparison with *C. elegans* is helpful, which is a nematode whose genome has been totally sequenced. The selected target is then subjected to appropriate studies to determine if it is essential for bacterial growth or involved in virulence/pathogenesis and to this end appropriate gene disruption and *in vivo* models are employed to validate the target. Arpida has several proprietary technologies and targets including several in-licensed from leading academic institutions.

Validated targets are cloned, expressed and the proteins purified. The purified proteins are then used to develop assays exploiting protein properties. If the function of the target protein is known then a functional assay is used, secondary assays are also developed based on knowledge of the metabolic pathway involved. However, Arpida also exploits proprietary technologies to identify the putative function of uncharacterised genes as well as technology which allows the search for interacting ligands without the prior need to know the defined gene function.

Currently Arpida staff are able to select and validate suitable targets and develop assays within four months. In general, Arpida develops several assays per year to maintain a continuous flux of 3–4 assays in the hit-finding and lead-generation phase.

3. Hit-Finding and Lead Generation

Assays are formatted in microtiter plates and automated for use with robotics. The assays are tested for reproducibility and for potential interference using a selected set of compounds. This pilot study is used to validate the assay procedure. The pilot study is a prerequisite to highlight any eventual anomalies and to allow re-adjustment of assays, prior to any screening of chemical and natural product libraries to identify inhibitory molecules. The selection of libraries is a second key step in the discovery process. The rule of five is applied to the libraries that are specifically tailored towards molecules with drug-like properties, *e.g.* molecular weight ranges from 150–450, clogP <5, less than five hydrogen-bond donors and less than 10 hydrogen-bond acceptors, use of filters to remove highly reactive compounds *etc.* Additionally, diversity comparisons, *e.g.* with the Tripos program, allow screening to be performed on less than one hundred thousand compounds from total libraries of several hundred thousand compounds without loss of chemical information.

Compounds exhibiting activity on a target are subjected to additional selection criteria to assess their specificity and selectivity. A simple selection involves the removal of non-specific compounds that exhibit activity against multiple unrelated target proteins. Secondary assays are then used to profile hits and generally exploit knowledge of the pathway or protein function. Additionally, compounds are assessed for their spectrum of microbiological activity. It is important to point out that target-oriented screenings can identify compounds that are both microbiologically active and microbiologically inactive. For microbiologically active compounds, Arpida uses technologies that allow the assessment of mechanism of action within intact cells, *e.g.* reporter gene assays as well as specificity by determining action on a presumed pathway. Arpida has also developed a technology to distinguish compounds which do not

Table. The drug discovery process

Target Selection
Identification of Putative Target
Target Selection
Target Validation
Definition of Assay Design
Assay Development
Assay Reagents
Assay Automation
Assay Validation (Pilot study)
Hit-Finding & Lead Generation
High-Throughput Screening (HTS)
Positives
Hits
Hit Profiling
Selection for Initial Analoging (Early lead)
Lead Optimisation & Development
Definition of Leads for Further Analoging (High-quality leads)
Pharmacokinetics & *in vivo* Models
Toxicity/Efficacy Window
Scale-up Synthesis
Safety Pharmacology
Chronic Toxicity & Toxicokinetics
Clinical Phase Trials

have intrinsic microbiological activity, and consequently are of no value for further development, from those which are microbiologically inactive due to failure to enter the cell. Such molecules are potentially of high interest as they are specific for the target but cannot be identified in cell-based screenings. Chemical evaluation of such compounds allows one to assess their usefulness as a lead.

Chemical evaluation consists of grouping all hits into appropriate chemical series based on their structural relations. Such grouping then allows a search into the structure base for all related molecules and their activity or inactivity against the target thereby allowing a finer definition of structural requirements for activity. If required, further compounds from the cloud area as defined by the diversity program can be selected for additional testing and consequently exploiting the full extent of the library. The chemistry team also assesses the chemistry feasibility, *e.g.* combinatorial or parallel synthesis approaches to generate a large number of compounds in a relatively short period to define structural features which are essential or chemical handles which can be modified. Initial analoging consequently generates a library of molecules either *via* combinatorial chemistry approaches or through analoging by cataloging. The determined structure–activity relationships are used to define the potential lead series. Determination of lead series molecules are also assessed for anti-microbial activity and lack of cytotoxicity. Arpida employs polarised epithelial cell lines which can be used to assess cytotoxicity but which also provide information regarding potential oral bioavailability of the molecules. Finally the lead is also assessed for lack of acute toxicity and *in vivo* efficacy in appropriate murine models.

4. Lead Optimisation and Development Candidates

This part of the process requires a focussed medicinal chemistry approach to add appropriate desired properties to the selected lead molecule. For example, the chemistry effort is focussed towards the improvement of solubility, stability or binding to the target protein. Alternatively, the effort may be driven by improvements in pharmacokinetic parameters, *e.g.* improvement of oral bioavailability or improvement in efficacy in murine models or better tissue penetration. Similarly, the effort may be focussed on improving the benefit to risk and enlarging the therapeutic window *e.g.* reducing toxicity or metabolism. Most of these improvements consequently require a 'fine-tuning' of the molecule to fit the target product profile and exploit different biological parameters.

Rational drug design and molecular modelling approaches are utilised when structural information at the target protein level is available. Arpida uses such rational approaches both in its lead optimisation program as well as in lead generation programs, docking of molecules into protein structures, working closely with the ETH in Zürich.

The chemical know-how gained during lead generation and optimisation can be applied to determine conditions that are suitable for adaptation to scale-up the synthesis process. For example, removal of chromatographic steps which create difficulties in the scale-up process and are not particularly suited to a manufacturing process. In addition, ideally the number of chemical synthesis steps should not exceed seven steps. Finally, alternative synthesis routes are also determined and low yield steps are improved to optimise the final yield of the product.

During the lead optimisation process several hundred grams of the compound are generally synthesised and used for animal studies as well as for *in vitro* studies with hepatocytes for metabolic stability. The mutagenic potential of the compound is assessed using the Ames test and mouse lymphoma tests. Epidemiological studies are performed on large collections of strains in the US, EU and Japan to evaluate antimicrobial activity on clinical isolates. At this stage a key requirement for any development candidate is the compound supply in view of further development. Generally, campaigns in kg quantities are performed under certified good manufacturing process (cGMP) to satisfy requirements for all studies up to Phase II clinical trials. The compound is appropriately formulated and checked for stability (typically accelerated stability tests are performed), both in liquid and in solid state. Safety pharmacology is performed in appropriate animal models and includes Irwin screen, cardiovascular and respiratory effects, and locomotor activity. Bioanalytical methods for compound determination in body fluids are established. Chronic toxicity studies are performed to determine the toxicokinetics, maximum tolerated doses and any adverse effects following multiple doses over a 2–4 week time period.

Arpida uses its network of drug-development partners as all above-mentioned studies are performed under GLP worldwide compliance or cGMP conditions for clinical trials. Upon completion of pre-clinical studies, documentation is presented to the regulatory authorities for permission to conduct Phase I trials. Phase I studies for human pharmacology trials are normally conducted in healthy volunteers but can include patients. Typically, these studies require single rising doses, repeated doses and the definition of dosing regimens for Phase II. Phase II trials are therapeutic exploratory trials generally performed on a small number of patients. These trials are normally followed by confirmatory clinical trials for efficacy and safety in patient populations.

Currently, Arpida has development candidates with promising activity against *Staphylococcus aureus* and against respiratory tract pathogens. An IND filing for the first compound is planned for the second quarter of 2000 with the aim to complete Phase I clinical trials by 1Q 2001. In addition, advanced discovery programs have also provided several lead molecules with novel mechanisms of action that are currently in the lead optimisation process for future development. Several new targets have also been identified and four of these targets are at various stages of development for hit-finding.

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bogar

Bogar AG
Veterinary Phytomedicines

R. Jonathan Richards*

Abstract: Bogar AG is a Zürich-based start-up company dedicated to the development and marketing of plant-based medicines for use in animals (veterinary phytomedicines). Backed by three venture capital groups, EPS Finanz AG, Zuri-Innovation, and ErfindungsVerwertung AG, the company has successfully completed its first year of operation, generating the data on their products required for their registration as veterinary medicines.

Keywords: Phytomedicine · Start-up company · Veterinary medicine

Bogar AG owes its existence to Dr. Marijke Frater, a chemist and expert in the field of plant-based medicines or phytomedicines as they are now known. She was the Medical Director of a company specialising in phytomedicines for human use, before setting up her own company, Labor Bogar, which was initially situated in her own home. She decided to branch out from the human field and to use her knowledge to develop a range of phytomedicines for veterinary use.

Knowing the difficulties in determining the active components of plants, as well as those additional components that may be vital to their effectiveness, Dr. Frater preferred to work with plant products as opposed to isolated chemical entities. This approach necessitated the development of formulations, which could readily be given to animals, notably cats and dogs. Dr. Frater's work led to the design of a suitable formulation base, which could be used with a variety of different plants.

Armed with a range of phytomedicines, Marijke Frater started to establish a network of Swiss veterinarians, who were keen to use her products. Although these veterinarians saw the benefit of the products and were enthusiastic about their use, there was a limitation. Not being registered medicines, it was not possible to make therapeutic claims for their use. This prompted Dr. Frater to evaluate the possibility of going that one step further and embarking on the task of generating the required data for medicines registration.

After spending time to develop a plausible business plan, it became clear that to achieve this ambition of registering these products as veterinary medicines, a significant expansion of the company would be essential and considerable funding would be needed. Eventually support was found and agreement reached with three venture capital groups, two from Zürich, EPS Finanz AG and Zuri-Innovation, and ErfindungsVerwertung AG from Basel.

EPS Finanz AG is an independent provider of innovative services within the fields of corporate finance, ecology efficiency, consulting and asset management. They support innovative, growth-oriented small and medium sized companies in the procurement of capital. Zuri-Innovation AG is a venture capital company, founded in December 1997, that focuses on seed and early stage projects. Of particular importance to them, is job creation and entrepreneurial initiative. At the start of the Bogar project, seed money was provided by ErfindungsVerwertung AG along with valuable support and advice. With the funding provided by these groups, a new company was founded; Labor Bogar was superseded by Bogar AG, which was officially registered as a limited company in December 1998.

Office and laboratory space were found at the former Hürlimann brewery in Zürich and a small staff of specialists were recruited. After equipping the laboratories, work commenced immediately with the various studies needed to demonstrate the quality, efficacy and safety of the products, as required by the registration authorities.

After one year, substantial progress has been made. Analytical methods have been developed, plant materials have been chemically finger-printed, production trials, stability trials, clinical efficacy and safety trials have all progressed well with no more than the usual inevitable hiccups encountered during the development of medicinal products.

The management team consists of two very experienced people. In July 1999 Jonathan Richards was appointed as General Manager. He brings to Bogar extensive experience, covering product development and registration, international business coordination, management and marketing, as well as a sound knowledge of the animal health industry. He originates from Great Britain, where he graduated in veterinary medicine from the University of London in 1970. After working for five years in mixed veterinary practice, he joined the Animal Health Division of Ciba-Geigy UK Ltd. and in 1983

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moved to their headquarters in Basel, working in Product Development. In 1989, transferring to the commercial side of the business, he worked in Area Management first in East Europe and then West Europe, before becoming Head of the Animal Health Division in France in 1992. Following the merger of Ciba and Sandoz and the creation of Novartis, he returned to Basel as Head of the Farm Animal Business Unit and later Global Head of Farm Animal Marketing.

Marijke Frater-Schröder holds a Ph.D. in chemistry and is an expert on medicinal plants. She is a board member of the Swiss Medicinal Society of Phytotherapy (SMGP) and the Swiss delegate and co-secretary of the scientific committee of the European Scientific Cooperative on Phytotherapy (ESCOP). After graduation, Marijke Frater-Schröder held positions at the Universities of Zürich, Leiden in the Netherlands and Alberta, Canada, working in a variety of disciplines including analytical chemistry, basic medical research, experimental toxicology, clinical immunology and biotechnology. In 1987 she moved into the pharmaceutical industry with Johnson & Johnson and in 1991 joined Bioforce AG, a Swiss company specialising in phytomedicines for human use, as Head of the Medicine Department.

Appropriately qualified people work in the laboratories of Bogar AG, a pharmacist is responsible for the monitoring of the clinical trials and they are supported by the required administrative staff. However, the intention at this stage in the life of Bogar AG is to remain small, outsourcing tasks whenever possible.

The field of phytomedicines is currently receiving a great deal of public interest. As many people look for alternatives to chemical pharmaceuticals for the benefit of their own health, so do they for the health of their pets. The market is growing, but so too are concerns about the unregulated use of phytomedicines. Bogar are sure that by choosing the hard route of medicinal registration, their future is assured.

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Chemspeed

Chemspeed Ltd
Automated and Unattended Parallel Synthesis Integrating Work-up and Analysis

Benedikt T. Haag*

Abstract: Automated parallel synthesis is a relatively new technology which is rapidly gaining interest year by year. The concept of parallel synthesis in combination with instrument automation has brought medicinal research to a new level of efficiency providing a powerful tool for the pharmaceutical companies' fight to decrease the time needed to bring new drugs to the market. Recently, companies involved in a constantly increasing range of applications have picked up this new trend.
Chemspeed Ltd is a young, Swiss-based company offering a range of innovative products for R&D departments of chemical companies. The core product line consists of semi and fully automated synthesizers for parallel synthesis, work-up and analysis. Chemspeed technology is used in the research and development of a broad range of chemical companies involved in medicinal chemistry, agrochemicals, material sciences, catalyst research, or similar areas.

Keywords: Automated synthesis work station · Combinatorial chemistry · Parallel synthesis

Parallel Synthesis

The pharmaceutical market has always been and still is extremely competitive. The number of attractive targets is relatively small. Established products cover the majority of diseases and leave only a little space for innovation. Rare diseases do not offer very tempting opportunities. As a consequence, most large pharmaceutical companies are working on similar indications, either trying to solve one of the few problems still open today (*e.g.* AIDS), or aiming to replace a standard drug which may have considerable side effects. Therefore, 'time to market' is crucial. If you are aiming for a several billion dollar product, you do not worry about hiring ten additional chemists or investing the corresponding amount of money in instruments, as long as you are going to be the first on the market.

In this context, medicinal chemists have been looking for new approaches, providing the competitive edge in research and development. Parallel synthesis has offered first benefits in these efforts. The synergy of combinatorial tools and workflow optimization can help to increase significantly the output of a synthesis lab. However, you might create a new bottleneck in testing this increased number of drug candidates. Consequently, biological testing has been the next step where efforts have been made to decrease the overall development time of a new drug. High-throughput screening has again put back the pressure on the synthesis lab. Therefore, pharmaceutical research departments are looking to speed up the generation of new leads even more. The automation of parallel synthesis has been brought to constantly increased levels. Major innovations have been concerned with the automation of synthesis involving extreme conditions or the combination of very different steps in a multi-step synthesis, *e.g.* the combination of solid- and solution-phase chemistry. In addition, work-up and analysis have been integrated increasingly in the automation process. Today, a broad range of reactions can be conducted not only automated, but fully unattended, including work-up by extraction or filtration integrating analysis by TLC, HPLC/MS, or similar.

The success of automation in medicinal chemistry has influenced a broad range of different application areas. Today, companies working on agrochemicals, in catalyst research, material sciences, fine chemicals, and many other fields are increasingly using very similar tools.

Chemspeed Ltd – Technology Leader for Automated Synthesis Workstations

Back in 1996 a group of medicinal chemists under the supervision of Dr. Rolf Gueller at F. Hofmann-La Roche collaborated in the idea of parallel synthesis. Soon, they recognized that maximum automation was the key to success.

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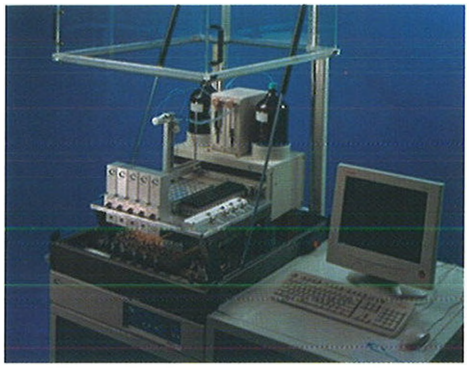

Fig. 1: ASW2000

Fig. 2: Glass reactors of ASW2000 / MSW500

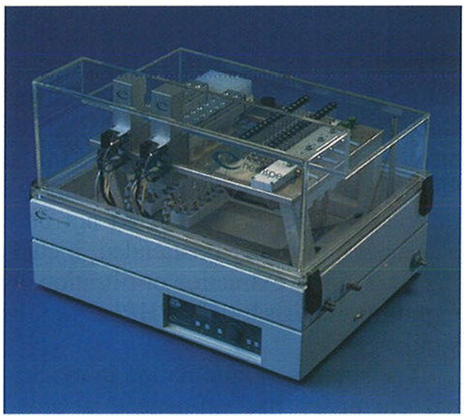

Fig. 4: MSW500

Fig. 3: The Chemspeed team

At the same time, they were not ready to agree on any compromises due to limitations of the equipment. They were convinced that the chemistry should define the features of the instrument, not the reverse! At that time, there were obviously no instruments available on the market that could cover their needs, so they started developing one of their own. The first prototype was successfully introduced the same year. Other chemists from Basel-based pharmaceutical companies began to ask for this product. Obviously, building synthesizers did not fit into the strategy of F. Hofmann-La Roche. As a consequence, Dr. Gueller and two coworkers took the risk to become independent and founded Chemspeed Ltd in spring 1997. It took the small team consisting of three chemists just about half a year to launch a product ready for the market. The instrument included various features that were completely new. The ASW2000 (Fig. 1) was the first automated synthesizer able to inject while shaking and heating or cooling. Additionally, the synthesizer featured a unique temperature range of –70 °C to +150 °C. But most important, the system was designed by chemists – knowing the needs of chemists! The heart of this synthesizer (and all subsequent Chemspeed synthesizers) consists of glass (Fig. 2) thus avoiding restrictions concerning reagents such as strong acids, bases or other highly reactive reagents and allowing complete visibility. It also featured a hood design to contain a second inert atmosphere allowing handling of air-sensitive reagents without restrictions.

In 1999 Chemspeed entered a new strategic area. Taking advantage of the technological edge of having the automated synthesis workstations in-house, custom synthesis of small libraries is offered. Relying on the flexibility of the equipment, Chemspeed has focused mainly on lead optimization so far.

Since its foundation, the philosophy of the Chemspeed team (Fig. 3) has not changed much. Development of new products and features usually emerges as a result of the strong relations with customers and is based on the needs of chemists. A strong R&D department takes care of incoming requests. Today, Chemspeed also offers semi-automated synthesizers (Fig. 4). Variable reactor sizes from 13 to 100 ml, on-line filtration are included in all models. Purification techniques as liquid/liquid or solid-phase extraction and various analysis methods as TLC are fully integrated and so do not require any intermediate manual steps. Chemspeed's products are well established on the market serving in most of the world's leading pharmaceutical companies.

After less than three years, Chemspeed employs more than 30 people worldwide. Chemspeed runs offices in the UK and in the USA and also operates in South East Asia. Privately financed and having only a small starting capital, Chemspeed has been profitable from the first fiscal year. The needs of the market has probably been the key to this success story which is somehow special to Switzerland. And our customers will continue to be both the focus and deciding factor of Chemspeed's future.

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cytos biotechnology AG

Cytos Biotechnology AG
Novel Technologies for Functional Genomics and Antibody Mediated Therapies

Claudine Blaser*, Wolfgang A. Renner, and Martin F. Bachmann

Abstract: The overall goal of Cytos is the creation of new technologies and products for broad markets by breakthrough innovations in the biomedical sciences. By adding eukaryotic viruses to the toolbox of modern biotechnology, Cytos has developed unprecedented and broadly applicable platform technologies for drug discovery and development. Our technologies enable and facilitate the discovery, manufacture, delivery, and display of proteins.

Keywords: Alphavirus · Biotechnology · Drug discovery · Protein expression · Vaccine development

Our History

Cytos Biotechnology AG was founded in February 1995 by Dr. Wolfgang A. Renner, Prof. James E. Bailey, and Prof. Hans M. Eppenberger as a spin-off company of the Swiss Federal Institute of Technology (ETH) in Zürich. Cytos operated in laboratories at the ETH until its new 1000m^2 research facility in Schlieren was finished in August 1999. The successful marketing of Cytos's new serum- and protein-free production processes for protein and vaccine products led to early revenues and has allowed the company to operate on a balanced budget since its incorporation. To finance the expansion of the company in 1999, Cytos raised CHF 2 million in loans and CHF 11 million in equity from leading international investors (Novartis Venture Fund, Innoventure (Credit Suisse) and Global Life Science Holding GmbH).

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Our Platform Technologies

DELphi – One Step Drug and Target Identification

Today, high-throughput screening and sequencing have triggered an explosive growth in the identification of new genes. However, the understanding of new gene and protein functions has not kept pace with this rapid development. To reduce this mismatch between pure sequence information and gene function, novel technologies are required that specifically link the biological properties and activities of a protein with the corresponding gene *in vivo*.

Cytos's novel screening and discovery technology DELphi directly addresses the above-mentioned need. DELphi is a virus-based expression screening system, which allows the reproduction of every single protein existing in the human organism and sifts through this functional protein array applying a desired set of screening parameters. As a result, the technology allows the isolation of the smallest subset of genes and proteins meeting defined functional properties such as *e.g.* a specific enzymatic activity, a common binding partner, or the induction of a whole cell response.

In a first step, a cDNA library from a particular tissue or cell type is converted into an alphaviral expression library. Infection of many different types of mammalian cells with this viral library results in high level expression of the corresponding proteins [1][2]. The alphaviral expression system employed by DELphi has four major advantages:

i) each virus in the DELphi library contains only one single recombinant cDNA,
ii) one physical viral particle infects one cell and initiates an infectious cycle,
iii) the progeny virus can readily be isolated from infected cells and
iv) the cloning procedure does not involve homologous recombination steps or integration/excision mechanisms.

The mammalian expression system ensures correct glycosylation and processing of each protein in the array as well as correct targeting of intracellular

proteins to the proper subcellular compartment. Two different screening systems and read-outs have been developed: the 'one gene per cell' format allows the identification of novel receptors for *e.g.* growth factors, pathogens, hormones or adhesion molecules. The 'one gene per well' format enables the identification of secreted molecules inducing a desired activity in target cells such as *e.g.* cell migration, cell activation or cell death (Fig. 1).

The 'one gene per cell' format:

A culture of mammalian cells is infected with the alphaviral expression library resulting in high level expression of only one gene per cell. Single cells that express a desired phenotype resulting from the exogenous gene are sorted in a fluorescence activated cell sorter (FACS), where up to 10^7 cells can be analyzed per hour. Every single cell is analyzed according to desired selection criteria such as surface expression of specified molecules, activation state, or cell size.

For the rapid identification of new receptors for known ligands, the infected cell culture is stained with the labeled ligand, and positively identified cells are sorted into a single well of a 96-well plate, containing a semi-confluent layer of mammalian cells. These cells are infected by the recombinant virus that is released by the sorted single cell, leading to rapid amplification of the selected cDNA clone and enabling RT-PCR and sequencing as well as immediate production of the protein of choice. The described method can easily be modified to identify proteins that trigger a certain signaling pathway within cells by *e.g.* using target cells that express GFP (green fluorescence protein) under the control of the NF-κB binding element.

Target Identification Using the 'One Gene per Cell' Approach

Cytos gained proof of principle for the 'one gene per cell' format by expressing a DELphi library derived from human umbilical cells in baby hamster kidney (BHK-21) cells and by screening these cells by FACS for binding of human IL-13. In two rounds of FACS sorting, eight cells that bound human IL-13 were identified in 10^6 events by indirect immunofluorescence labeling with a tagged IL-13 and viruses were cloned and sequenced. Fig. 2 shows typical FACS analysis for cells stained with tagged IL-13 (IL-13 FLAG) and with propidium iodide to exclude dead cells.

The 'one gene per well' format:

An alphaviral expression library is constructed from any tissue or cell type of choice, and 100 viral particles per well are incubated on a semi-confluent BHK-21 cell layer in 96-well plates. Supernatants containing secreted proteins encoded by the recombinant viruses are harvested and their activity is assessed on appropriate target cells with respect to differentiation, activation, cell death promotion, enhancement of survival or migration. Viruses from wells that contain proteins with a desired activity can thereafter be re-tested under limiting dilution conditions and subcloned by plaque purification. The gene of interest is then easily cloned and sequenced. Using this approach, Cytos has successfully identified novel proteins inducing activation of dendritic cells, one of the major key players in immune responses.

pCytTS – An Inducible Expression System for Bioprocess Applications

The application of cutting-edge protein expression technology is essential for elucidating gene function, developing HTS, and determining protein structure. Certain classes of important drug targets such as kinases, seven transmembrane receptors or ion channels are inherently toxic and can therefore not be produced in sufficient quality or quantity.

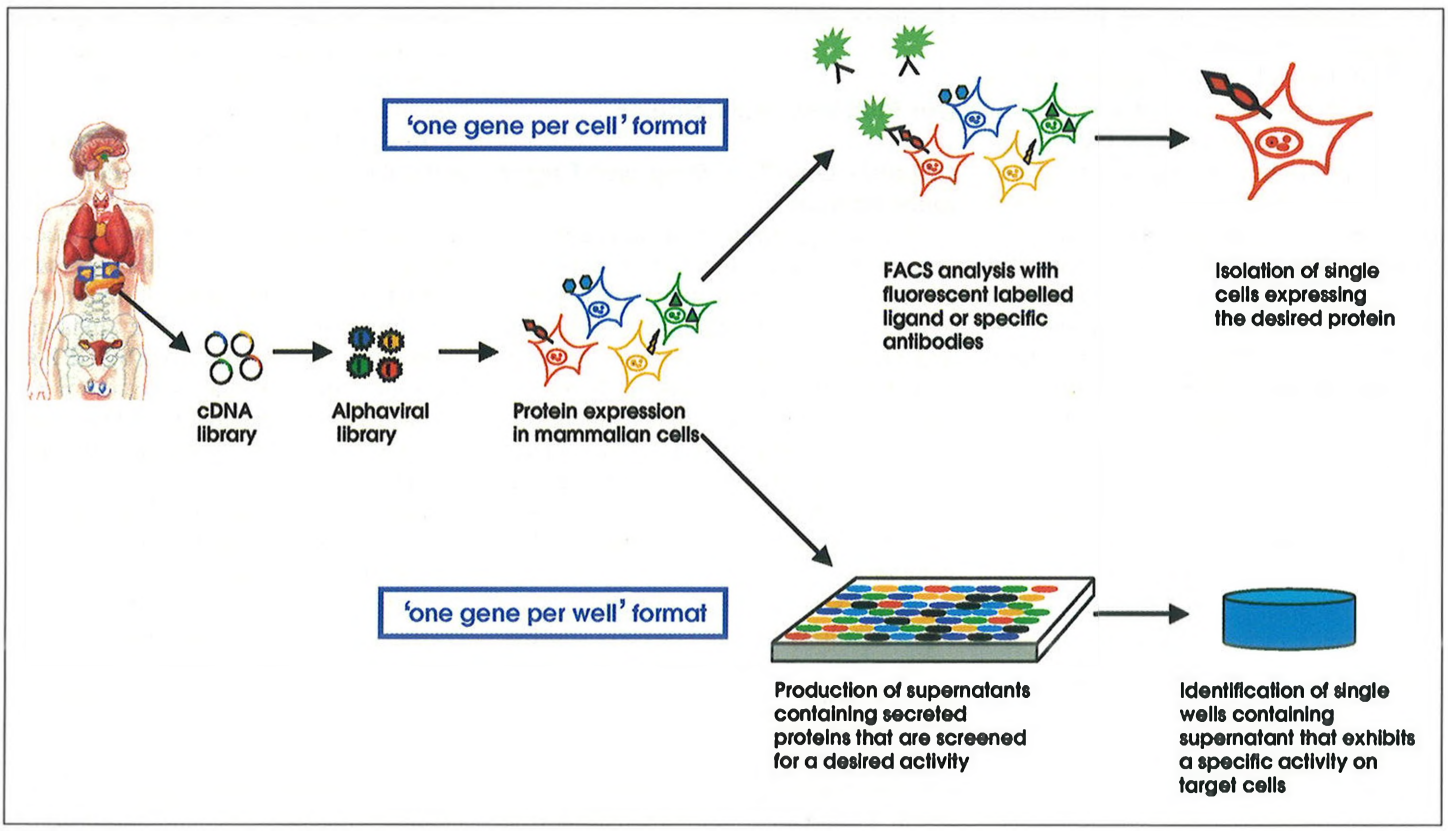

Fig. 1

To address this limitation in the drug development process, Cytos has developed a novel expression system, which tightly links the expression of the gene of interest to the ambient temperature. The system is characterized by undetectable basal level expression at 37 °C, precise control of gene expression between 35 °C and 29 °C, and high-level expression at 29 °C (with a routine induction coefficient above 10 000). The kinetics of induction and repression lie in the range of hours and are not subject to slow diffusion and clearance mechanisms as it is the case for chemical inducers. These unprecedented characteristics make the pCytTS system a useful tool for the production of highly toxic proteins. Stable production cell lines for these proteins are established and grown at 37 °C to high cell densities without adverse effects of the product on cell growth or survival, whereas in a second stage of the process, expression is induced by lowering the temperature [3].

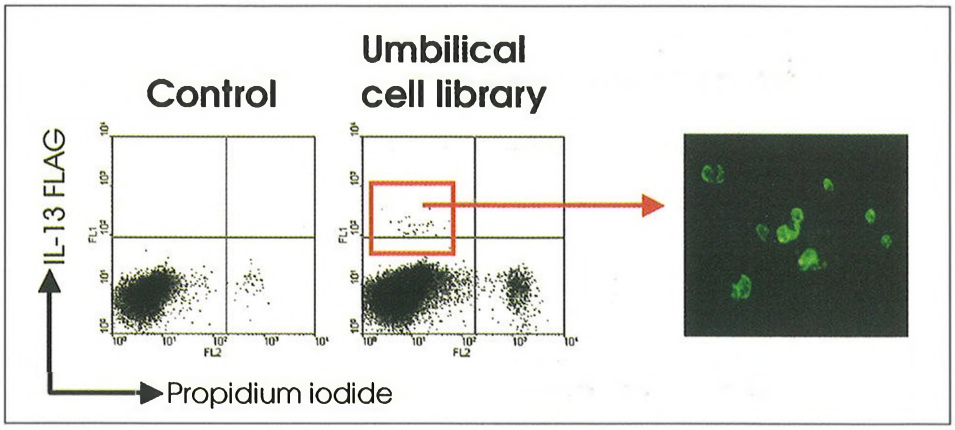

Fig. 2

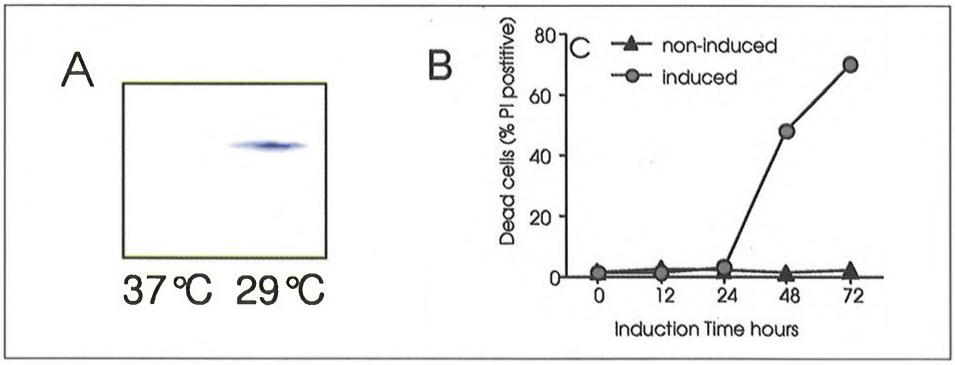

Fig. 3

Expression of a Highly Toxic Protein: RipDD (Rip Death Domain)

BHK clones stably transfected with pCytTS-RipDD were established. Upon induction at 29 °C, RipDD was expressed (Fig. 3A), and cells died within two days due to the expression of the toxic protein as shown by staining with propidium iodide (Fig. 3B).

AlphaVaccine – A New Generation of Vaccines

Of any medical intervention, vaccine development has one of the most far-reaching impacts on human health today [4]. Traditionally, most vaccines were either attenuated to reduce the virulence of the pathogen or inactivated by chemical agents. However, these classically produced vaccines still harbor the risk of disease induction. On the other hand, vaccination with protein subunits alone of the pathogens often failed to elicit a strong immune response. To circumvent these major drawbacks, Cytos established the novel vaccine technology AlphaVaccine. The technology's hallmark is the generation of viral-like particles (VLPs). This system takes advantage of the intrinsic ability of some viral capsid and envelope proteins to self-assemble in the absence of genomic DNA into highly organized particles. The resulting VLPs lacking the viral genome are non-infectious, cannot replicate and are therefore completely safe. This scaffold can be decorated *in vitro* with various antigens according to the principles of a modular assembly system. To facilitate the decoration with antigens, the carrier proteins and the target antigen have been altered to include specific attachment sites. The engineered complementary attachment site on viral particles and recombinant antigens associate spontaneously *in vitro* (Fig. 4). The resulting VLPs have, due to their highly repetitive surface configuration, the potential to induce a strong B cell and cytotoxic T cell response, both of which are known to contribute significantly to a protective immune response against any pathogen [5][6].

Based on the AlphaVaccine technology, three different vaccine strategies can be envisaged:

1) Vaccination against major life-threatening pathogens such as HIV, malaria or toxoplasmosis can be performed by coupling pathogen-derived antigens to the surface of VLPs.
2) Growing evidence suggests that tumors express target molecules suitable for a therapeutic immune reaction. Yet tumor cells lack the prerequisite for appropriate antigen presentation and hence the immune system does not respond. The identification and availability of tumor-associated antigens now allows the activation and amplification of the patient's immune reaction against the tumor by vaccination. Thus, tumor-associated antigens coupled to VLPs represent a very promising and powerful mean to induce protective anti-tumor responses.
3) The concept of vaccination against self-antigens could even be pursued further. Many autoimmune diseases are characterized by a rather uncontrolled activity of inflammatory mediators such as *e.g.* tumor necrosis factor (TNF)-alpha in rheumatoid arthritis [7]. The targeted elimination of these mediators represents a desirable goal for the treatment of autoimmune disorders. Using the AlphaVaccine technology, self-molecules such as TNF-alpha can be coupled to VLPs and used for vaccination. Upon B cell activation, neutralizing antibodies against TNF-alpha are produced, which abrogate its detrimental activity and could ameliorate the clinical symptoms of the disease.

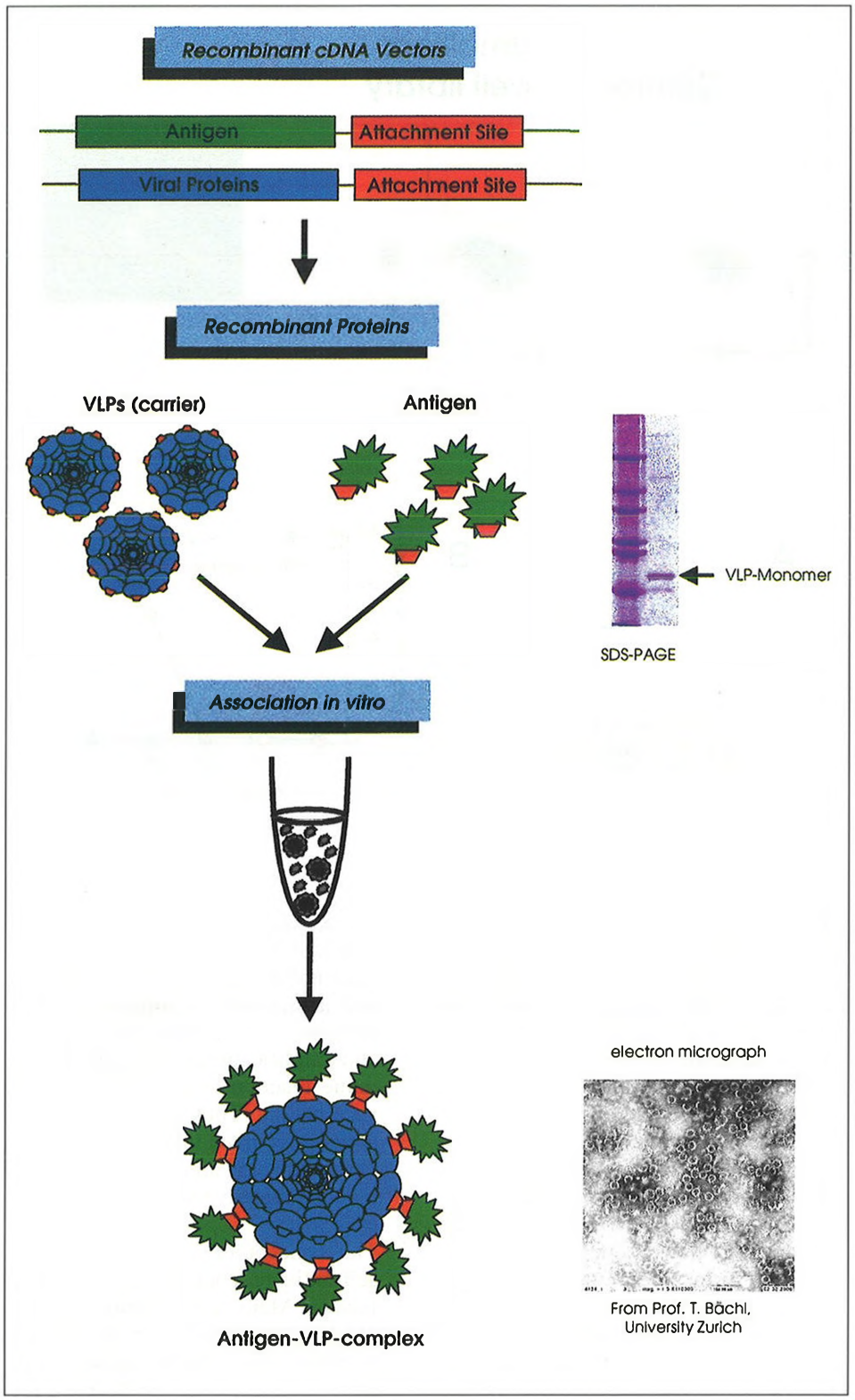

Fig. 4

Outlook

Cytos has achieved a complete vertical integration of its three platform technologies, enabling fast production of newly discovered DELphi proteins by the pCytTS system and transfer of potential product candidates into its own vaccination program.

Today, large pharmaceutical companies strongly rely on in-licensing new products from biotech companies to fill their drug discovery pipeline and to achieve a desirable growth rate. Due to its vertically integrated IP portfolio, Cytos is in a strong position to offer complete discovery and development solutions to the pharmaceutical industry. To offer to its customers the highest possible value Cytos is building a scientific network with leading academic groups in Europe and elsewhere to specifically combine outstanding scientific knowledge with excellent technical expertise. The exclusive access to this comprehensive pool of knowledge provides our customers with a major advantage in drug discovery and development.

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DISCOVERY TECHNOLOGIES LTD.

Discovery Technologies Ltd.
Drug Discovery Services

Henri Zinsli*

Abstract: Discovery Technologies Ltd. provide access to large chemical libraries, develop a broad range of biological assays and perform ultra high-throughput screening in our HTS Factory at industrial scale to meet the specific needs of our customers from the pharmaceutical, agrochemical, and biopharmaceutical industries worldwide strictly on a fee-for-service basis and with no intellectual property rights retained.

Keywords: Assay development · Chemical libraries · Discovery services · uHTS

Mission

Discovery Technologies Ltd. (DTL), a member of the San Diego, CA, based Discovery Partners International Group, was founded in 1997 and was initially largely financed by the Novartis Venture Fund and local banks. DTL offers integrated discovery services to life sciences companies worldwide. These services include assay design and development; ultra high-throughput screening (uHTS) of its extensive in-house chemical libraries and uHTS of customer collections.

Technology Platform

Discovery Technologies Ltd. is experienced in developing and optimizing new assays for the HTS Factory. Various detection methods/readers integrated into the HTS Factory contribute to the high degree of screening customization that Discovery Technologies Ltd. can offer its customers.

Discovery Technologies Ltd. offer access to a collection of almost 600 000 discrete organic compounds for screen-

Figure

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ing in the HTS Factory. An SD file with a representative selection of 10% of structures of the entire library is disclosed to customers for evaluation purposes. The conditions and terms for the access to chemistry are defined on an individual customer basis. The customer receives the structures of all compounds as hits under the pre-defined criteria.

Discovery Technologies Ltd. has developed and implemented its proprietary HTS Factory uHTS automated system, enabling a faster and more efficient identification of small molecules with the desired biological activity. The HTS Factory utilizes industrial handling and automation technologies and has a high screening throughput capability in 95, 384 or lower volume plates.

Our services typically comprise:

- uHTS
- Target production: rec. proteins, transformed cell lines
- Development of assay types for cellular and molecular targets as well as for microbes and plants
- Assay technologies: all commonly used, readouts including HTRF®, FlashPlate®, and SPA.

If customers have their own developed assays, we adapt such assays to our uHTS technology.

Human Resource Assets

A highly motivated, interdisciplinary team of 25 employees, half of whom hold an academic degree, guarantee innovation and excellent services. The company is headed by a management team with many years of combined management experience in discovery outsourcing services, as well as the pharmaceutical and agrochemical sectors:

- Dr. Henri Zinsli, Chairman & CEO
- Dr. Helmut Kessmann, Sr. VP Business Development and Marketing
- Dr. Bernhard Schnurr, VP Operations
- Dr. Peter Zbinden, VP IT & Chemistry

Discovery Services

Discovery Technologies Ltd. pursues a strongly customer-oriented business strategy. Access to the HTS Factory, assay development and chemical libraries are available on a fee-for-service basis. Speed, flexibility and customized service contracts are core characteristics of our discovery services. Collaborations may range from a single screening project to committed long-term collaborations.

Typically we offer:

- Assigned project leader working closely with customer during project
- Targets, assays and libraries developed/provided either by customer or us; any combination thereof can be agreed upon
- Additional discovery services, including design of exclusive and focussed libraries and lead optimization upon customer request
- Work-related fees for target production, assay development, uHTS and fee for use of our libraries and additionally required services
- Detailed report on project results
- Chemical structures for active compounds identified from our libraries
- Any electronic data transfer formats.

All collaborations are on a fee-for-service basis, with no milestone or royalty payments!

Collaborations

Discovery Technologies Ltd. is interested in long-term collaborations and welcomes any opportunity to explore alternative business models with future collaboration partners.

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ESBATech AG

ESBATech AG
Taking Yeast from the Brewery to Drug Discovery

Dominik Escher* and Alcide Barberis

Abstract: ESBATech AG is specialized in pre-clinical research which comprises the identification of disease-relevant target genes (functional genomics) and lead compounds (drug discovery). For identification and validation of target genes, ESBATech has developed three novel functional genomics technologies. These technologies are currently being applied to the field of Alzheimer's disease, breast cancer and ovarian cancer. For lead compound identification, ESBATech has developed two novel platform technologies which are applied to skin cancer. Furthermore, ESBATech has developed a unique antibody platform technology which can be applied to the areas of therapeutics, diagnostics, and functional genomics. All these platform technologies utilize the model organism yeast which enables the rapid and inexpensive reconstitution of *in vivo* molecular components of human diseases. High-throughput screenings to cure a disease at the molecular level or to identify novel target genes are routinely performed by analyzing more than 10 million candidates in parallel within two weeks.

Keywords: Drug discovery · Functional genomics · Lead compound identification and optimization · *Saccharomyces cerevisiae* · Target gene identification and validation

The Company

ESBATech is a spin-off biotechnology company in its early seed phase derived from the Institute of Molecular Biology of the University of Zürich. The company was founded by Dominik Escher, Alcide Barberis and Adrian Escher in September 1998 as a Swiss joint-stock company (AG). Before the official foundation, ESBATech was a winner of the business plan competition 'Venture 98' organized by the Eidgenössische Technische Hochschule (ETH) of Zürich and McKinsey Switzerland. ESBATech started its research activities at the beginning of February 1999. ESBATech has recently received the KTI Start-up label. ESBATech currently employs four scientists and its facilities are located on the campus of the University Zürich at Irchel.

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Yeast as a Model System for Drug Discovery

The early stage of the drug discovery process in the pre-clinical phase starts with the isolation of relevant target genes involved in a certain disease and the subsequent identification of lead compounds that affect the function or the product of such target genes in a desired way. More than 90% of the discovered lead compounds fall out of the development pipeline in late pre-clinical and clinical trials. Therefore, there is a need to have more rapid and reliable screening technologies which identify disease-relevant target genes and effective lead compounds in a short period of time. ESBATech performs screenings in the living organism yeast to meet these needs for the drug discovery process. A very important aspect is that yeast and human cells are very similar at the molecular level. For instance, human proteins which activate a gene in human cells fulfil the very same function in yeast. The same is true for yeast proteins when tested in human cells. Thus, yeast represents an optimal model organism in which screenings can be performed in living cells under conditions very comparable to human cells. In addition, yeast has the unique feature that a human gene can be introduced at any desired location in the yeast genome within one to two weeks. Comparable experiments (gene knock-out or gene re-

placement) in mice or human cells take several months up to several years. Thus, putative molecular components of a pathological process of a human disease can be reconstituted in yeast in a very short time.

ESBATech has developed several new platform technologies supporting the whole drug discovery value chain as depicted in Fig. 1. Common to all these platform technologies is the model organism yeast, in which molecular components of human diseases are reconstituted. These transgenic yeast cells can still survive under normal conditions. However, when these cells are subjected to special selection, which is different for each platform technology, they no longer survive and are dependent on the presence of a target gene with the required biological function (functional genomics technologies) or on the presence of a biological active substance which does not have harmful side effects on the cell (lead compound identification technologies). Cells containing the required target gene or lead compound can thus survive and divide to form visible colonies (Fig. 2). With these various platform technologies it is now possible to screen for many disease genes and possible lead compounds in the transgenic yeast cells in parallel (more than 10 millions of candidates within two weeks including a first validation). In the following section the different ESBATech platform technologies are outlined.

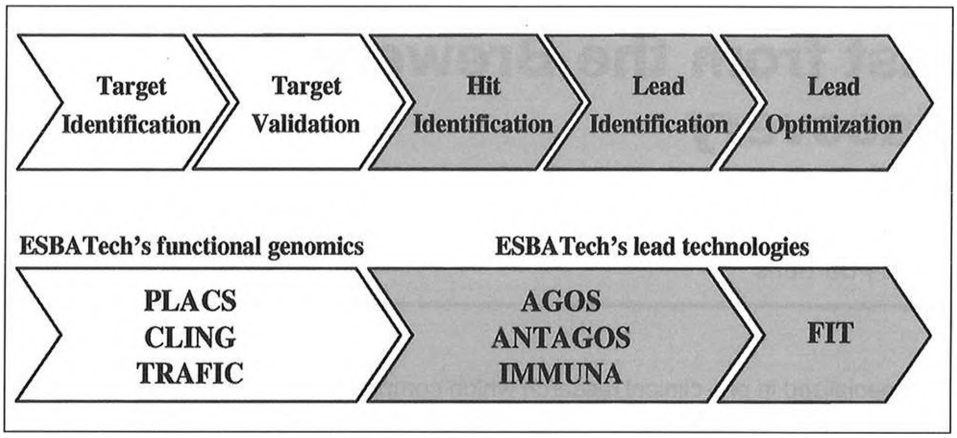

Fig. 1. Value chain of drug discovery aligned with ESBATech's matching platform technologies. Modern drug discovery starts with the identification of disease-relevant target genes (Target Identification). Subsequently the *in vivo* function of the target gene has to be validated (Target Validation). The next step comprises the identification of substances which interact with the protein derived from the target gene (Hit Identification). These hits are then tested whether they also have the required biological activity (Lead Identification). Afterwards these lead compounds are optimized to further improve their activity and to weaken unwanted side effects (Lead Optimization). ESBATech has developed functional genomics technologies for the identification of proteases active in different cellular compartments (PLACS and CLING) and factors involved in gene regulation (TRAFIC). Furthermore ESBATech applies technologies for the direct identification of agonistic (AGOS) and antagonistic (ANTAGOS) lead compounds. Using IMMUNA it is possible to identify single-chain antibodies for intracellular applications. Lead compounds are then further optimized using the FIT technology.

Functional Genomics for Target Gene Identification and Validation

PLACS and CLING Technologies: Several diseases are believed to be caused by the cleavage of cellular proteins by molecular scissors (called proteases). Cleavage could lead to a loss-of-function of the protein or the cleavage product may have harmful effects on the cell. ESBATech has developed PLACS and CLING as novel functional genomics technologies to identify proteases which cleave in different cellular environments (oxidizing and reducing environments). These technologies can also be applied to identify the unknown targets of an already known protease. One of the major

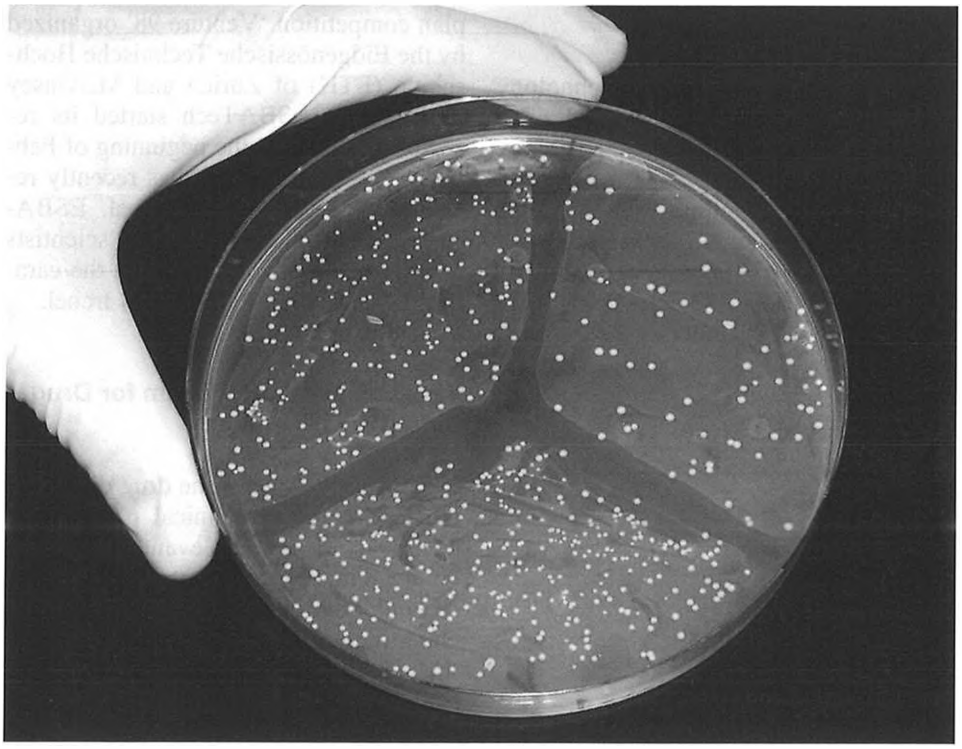

Fig. 2. Transgenic yeast cells containing molecular components of a human pathological process cannot survive under selective conditions. In a screening process, each individual yeast cell tests an independent human gene (for functional genomics) or a different potential lead compound. The cell can only survive if it contains a human gene or a lead compound with the required function, thus allowing replication of the cell which leads to the formation of a visible colony (white dot).

advantages of PLACS and CLING is that the screening for the unknown protease or its targets occurs in the same subcellular compartment in yeast cells as in human cells. The different compartments within a cell show remarkable differences in terms of acidity, oxidizing environment and composition of factors, and therefore many proteins are only functional in their correct location in the cell. Thus, PLACS and CLING are powerful functional genomics technologies which uncover novel disease-relevant proteases or their targets for subsequent drug discovery. ESBATech currently applies PLACS and CLING in a collaboration with Hoffmann-La Roche in the field of Alzheimer's disease.

TRAFIC Technology: An important task of future drugs will be to specifically modulate expression of genes involved in human diseases. To this purpose, the factors regulating gene expression must be characterized. Up to now, there was no technology available which allowed broad screenings in a living organism to identify new factors regulating gene expression. The unique feature of the TRAFIC technology is that extensive screenings (more than 10 million different candidate genes) can be performed in parallel (within two weeks). This opens up the possibility to uncover networks of factors regulating expression of genes which are involved in a certain disease. Cancer is a typical example of a disease caused by aberrant gene expression. The identification of novel factors involved in aberrant gene expression adds important puzzle pieces to the picture of cancer biology and provides potential new drug targets. At present, ESBATech applies TRAFIC to the fields of breast and ovarian cancer.

Lead Compound Identification and Optimization

AGOS Technology: In several pathological processes, important proteins are modified so that they lose their original function. A consequence of these mutations is, for example, that cells can divide and grow fast, thus leading to cancer. Drugs reverting this modification would therefore restore the original activity of the protein and prevent further growth of cancerous cells. Such a drug would act as an agonist. The ESBATech AGOS technology identifies agonistic lead compounds which show the required biological activity. AGOS is currently applied to identify agonistic lead compounds for factors involved in gene regulation. However, AGOS technology can be applied to any target in the cell.

ANTAGOS Technology: A form of skin cancer (invasive neoplasia) is believed to be initiated by the interaction between two proteins (derived from so-called oncogenes). Many other pathological processes might also be caused by the interaction between two critical proteins which normally does not occur in healthy cells. A drug which can prevent this interaction, thus blocking the two critical proteins, would act as an antagonist and would have the potential to stop the disease. The ANTAGOS technology identifies lead compounds which block interactions between proteins, both inside the cell and on the cell surface such as between receptors and ligands or viruses. ESBATech currently applies ANTAGOS to the field of skin cancer in a collaboration with Prof. Gerard Evan from the University of California in San Francisco.

IMMUNA Technology: Antibodies are preferred tools for biochemical and molecular biology research, diagnostics and medical applications due to their high affinity and specificity to the antigen and due to their high stability. Single-chain antibodies are a shorter version of natural antibodies and basically have the same biological activities. Single-chain antibodies expressed within the cell (*e.g.* cytoplasm or nucleus) are called intrabodies. ESBATech has developed the IMMUNA technology which allows direct screening for antibodies against targets within the cell. This opens up broad applications for the IMMUNA technology: IMMUNA-derived intrabody can be expressed in a transgenic model organism (*e.g.* Drosophila, mice) to specifically interact with a defined part of the target protein, thus knocking out the specific function associated with this part of the protein, while leaving intact the rest of the protein (functional genomics). For therapeutic purposes the antibody can be applied in gene therapy as a highly specific agonist or antagonist of a protein within the cell. Furthermore, IMMUNA-derived antibodies can be applied to the field of diagnostics.

FIT Technology: Immediately after a lead compound has been identified through the application of ESBATech's platform technologies AGOS, ANTAGOS and IMMUNA, it can be optimized using the FIT technology. The required biological function is further enhanced while, at the same time, unwanted interactions which can cause side effects are eliminated. ESBATech has successfully applied FIT to further improve single-chain antibodies for intracellular applications that were identified by the IMMUNA technology.

Outlook

ESBATech aims to become a world leader among the biotechnology companies specialized in yeast-based functional genomics and drug discovery. ESBATech seeks to start collaborations with pharmaceutical companies. The ability to enter into such collaborations, in addition to generation of the required revenues, provides a due-diligence process for which ensures validation and further improvement of the various ESBATech platform technologies. For example, the collaboration with Hoffmann-La Roche was initiated at the blueprint stage. Within a short period of time (less than six months), ESBATech succeeded in integrating this blueprint into the PLACS and CLING technologies and has recently shown the feasibility of the screening systems to Hoffmann-La Roche. This achievement shows the high level of competence and know-how for yeast-based technologies at ESBATech. ESBATech will, besides further applications of the existing platform technologies, also develop novel platform technologies, thus allowing us to occupy a leading position in yeast-based functional genomics and drug discovery.

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Fluitec AG
Continuous Mixing and Gasification Using Static Mixers

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Abstract: Fluitec AG is a young, innovative company working in the field of mixing and reaction technology with the use of static mixing elements. Its growth and reputation is the result of creative thinking combined with many years of experience. Numeric models are used to calculate and simulate the efficiency of chemical reactions or homogenization processes. Much of the research and development work in this field is done in close collaboration with the Departments of Chemistry and Mechanical Engineering of the University of Applied Sciences Winterthur (ZHW), where all of the Fluitec engineers qualified. One particular project entitled 'Gasification of Biosuspensions' was commissioned by the Swiss Commission for Technology and Innovation (CTI). Fluitec AG is based in Winterthur, Switzerland's historical heart of mechanical engineering, and is now entering its sixth year.

Keywords: Bioreactors · Bubble-free aeration · Gas-liquid contacting · Gasification · Heat exchanger · Homogenization, wastewater, cell cultures · Static mixing

The principle of static mixers is convincingly simple: strongly defined geometrical devices, the static mixing elements, are inserted into a tube in a way that prevents any motion of these elements [1]. While flowing through such an equipped tube, the gaseous or liquid media are mixed only by means of pump energy (Fig. 1). The micro- and macro-turbulences generated, such as the splitting and rearranging of the currents, overturning, dispersing, vortexing, *etc.*, allow a well-understood and characterized homogenization or heat- and mass-transfer process to take place. The energy dissipated results in a pressure drop, ensuring a permanent and constant effectiveness over the whole mixer's length. Dead spots and inefficient highly localized energy dissipation are thus avoided.

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Economic and Safety Advantages

Low investment and maintenance costs, lack of moving parts and high efficiency make static mixers an attractive alternative to stirred tanks. Safety of critical reactions is improved significantly by the greatly reduced reaction volume, the continuous and well-controlled process and the opportunity of direct combination with tubular heat exchangers. In monotube heat exchangers, like in shell-and-tube heat exchangers, heat transfer can be increased by a factor of five to ten, thus allowing equipment of a reduced size. The continuous, radial mixing characteristic also generates a very narrow residence-time distribution compared to empty tubes. This fact is of special importance when it comes to avoiding unwanted side-products or to controlling polymerization processes.

Applications in the Field of Chemical and Biochemical Engineering

Due to the wide field of applications, there are very few standard solutions for processes involving static mixers. The elements not only differ with regard to their geometry, but also the materials from which they are made [2]. These range from PTFE, PVC and polypropylene through various grades of steel, titanium, tantalum to glass. The extreme diversity of static mixers allows them to be used in all kinds of industries such as:

- chemical and petrochemical
- food processing
- pharmaceuticals
- biotechnology
- plastics polymerization and extrusion
- wastewater treatment (namely aeration, deferrization, flocculation, in-line pH neutralization)
- flue-gas treatment (*e.g.* selective catalytic reduction), and others.

For highly abrasive solid particles or highly viscous media, the specially rigid CSE series was developed and manufactured in cast stainless steel (Fig.1). All mixing elements are self-cleaning.

Small Gas Bubbles – High Efficiency

Static mixers are ideal for gassing liquids, for example in biotechnology or chemical processes such as oxygenation, ozonization or hydrogenation. Using conventional dosing equipment, however, the large gas bubbles released must be broken down by pump energy in order to enlarge the interfacial area. This process

is often limited by the energy consumption and the flow velocity created (residence time, length of the pipe).

In order to control bubble size more effectively, the *FLUITEC Small Bubbles Reactor* (*FSBR*) was developed [3]. It consists of a combination of microporous tubular (sinter) material and an inserted static mixer (Fig. 2). The gas phase penetrates through the microporous material from an annular into the inner cylindrical space through which the liquid is circulated. The liquid phase shears-off the bubbles at a very early stage (*statu nascendi*), while they are still being formed (Fig. 3) [4]. The static mixer is useful for creating higher turbulence at the porous tube wall, thereby renewing the stationary liquid film surrounding the gas bubble. Since the very small, rigid microbubbles do not coalesce, the risk of separation of the two phases in a tube is reduced.

If this gassing device is mounted vertically as an air-lift, the liquid is driven by the rising gas and no pump energy is required (Fig. 3 and Fig. 4). Mixing and aeration are achieved simultaneously. Energy is used exactly where needed, both to generate small bubbles and to drive a liquid circulation.

Tests with yeast cultures and chemical applications have shown that the mass transfer rates are up to eight times greater than with aerators using conventional nozzles or spargers making this device attractive for use in wastewater plants. Various materials can be chosen for both elements, microporous cylinder and static mixer, which provide a useful degree of freedom with respect to hygiene, corrosion or investment costs. The unit can be easily scaled-up or combined with several units.

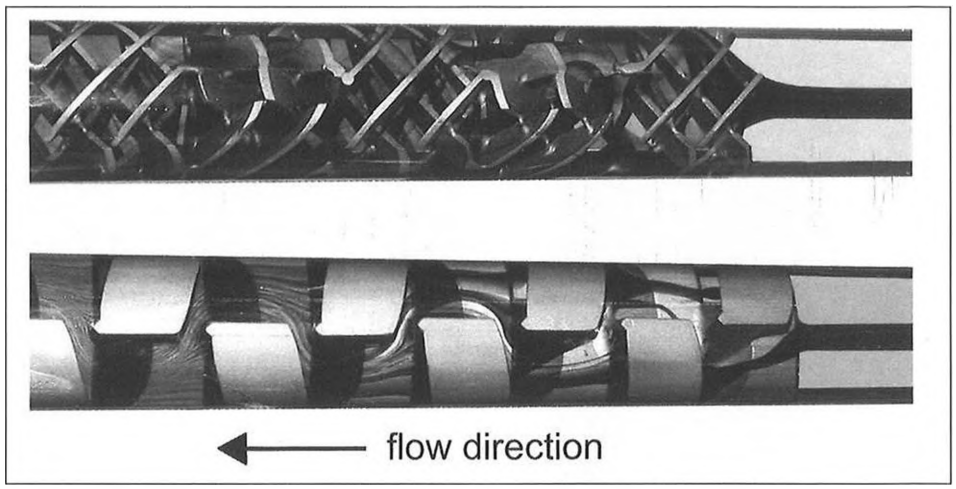

Fig. 1. Mixing of two viscous fluids in a CSE-X mixer (top) and in a CSE mixer (below) under a laminar flow regime (in contrast to gas dispersion) from right to left. Well visible is the mixing of the dyed additive with the continuous, colorless phase.

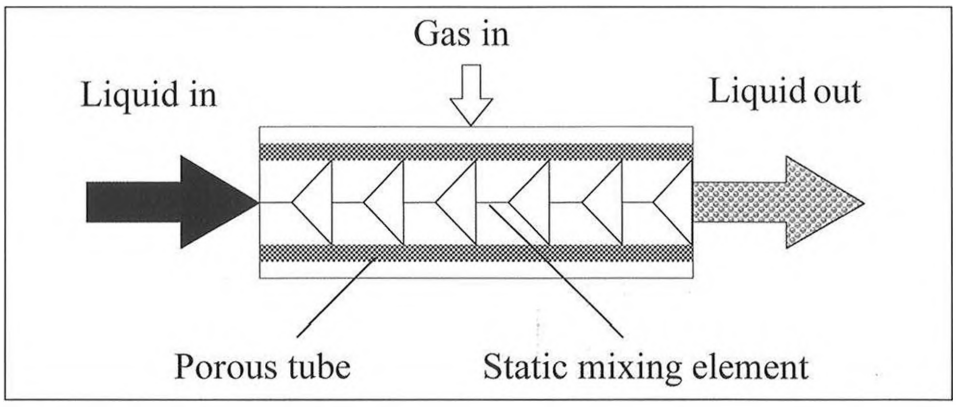

Fig. 2. Design of the patented Fluitec-Small-Bubbles-Reactor (FSBR). The gas is pressed through the porous tube into the liquid flow. Turbulences, created by the static mixer, shear-off the bubbles in a very early stage of growth, creating microbubbles that do not coalesce (see also Fig. 3).

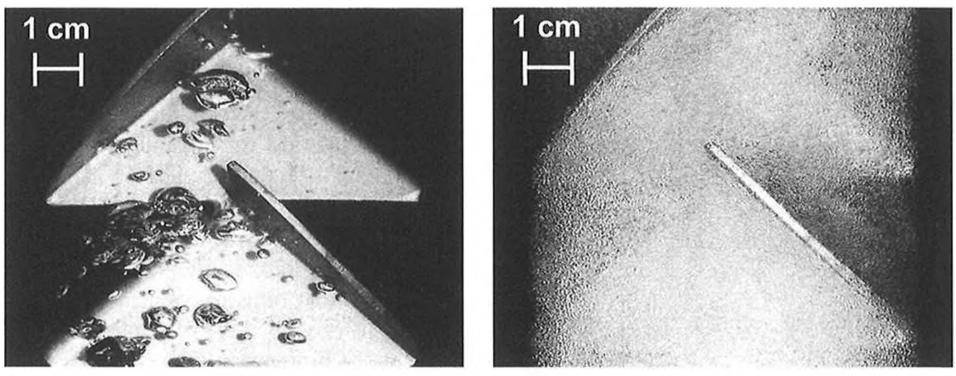

Fig. 3. The dosage site influences the bubble-size distribution significantly. In contrast to the use of spargers with drillings of 1 mm diameter (picture to the left; bubble size up to 10 mm) the FSBR generates much smaller bubbles leading to higher mass-transfer rates (picture to the right; bubbles smaller than 1 mm). Experimental conditions in the two experiments are identical: air-lift reactor; DN 100; gas flow rate 2 l min^{-1}.

Bubble-Free Aeration for Cell Cultures

Studies carried out by Fluitec and ZHW on the aeration of biosuspensions also represent a special field of application. Interest in the production of important biological products, such as vaccines, hormones and therapeutics, using animal cell cultures is greatly increasing. Cultivations of these generally shear-force sensitive cells, however, often do not allow the use of bubble aeration. Several studies have indicated that sparging-caused cell damage is mainly a result of cell interaction with erupting bubbles at the air–liquid interface [5]. The high-speed liquid motion of a bursting bubble generates intense hydrodynamic stresses and causes severe cell damage in the liquid layer surrounding the bursting bubble [6]. Agents which increase viscosity may reduce the shear forces, but they also clearly restrict mass transport in the liquid phase, and cause serious problems in down-stream processing [7]. Cell-stabilizing agents such as calf serum, are very expensive, a serious hazard for infections, and often make validation very problematic. Because of this, membranes are often used for bubble-free oxygenation. However, up to 3000 me-

Fig. 4. Gas-bubbles in an air-lift reactor. Picture taken under same flow rates after switching from sparger to FSB aeration.

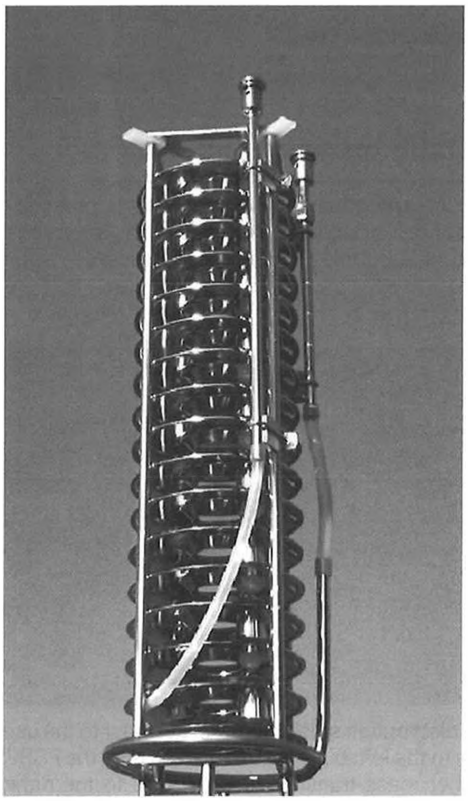

Fig. 5. The Air-Trap-Aeration unit as it is used for the aeration of hybridoma cells in a standard 25 litre bioreactor.

ters of silicon tube per cubic meter liquid are necessary to provide sufficient amounts of oxygen. Problems are caused by the space required, integrity and sanitation of the equipment and the limited long-term stability.

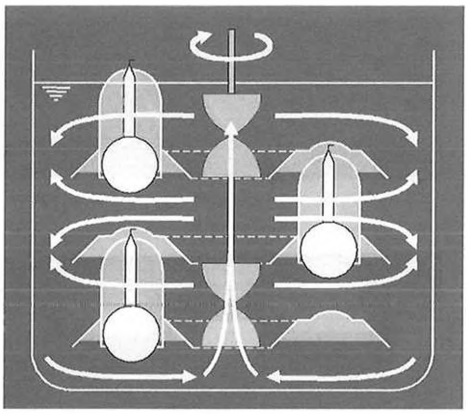

Fig. 6. The special stirrer-type generates a strongly defined fluid dynamic, that create high surface exchange rates and thereby increase mass-transfer significantly.

Complete Gas Transfer, No Foam

Air-trap (Fig. 5) technology combines the advantages of spargers and membranes, while eliminating the handicaps of these methods [8]. Based on the principle of surface aeration under the liquid level, this technology is capable of increasing the ratio of area to volume by an order of magnitude and more.

To inhibit or prohibit the free rising motion of a continuous gas phase, mechanical traps shaped as the upper half of a horizontal torus are used (Fig. 6). Through an auto-regulating float-valve in each trap, the gas is guided into the gas space of the next trap above. Hence, the formation of bubbles is avoided while a stable, continuous gas phase is generated from the bottom of the reactor to its top, which facilitates an extremely wide range of gas flow rates. A special spiral stirrer creates both mild mixing and the effective renewal of the liquid surface. The unit can be scaled up either geometrically or by multiplication of units, *i.e.* the number of air traps in the stack. Without any alterations or additional control devices, the device is easily inserted into any kind of bioreactor. The set-up is simple and working conditions remain stable over the long-term, since no delicate components such as membranes or tubes are needed. The economy of the process is even further improved by the reduction in the amount of gas required. Because of the possibility of the complete depletion of the gas, less than 5% of oxygen is necessary compared to spargers. The efficient removal of metabolic gas, such as CO_2, is effectively achieved. This makes this system also attractive for different kinds of expensive or reactive gases in chemical applications. Additionally, formation of bubbles, foam and aerosols is prevented.

A variant of this trap system, in which the gas is substituted by an immiscible light liquid, is also useful for continuous *in-situ* liquid–liquid extraction where the formation of small droplet dispersions must be avoided.

Technology Transfer

The University of Applied Sciences, Winterthur (ZHW), is in the process of developing and investigating new devices and procedures by providing know-how and technology transfer – focussed, but not exclusively, on small and medium sized enterprises [9]. The project 'Gasification of Biosuspensions', for example, is a collaborative venture between the Commission for Technology and Innovation (CTI), Bern, Fluitec AG, Winterthur, and Novartis Pharma AG, Basel, who are working together as industrial partners. The aim is to help Swiss companies with know-how and research infrastructures from Universities, and to bring industrial needs and requirements into the classroom.

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GENE DATA

GeneData AG
Integrated Bioinformatics Solutions for Genomics and Proteomics

Andreas Hohn*

Abstract: GeneData is rapidly becoming a leading provider of data analysis technologics for genomics and proteomics applications. GeneData has built up considerable expertise in the handling and analysis of genomics and proteomics data and imparts its knowledge to the life science community by providing consulting support as well as customized software solutions for data storage and analysis. GeneData adds scientific and commercial value by extracting information from huge volumes of data and by comparing sequence, gene expression, protein expression in connection with laboratory and clinical data.
GeneData was founded as a Swiss Aktiengesellschaft in 1997. It is an independent company wholly owned by its founders and staff. GeneData's offices are located in Basel (Switzerland) and in Munich (Germany) – close to some of Europe's leading life science industry and biotechnology centers. As of December 1999, GeneData employs more than 20 bioinformatics experts. GeneData's customers include leading life science companies such as Bayer, Boehringer Ingelheim, Byk Gulden, Hoechst Marion Roussel, Novartis Agro, Novartis Pharma, and Schering.

Keywords: Bioinformatics · Consulting · Data analysis and development · Software development

GeneData is a two-year-old Swiss bioinformatics company specialized in providing customized software and consulting support for the analysis of genomics and proteomics data. GeneData targets global life science companies with customized software solutions that are built to scale and fit within a company Intranet. GeneData's partners receive additional expert scientific advice on how to best analyze their data, improve experimental design, and optimize resources. Following this business strategy, GeneData has already attracted six major life science companies and is discussing partnerships with several smaller biotechnology companies.

The team that founded GeneData were previously members of the Scientific Computing unit at Ciba-Geigy, before its merger with Sandoz to form the life science giant Novartis. The founders (Othmar Pfannes Ph.D., Dr. Hugo Flühler, Alistair Smith Ph.D., Dr. Andreas Krause) identified a promising business opportunity in applying their computing and data analysis skills to the rapidly growing genomics field, thus helping life science companies discover information relevant for drug discovery in a jungle of public and proprietary data. Novartis had set up a venture capital fund, the Novartis Venture Fund, to encourage entrepreneurship and spin-off companies. GeneData tapped into this source of cash and raised enough money to develop its first successful product, the GeneData WorkBench™, a user-friendly gene sequence analysis software package.

The license fees earned from GeneData WorkBench™ together with consulting services enabled the company to address the growing need for sophisticated expression data analysis software. GeneData assisted companies such as Bayer, Boehringer Ingelheim, Novartis Pharma and Schering in the analysis of data from gene arrays and 2D protein gels, and the cash gained through the consulting work was in turn used to develop the company's first large-

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scale project, GeneData Expressionist™, which took two years and $2 000 000 to develop.

The company believes that the technology for analysis of gene sequences has reached a saturation point and that customers are demanding solutions that go beyond simple sequence comparisons in high-throughput mode. Beginning in 1998 and in partnership with Bayer AG, GeneData developed a new strategy for efficiently analyzing and comparing completely sequenced genomes regardless of size or number of genomes. This strategy, implemented in the GeneData Phylosopher™ system, was first applied to infectious disease research and enabled Bayer this year to streamline their search for novel bacterial targets. Over fifty percent of the thousands of genes identified in bacterial genome sequencing projects have an unknown function, and by using the computer Bayer could now quickly identify novel, essential genes, perform a functional characterization and select the best candidates for further validation in laboratory experiments. GeneData Phylosopher™ identifies essential genes in microorganisms by using GeneData's own proprietary algorithms to extensively compare both bacterial and eukaryotic genomes. The system identifies targets of desired spectrum and selectivity, identifies functional domains, and predicts biochemical and cellular function.

'Over fifty percent of the thousands of genes identified in bacterial genome sequencing projects have an unknown function' says Othmar Pfannes, CEO at GeneData, 'and by using the computer, Bayer is now able to quickly identify novel, essential genes, perform a functional characterization and select the best candidates for further validation in laboratory experiments.'

The GeneData Phylosopher™ technology produces knowledge that integrates well with GeneData's other large-scale data analysis systems, GeneData Expressionist™ for mRNA expression data, and GeneData Impressionist™ for protein expression data. GeneData Expressionist™ is likely to become the company's new flagship, as several partners have already lined up to become early customers of the new software version that combines over two years of experience in gene expression data analysis. GeneData Expressionist™ derives expression data from both cDNA and oligonucleotide arrays. GeneData believes that the system handles large volumes of complex gene expression data like no other software system, giving the researcher tools to retrieve data on a company-wide basis and perform complex analyses in an efficient and automated fashion. GeneData Expressionist™ also distinguishes itself from competing software products by strongly emphasizing the analysis of data quality. 'Assessing data quality is essential for the large-scale studies performed by our customers, yet this feature is typically missing in other software because it requires an understanding of how the data is generated' states Pfannes. The quality tools implemented in GeneData Expressionist™ allow users to make clear statements on the sensitivity and reproducibility of their data and to fine-tune the parameters of their analysis.

And finally, GeneData has built a relational database, GeneData CoBi™ (Core Biology database) which serves as a foundation to store genomics-related data, laboratory experiments data and clinical data. This database forms the link between the individual GeneData software products and the basis for establishing a genomics information management system that includes in-house proprietary information.

'Maintaining a competitive edge in this type of business is a big challenge', acknowledges Othmar Pfannes, CEO at GeneData. 'Genomics-based technologies are new, and concepts how to analyze the data have not yet been developed. It took more than ten years to develop powerful algorithms for analyzing gene sequences. With new high-throughput technologies entering the market and the human genome just around the corner, the next generation bioinformatics software must be developed as soon as possible.' To keep ahead of the crowd, Pfannes says they need 'to employ the best data analysis experts for developing novel proprietary algorithms and software engineers familiar with the newest in Intranet computing while keeping a close watch on developments in genomics.'

An essential strategy GeneData is taking to ensure the business gains momentum, is to form very close relationships with a small number of carefully selected partners, especially those in Europe. 'Building lasting relationships with Europe-based companies is our most important and biggest goal at the moment,' said Pfannes. The reason for this is two-fold. Firstly it allows GeneData to remove the stumbling blocks arising in genomics data analysis and in turn keep their technology up to speed with the problems of the day. Secondly, GeneData is located near some of the largest life science companies and the fastest growing biotechnology areas and 'the expertise gained here will allow us to expand rapidly into other areas.' Currently the company does not yet have a US office, but according to Pfannes, 'we are looking there and in Japan.'

The company is in the enviable situation to fund itself and its growth largely through revenues from software licenses and consulting projects. Pfannes states that 'with the recent release of GeneData Phylosopher and the upcoming release of a new version of GeneData Expressionist, our software products remain unmatched, and we are close to signing contracts with several pharmaceutical companies'. Pfannes thinks that this will raise enough cash to further develop the existing products, implement new approaches and integrate them even tighter into a global bioinformatics platform. The next move will be to team up with biotechnology companies because 'our data analysis technology in combination with innovative genomics technologies could have a large impact on drug discovery, toxicology studies and the diagnostics market.'

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GeneMaLK AG

GeneMaLK SA
Ticino, the Rising Biotech Region? Reasons for Potential Success

Marco Traub*

Abstract: Ticino, the southern region of Switzerland, has reached the forefront of a potential economic evolution within the biotechnology sector. With a highly developed infrastructure, Ticino is strongly related to the European pharmaceutical industry. Small and Medium Enterprises (SMEs) located in Ticino can provide highly developed services and products for the pharmaceutical companies and advance their own research and developmental activities. The major limiting factor for any further development of the economical growth of SMEs is the flow of investment money into this region. Generating investor relationships towards SMEs, catalysed by the local government, could be beneficial. The promotion of strong alliances between academia and SMEs with synergistic effects for the development of innovative products should be an additional duty for the local governmental authorities. The further enforcement of biotechnology at the recently founded Lugano University is a prerequisite.

Keywords: Combinatorial chemistry · Drug design · Molecular diagnostics · Xeno-transplantation

GeneMaLK SA was founded in Agno in early 1996. The company is based on immunological and molecular biological methods directed to pharmacologically relevant targets. In particular, the characterisation of opioid receptors within the human brain has been the primary research subject of the founder. The Janssen Research Foundation (CH, D) was the major sponsor for research activities in the US and Switzerland. After gaining management experience within the biotech industry, setting up the company in southern Switzerland was a consequent step forward, building up its own business and research structures aimed on molecular diagnostics and combinatorial chemistry. From the start, GeneMaLK SA has offered a GMP peptide service, protected amino acids and peptide libraries. The RTD activities are aimed at *e.g.* the development of novel detection assays for the diagnosis of genetic disease [1].

During its brief existence, GeneMaLK SA received in 1997 an Exploratory award from the European Commission (4th Framework Programme) and subsequent funding from the European Commission and the Bundesamt für Bildung und Wissenschaften CH. A second Exploratory award was granted to GeneMaLK SA in 1999 from the European Commission within the 5th Framework Program.

Ticino, with its highly developed infrastructure and central location within Europe, is a base factor for the successful operation of GeneMaLK SA. Biotech companies (*e.g.* Bioferment) or pharmaceutical companies (*e.g.* Boehringer Ingelheim (Pharmaton)) have discovered the advantages of the Ticino region. The excellent academic education in Switzerland offers a competitive source for manpower. The open-minded Ticino authorities have been helpful for the further development of GeneMaLK SA.

For the future development of this region, it is necessary to pipeline seed and venture money into small and medium biotech enterprises. One concept could be the creation of a Ticino high-tech investment fund, which could combine biotechnology and Internet-based companies. Once the government realises the importance of the new economy (compared to the dinosaurs in the Basel area) as the real pacemaker for employment, programmes for acquiring risk money should be initiated in the near future. Within this context competition between the regions should make sense. The extremely high performance of the NASDAQ over the past months is a clear indication that risk can generate high profits (no risk – no fun).

The major objective for the RTD project of the 4th Framework Program is the development of GeneMaLK's novel, highly sensitive PCR-based detection method for both the molecular diagnosis and therapeutic monitoring of diseases which are related to genetic disorders and infections.

The rationale of this project is based on the fact that millions of patients throughout Europe and also worldwide

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suffer from diseases of this kind. Clearly, in view of the large number of patients involved, novel and efficient diagnostic methodologies would be of particular importance and value. Such fast, efficient and in particular low-cost methods could save considerable expense to the public and health organisations. Low-cost diagnostic methods would further allow more regular (routine) testing and medical check-ups and thus provide the potential for the early detection of diseases and, in turn, earlier treatment. Frequently, more expensive therapeutic measures such as operations, irradiation and chemotherapy could thus be avoided. Another bonus would be the reduction in numbers of clinic patients with their individual suffering. The monopolistic market position of Roche is an other trigger, producing a strong demand for such alternative low-cost PCR diagnostic assays.

As a possible target for the proof of concept, insulin-dependent (type 1) diabetes mellitus (IDDM) was selected because of its significant occurrence in the European population. IDDM has an average prevalence of 0.5% in western Europe. It affects mainly children, adolescents and young adults who share a similar genetic background. IDDM is a T-cell-mediated autoimmune disease manifested by selective destruction of pancreatic β-cells. Such predisposition is conferred by a number of gene loci, the largest part of heritable susceptibility is marked by variation in the HLA region on chromosome 6p, mainly due to HLA DRB1, DQA1 and DQB1 alleles.

Biochemical properties of susceptible HLA D molecules differ from protective or neutral alleles and act differently in the regulation of the T-cell response. This T-cell response may be triggered by an endogenous retroviral antigen acting like a superantigen. It has been recently demonstrated that the presence of an endogenous retroviral DNA element within the HLA DQ region, namely the HLA DQ-LTR3, was significantly associated with IDDM [2]. Furthermore, this LTR is of a selective predisposing nature if it resides on a haplotype linked to the HLA DQB1+0302 allele. There it adds to the relative risk conferred by the HLA DQ allele alone and can be used as an additional marker for susceptibility screening in families and the general population including new-born infants. Thus, the proposal aims at identification of individuals at risk for the development of later IDDM.

GeneMaLK AG has recently focussed on RTD activities towards xeno-transplantation and the development of antiviral drugs (Collaboration partner M. Ahmed [3]) using the synergistic effects of the expertise in the areas of PCR technology and combinatorial chemistry.

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ISSN 0009-4293Global Surface AG

Global Surface
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Global Surface AG

Coatings with Siloxane Layers in Nanoscale Thickness: Hydrophobization, Adhesion Promotion, Corrosion Protection

Martina Hirayama[a,b]*, Walter R. Caseri[b], and Ulrich W. Suter[b]

Abstract: Inorganic and organic surfaces can be modified with ultrathin poly(siloxane)s which initially contain silicon–hydrogen bonds. In presence of an activator, the polymers strongly adhere to various surfaces, *e.g.*, to metals, ceramics and wood. The layer thicknesses are in the range of monolayers, *i.e.*, in the nanometer range. Such layers can be used, *e.g.*, for hydrophobization, adhesion promotion and corrosion protection.

Keywords: Adhesion promotion · Coating · Corrosion protection · Hydrophobization · Siloxane

The Company

The Global Surface AG, a spin-off company of the ETH Zürich, was established in 1997. Global Surface specializes in surface chemistry and technology. The main activities of Global Surface are problem solutions for coatings with the objectives adhesion, protection, lubrication and anti-adhesion. The specialty of Global Surface is a novel patented method, which enables the coating of surfaces with thin and ultrathin layers down to one nanometer thickness, as described below. This method opens completely new possibilities for a multiplicity of coating applications.

Introduction

Poly(siloxane)s are widely used in coating technology, *e.g.*, as water-repellant, anti-stick, or lubricating layers. However, the application methods are often connected with difficulties, in particular in the context of the manufacture of thin films. We have developed a novel, versatile method which allows to prepare ultrathin, homogeneous and strongly adhering siloxane layers to the surfaces of various materials, such as metals, metal alloys, glasses, silicon wafers, ceramics, rock, artificial stone, wood, paper, textiles and plastics [1–5]. The related layers are simply prepared by using solutions with the siloxane containing Si–H bonds and an activator. The solutions can be applied by spraying or brushing the solution on the surface or by immersing the surface into the solution (also called adsorption from solution). It has to be emphasized that the bound siloxanes, which initially contained Si–H bonds, can be bound exclusively in the presence of an activator; the detailed mechanism of the transfer of the siloxanes to the surfaces and the nature of the bond of the siloxanes to the surfaces, however, are not known yet [1–5]. The layer thicknesses finally obtained are in the range of a few nanometers, *i.e.*, a monolayer [1–5]. In the following we present some examples and applications for ultrathin layers prepared with our technique.

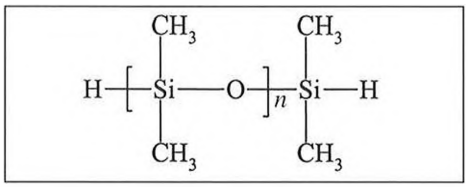

Fig. 1. Structure of hydride-terminated poly(dimethylsiloxane) (PDMS(H))

Examples

A. Hydrophobization

Si–H-terminated poly(dimethylsiloxane), PDMS(H) (Fig. 1), builds strongly bound hydrophobic polymeric surface layers on inorganic and organic surfaces, as evident, *e.g.*, from contact angle measurements (Table 1) [1–5]. Such layers can be used, *e.g.*, as water repellant, anti-stick and lubricating layers.

B. Adhesion Promotion

Poly(hydromethylsiloxane) (PHMS) forms strongly adhering layers on inorganic and

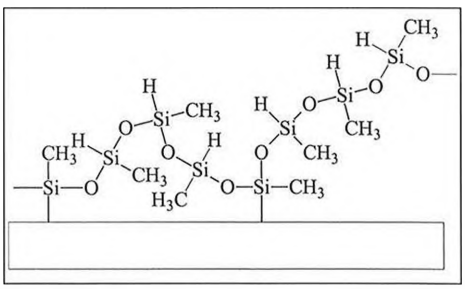

Fig. 2. Sketch of a surface modified with a PHMS layer

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Table 1. Advancing contact angles of water on strongly adhering monolayers of PDMS(H) on different surfaces [1–5]. All surfaces not treated with PDMS(H) and an activator show contact angles <80°.

Surface	Contact Angle [°]
aluminum	120–130
iron	111–123
V2A steel	115
titanium	113
chromium	113
cooper	115
gold	115
glass	100
silicon wafer	105
aluminum oxide ceramic	118
clay	125–138
stone from Lecce	115–125
sand stone from Bern	108–131
coloured sand stone	106–116
red sand stone	115–127
concrete	114–132
maple	113–133
oak	120–133
poplar	124–133
paper	116–126
cotton	130–137
viscose	130
silk	110–120
PET	105

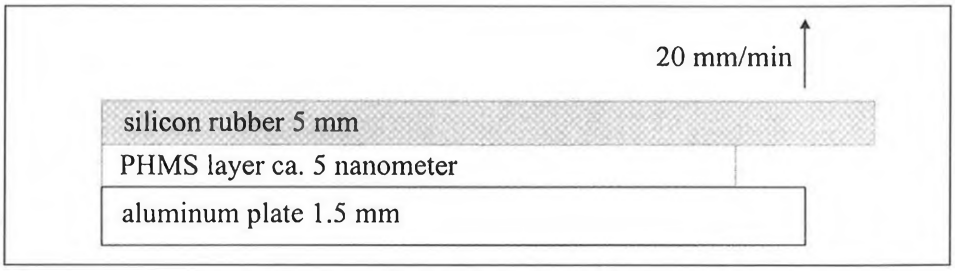

Fig. 3. Sketch of the sample geometry used for peel resistance tests

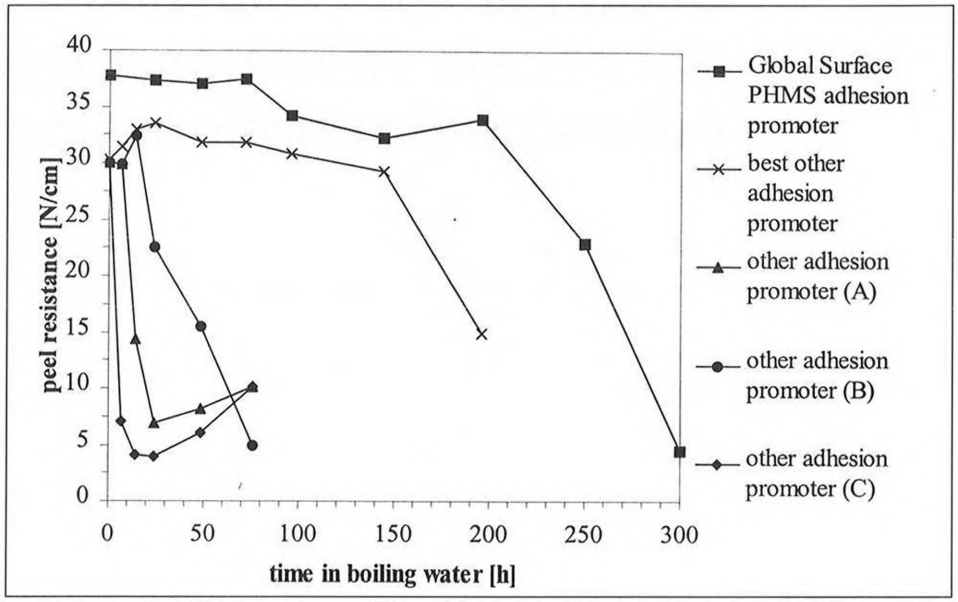

Fig. 4. Peel resistance tests

organic surfaces [1–5]. A fraction of the Si–H bonds are activated and undergo reaction with the surfaces, others are still intact in the layer and can be used for further reactions on the surfaces (Fig. 2).

These PHMS layers (Fig. 2) were used, *e.g.*, to promote the adhesion of metals to two-component silicon rubbers, where the curing process is based on the catalytic hydrosilylation of olefins. Peel resistance tests were performed with plates of aluminum according to DIN EN 1464 (Fig. 3). No peel resistance could be measured without a PHMS layer, while a value of 37 N/cm was found after the aluminum plates had been coated with PHMS. Cohesive failure was always observed. In addition, this system was immersed in boiling water for various periods of time in order to get an impression of the resistance of the adhesion promoter towards hydrolysis and temperature. Remarkably, the initial peel resistance decreased only slightly within 200 h in boiling water (Fig. 4), and the corresponding failures were still of a cohesive nature. After 200 h exposure to boiling water, the peel resistance started to decline and reached 6 N/cm after 300 h of immersion (Fig. 4). For comparison, Figure 4 also shows results obtained with commercial low-molecular-weight organosiloxanes. These experiments clearly demonstrate that surface-bound PHMS layers can act as adhesion promoter to two-component silicon rubbers in which silicon–hydrogen groups are present.

Table 2. Corrosion protection with and without PHMS layers on aluminum surfaces coated with a polyester

Test	PHMS	time	diagonal cross	undamaged area
A	–	10 cycles	100% infiltration up to 10 mm broad	m 4 / g 3[a]
A	PHMS	10 cycles	no infiltration	m 2 / g 1[a]
B	–	500 h	10% blisters <1 mm Ø	no blisters
B	PHMS	500 h	no blisters	no blisters

A: Kesternich test (SO_2) according to DIN 50018 KFW 2, OS

B: Acetic acid sodium chloride spray test according to DIN 50021 ESS

[a] Designation of degree of blistering of paint coatings according to DIN 53209

C. Corrosion Protection

The PHMS layers as described above (Fig. 2) were also used, *e.g.* for corrosion protection of aluminum surfaces coated with a polyester. First the PHMS layer is applied on the aluminum surface followed by application of the polyester. The results shown in Table 2 clearly demonstrate that surface-bound PHMS layers protect aluminum surfaces more effectively from corrosion than standard systems tested for comparison.

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HiTech Photopolymere AG

HPT HiTech Photopolymere AG
An Alternative Approach to Niche- and Specialty Products for Photoimagable Lacquers

Diethard Kapp-Schwoerer*, Kurt Meier, and Charles Gantner

Abstract: HTP HiTech Photopolymere AG develops, manufactures and sells worldwide ready-to-use lacquers for the photolithographical production of metal parts. The products are designed to be applied onto various substrates, such as metals, alloys, glass and other surfaces.

Keywords: Chemical machining · Imagable · Photopolymer · Photosensitive · Resist

Shrinking Number of Suppliers Influences Expenditure on R&D for Special Products

The number of suppliers for photochemical processes, especially for photopolymers, is declining. Enterprises are merging (*e.g.* Shipley + LeaRonal → Shipley-Ronal) or focussing their activities on their core products to defend their leading market positions (*e.g.* sale of the Polymer Division of Ciba Speciality Chemicals AG to MGPE (Morgan Grenfell Private Equity)). This concentration results in less money invested into R&D projects targeted at products exhibiting unique properties, but lacking the potential to generate a 'reasonable' ROI. Users with special requirements for product performance are often urged to implement a commercially available, multipurpose product in their manufacturing processes. If they do so, in almost all cases, they have to accept compromises on service and support from the suppliers. In addition, yield numbers may suffer due to the borderline performance of the product.

Product Development in Niches: There's Another Way to do it

In May 1997 HTP HiTech Photopolymere AG (HTP) was established in Birsfelden, Switzerland. Founding a new company, active in R&D and the manufacture of photoimagable materials, at that time was a remarkable step. The three founders, Charles Gantner, Dr. Kurt Meier and Diethard Kapp-Schwoerer – all former employees of the 'Electronic Materials' Group within Ciba Speciality Chemicals Corp. – agreed to target the 'Chemical Machining' market.

The concept of the company is the development of special polymers in close cooperation with the user. 'This way we profit from our experience as a research-oriented company, creating real innova-

From left to right: Diethard Kapp-Schwoerer, Kurt Meier, Charles Gantner

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tion', says Dr. Kurt Meier. Already several selected projects are being worked on in the R&D laboratory. HTP is convinced that only the involvement of the end user, providing his expertise on performance requirements, can lead to successful implementation into well-established manufacturing processes. Teaming up with the user ensures that development – with its iterative processes – leads to commercial products within a given timeframe. 'Customer-oriented R&D, also for smaller and middle-sized prospects, is our strength, as compared to the large photopolymer manufacturers', Charles Gantner mentions, pointing to the successful introduction of DiaEtch 100 at a major PCM customer. 'Medium term not the payout of dividends to shareholders is the goal, but to secure the existence of the company', Diethard Kapp-Schwoerer emphasizes, who is responsible for marketing and the strategic planning.

The achievements accomplished so far show this philosophy to be right. Within the short time of the company's existence, resist materials could be developed which can be used on a variety of surfaces without any compromise.

Customer-Specific Product Development

The end users must also adapt to the changed priorities of large-size suppliers and smaller product-developing enterprises. Without any doubt, companies like HTP can help the manufacturers, who seek specialization and expertise, to add more value to their products by offering specifically developed materials. On the other hand the customer must be ready to pay its share for such R&D projects beforehand, since the resources do not allow an advance financing and usually such specific solutions do not create a large turnover. This cooperation ensures, that investments in R&D is done only in areas where:

- new and better products return a higher added value and
- the chances for success are expected to be high by both the user *and* supplier.

Targets for 2000

HTP anticipates a good profit for the current year. The demand for products has significantly increased. According to the company owners, the level of awareness of HTP among the users of photopolymer materials is very important for the successful implementation of products and services. After three years this was positively noted and reflects the fact that a number of research projects have a great chance to turn into commercial products, returning a sustainable profit. The balanced result in 1999 nourishes the expectation for restrained structural growth in the years to come.

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MatSim®
Materials Simulation GmbH

MatSim GmbH
Palmyra – Cost-Saving Materials Design at the Click of a Mouse

Albert H. Widmann*

Abstract: What do car bumpers, the space shuttle and false teeth have in common? They are all made from special materials designed to meet the most demanding of specifications. MatSim GmbH has developed the computer program *Palmyra* that simulates the physical properties of high-performance composite materials before they even go into production.

Keywords: Composites · Computer-aided materials design · Numerical simulation · Physical properties

Palmyra and the Virtual Search for New Materials

New materials are needed in all fields of life. More often than not, these are composite materials built as a heterogeneous mixture of different components. So far there were no theories available to accurately predict the properties of such mixtures. Things changed when the first ver-

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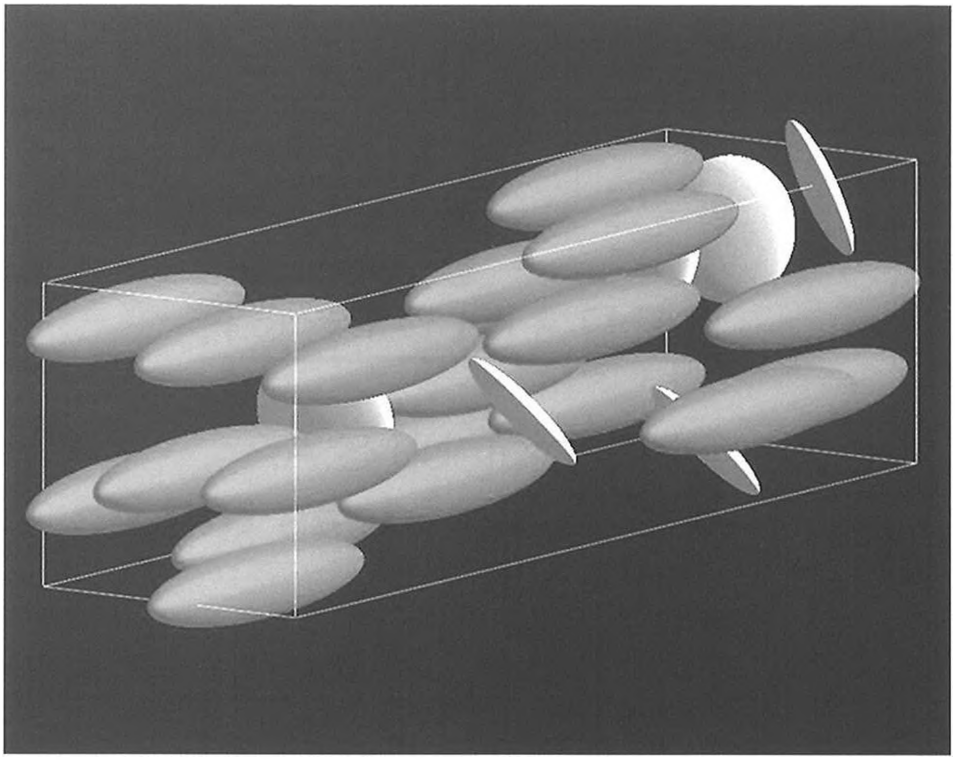
sion of *Palmyra* by MatSim was used by two of the world's leading chemical companies in autumn 1999.

Just one year before, MatSim GmbH had been established as a spin-off company of the Swiss Federal Institute of Technology (ETH). During the first business year, MatSim focused its activities on the development of a user-friendly software package named *Palmyra* that uses a recently developed finite element method to calculate the physical properties of heterogeneous materials [1][2]. The new method had already been successfully applied to calculate the mechanical properties of fiber-reinforced polymer-matrix composites; measurements of the real materials showed a very high accuracy of the results obtained by the numerical simulation [3]. However, *Palmyra* is not limited to the simulation of polymer composites; any combination of metals, ceramics, and polymers can be examined by the software in order to calculate physical properties such as elastic constants and stiffness, thermal expansion coefficients, thermal conductance, dielectric constants, electric conductivity, transport properties, *etc.*



Three-phase polymer composite with 20% rubber particles (elongated after extrusion) and 5% mica particles (platelets). With *Palmyra* it is possible for the first time to predict how the properties of this material will be affected by changing volume fraction, geometry, and distribution of the inclusions in the polymer matrix. (Picture: MatSim GmbH).

Winning Project at the Hannover Fair

After the successful market introduction of *Palmyra*, the software became a winner of 'Technologiestandort Schweiz' and therefore has the opportunity to be presented at the Hannover Messe 2000. The strong advantages of using *Palmyra* for the materials design is the great reduction in development time for new composites and the ecological soundness, since new materials do not have to be produced and tested, unless the software calculates that their properties will fulfil the requirements.

Indeed it is likely that with computer-aided materials design, we will soon have completely new materials that will bring tangible improvements to many areas of our lives.

MatSim – Materials Simulation

MatSim GmbH was established in 1998 by Dr. Roger Baud (CEO), Dr. Andrei A. Gusev, Prof. Ulrich W. Suter, and the author (CTO). The goals of the company are the development of user-friendly commercial software for the design of new materials and to support its customers in finding the perfect materials mixture for a defined set of requirements. The company currently has two employees and plans to grow quickly in order to keep the world leadership in this new technology.

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MEDABIOTECH

Medabiotech S.A.
We Bring Ideas to Life™

Wil Hazenberg*, Jeremy Lack, and Cathy Lawi

Abstract: Medabiotech is a Geneva-based venture services company acting in the life sciences. The company acts as a catalyst between the players involved in the successful exploitation of new technologies or inventions with clients in the research community (universities, start-ups and individual researchers), industry (big pharma and multinationals) and the financial community (venture capitalists, banks and business angels).

Keywords: Licensing · Medabiotech · Seed capital · Start-up · Technology scouting · Technology transfer · Venture capital

Since its incorporation as a Swiss S.A in 1998, Medabiotech has been involved in the creation and management of start-ups. It is a venture services company for start-ups and early stage technologies in the life sciences. Its team of six people includes three scientists and two lawyers with extensive experience in industry, business development, intellectual property, technology transfer, and the creation and management of start-up companies. The hands-on experience with start-up companies and technology transfer processes are the company's main strengths and are complimented by its wide range of industrial contacts and international network of experts in the life sciences. The company's clients range from individual scientists and universities to venture capital firms, start-up companies and multinationals. Scientists, bankers and industrialists tend to view the same technology from different perspectives, and speak different languages. A scientist is typically concerned with the basic validity of the research, and will be motivated to publish results as soon as possible in a leading scientific journal. A banker or venture capitalist will be looking at the opportunity in terms of a return on investment. Finally, an industrialist will be thinking in terms of market trends, core competencies and next-generation products. Whereas the scientist will be talking about 'probes', 'blots' and 'signal-to-noise ratios', bankers will focus on a technology in terms of its 'exit strategy', evaluating the technology through a variety of cash-flow models and 'option-pricing valuation extensions'. Industrialists will consider the technology in terms of 'years to market', 'scale-up', and department budgets, using yet another set of words that scientists (and sometimes even bankers) may not be familiar with. Because science is so specialized and bio-medical products are becoming more and more interdisciplinary, it is difficult and not cost effective for large companies to retain the same levels of all scientific expertise in-house. Start-up companies are also not equipped to face the multiple barriers of clinical trials, product registration, legal clearances, marketing and technical services and sales support that developing and selling a product require. There is thus a mutual need for industry to establish stronger links between academic sources and small start-up companies, who often do not know how or whom to approach in multinationals. At the same time, universities in need of money look to industry for new sources of income. There is, therefore, a strong need to translate and help build bridges between these partners who need each other badly, and yet do not easily communicate with each other. Medabiotech acts as a catalyst between these different communities.

Medabiotech is itself a start-up company and transfers this entrepreneurial spirit to the work with other young companies in that it provides its services on the basis of equity and success fees while working with such clients. These services include assessment of outstanding life science projects, establishing a business plan, providing business and drug development assistance, identifying (future) strategic partners and finding the initial

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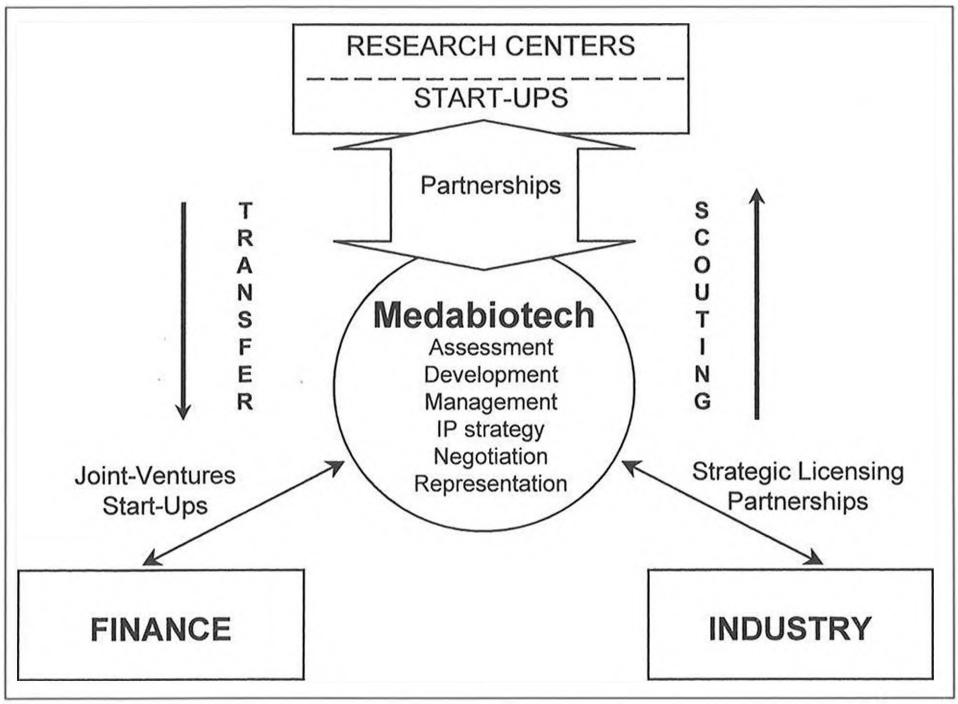

MEDABIOTECH's business model and network

capital. Medabiotech works closely together with the entrepreneurs and founders of a new venture with a common goal: the establishment of a prosperous business. By taking an active role in the creation of new companies Medabiotech can be seen as a private incubator, filling in the missing pieces of the puzzle necessary for the success of the start-up company. The involvement is not limited to the initial start-up period but continues focusing more on the commercialization of the products or technology in the form of business development, additional financing rounds or negotiations with industrial partners.

Medabiotech has established strong relations with universities, research centers, and start-up companies, for which it has been providing business development support since it started its activities. This has enabled the company in turn to provide technology and product scouting services for the industry, using its privileged access to research groups and technology transfer authorities. The company typically visits the universities and research centers it works with every few weeks, and then it closely follows promising inventions until they have reached a maturity stage where the company feels they can be presented to strategic industrial partners.

Medabiotech also works with several technology transfer offices in Europe, Israel and North America and assists a large number of individual scientists and start-ups in their technology transfer.

With the increased availability of both risk capital and life science start-ups, the need for proper due diligence and assessment on all aspects (science, management, intellectual property, *etc.*) of these ventures remains the key for success of the venture as well as of the investments. Medabiotech assesses new technologies and start-ups from a scientific as well as an industrial perspective for venture capital companies and individuals who do not have this type of very specialized knowledge in-house. Medabiotech also advises financial institutions on private placements and investments in publicly traded companies. The company recently started to manage and advise an Israeli seed fund for life science investments in Israel and is looking to expand this activity to Europe with the creation of a fund for early-stage life science opportunities.

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mifaco chemicals ag

mifaco chemicals ag
Micronization of Active Pharmaceutical Ingredients

Dieter Krimmer*

Abstract: mifaco chemicals ag is a young and dynamic company that provides several services. The services are: a) CMC management: This involves all technical aspects during the development of a new drug. For generic drugs, mifaco chemicals' experience can also be counted on. b) Micronization of APIs: mifaco chemicals is specialized in contract micronization of APIs. Micronization is performed under cGMP conditions in multi-purpose lines. Each line is located in dedicated suites. Our specialty is micronization below 10 µm.

Keywords: cGMP/GMP · CMC management · Consulting · Micronization · Particle size distribution

mifaco chemicals is the outsourcing partner for the pharmaceutical industry focusing on size reduction for active pharmaceutical ingredients and other ingredients. Our aim is to establish a partnership with our clients, not only providing the micronization capacity. We are able to provide a variety of value-added services, such as:

- validation expertise and personal contacts with the authorities in US and Europe,
- CMC management,
- marketing ideas.

Nevertheless such services are supplementary to the manufacturing capabilities that mifaco chemicals specializes in.

mifaco chemicals was founded in 1997 with micronization as the strategic focus. The technical concept has been proven in the meantime, setting new standards in the industry. The core competence of the personnel ensure that manufacture is carried out according to current Good Manufacturing Practice (cGMP). Furthermore, we have a good understanding of the pharmaceutical industry, which helps to accelerate FDA or other government approval.

Fig. 1. View of the clean rooms and HVAC systems

The equipment was constructed in 1997/1998 and the modern plant has been fully operational since the final quarter of 1998. mifaco chemicals was successful inspected by several leading pharmaceutical companies. The two industrial micronization lines and one benchscale laboratory plant mill offer following possibilities:

- Micronization can be performed with nitrogen or oil-free compressed air, both also at lower temperatures.

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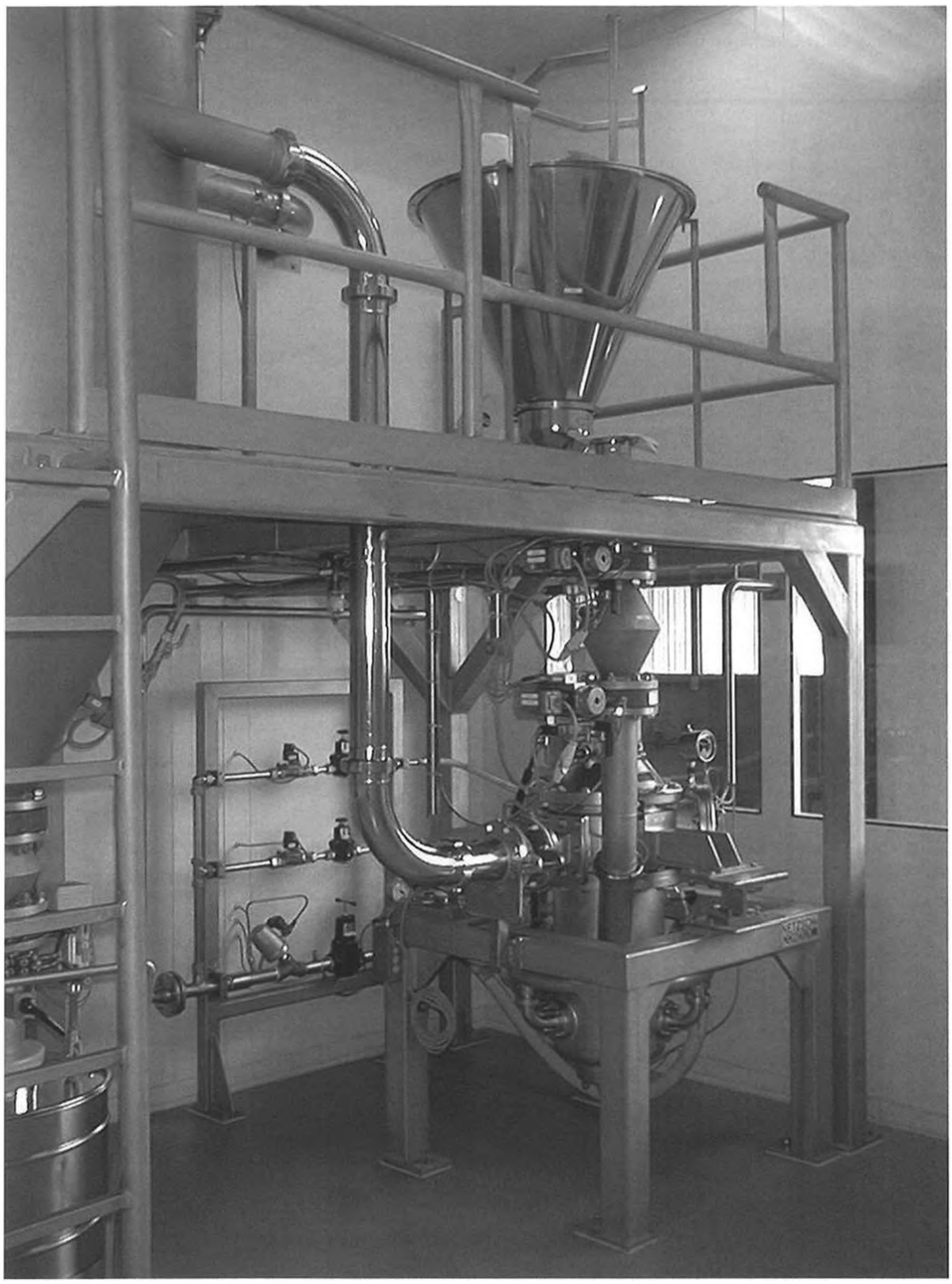

Fig. 2. Micronization line CGS 32

- Product handling is performed in closed systems and air-conditioned rooms (Fig. 1).
- Batches for micronization can be from 100 g up to several metric tons.
- Fulfillment of the latest requirements of the authorities.
- Sterile micronization

The plant offers the following properties. The mills are in completely separated cabins with locks for material and for personnel. The concept was discussed with the authorities (FDA) and accepted before construction. Each micronization line has a segregated air conditioning system to avoid any cross-contamination. Micronized and unmicronized products are stored in separated warehouses. The scientist responsible for QA ensures that only released material will be micronized or will be sent back to the partner.

Our Personnel:

- For CMC management: 2–5 chemists/ pharmacists
- For micronization: 1–2 chemists, 1–2 lab technicians, 3–5 chemical workers
- For administration: 1–2 controllers

The Equipment (Fig. 2):

- Fluidized-bed jet mills
- A classifier secures the desired particle size. All equipment has been constructed from stainless steel with pharmaceutical-grade surfaces. The micronization cell is not coated to avoid any electrostatic charging. Cleaning can be performed quickly and easily (cleaning validation).
- Preparation of the milling gas. The milling gas is oil-free compressed air or nitrogen (medical grade). The temperature of the milling gas can be chosen between 1 °C and 25 °C; possibility of adaptation of the air conditioning.

Laboratory:

- Sieving analysis for particle sizes above 100 µm. Laser scattering method for particle sizes below 100 µm. Six different methods for evaluation can be used, *i.e.* the Fraunhofer method. A dry powder module and a module for liquids are available. All retention samples are stored for seven years for any requests.

The Documentation:

- Master validation plan (systems and processes)
- The equipment was qualified according cGMP (DQ, IQ, OQ, PQ).
- This qualification forms the basis of a prospective validation of APIs.

Batch Documentation:

- After micronization, each customer receives a complete batch documentation in accordance with cGMP. This documentation will be stored for ten years.

The Unique Set of Capabilities Offered to our Partners:

- A constant and very tight particle size distribution, which is the best assumption for an optimal galenical process.
- Specialization for a particle size distribution less than 10 µm.
- With the micronized substances, you meet every time the demanded specifications of your dissolution profile.

CMC Management: C (Chemistry), M (Manufacturing), C (Controls)

We offer consulting in the complete technical area, for example:

- basic design of new equipment
- qualification of the equipment
- validation of systems and processes
- support in the registration and much more

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MIM Systems Ltd

Mold in Mold: a New Rapid Tooling Technology for Injection Molding

Jean-Marc Boéchat*

Abstract: MIM Systems Ltd has developed new technology to produce plastic injection molds based on the Metal Injection Molding process. This is a rapid tooling method which allows tooling production time to be cut by a factor five to ten and tool price by half compared to traditional methods. The molds produced by this technology, called Mold in Mold, are made out of steel, hence they have mechanical characteristics similar to the production tools used today. Moreover, the mold in mold technology also speeds up the tuning of the molds required to optimize parts production. It is especially efficient for the production of parts with very elaborate geometrical features. By reducing the tooling price, the production of small or limited series of parts by injection molding becomes economically feasible.

Keywords: Metal injection molding · MIM · Molds · Plastic injection molding · Rapid tooling

MimSystems' History and Company Profile

MIM Systems Ltd was established in the spring of 1998 in the aftermath of the Novartis Research Center Marly closure and its displacement to Basel. It is based in London with its main operation center in Marly, Switzerland. The company is active in the rapid tooling business for injection molding. Thanks to its proprietary technology, MIM Systems Ltd can offer a very fast service at a competitive price to the polymer industry. Its business activities extend also into consulting for companies interested in Metal Injection Molding (MIM) that don't have the required expertise in-house. The company employs two full-time and one part-time staff at the present time.

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Introduction

The need for speed is becoming a question of survival for injection mold fabrication. The production of a small or limited number of parts is a challenge for companies active in the custom business where the high price of normal tooling kills a number of projects. East Asian groups, very active on the market, also fuel the competition. In this ever-changing environment, it is a little bit like in the old west: the one who draws his tool first wins. To address this situation, we have developed a new technology for mold making which has the potential to cut the time to market by a factor five to ten and the tool price by a factor two.

The Mold in Mold Technology

This technology, as its name suggests, is based on a paradox; building molds out of molds. We build the molds with the exactly the same technique that you would normally use to produce the parts, by injection molding. However, the molds we produce are made out of genuine steel that can be hardened to more than 50 HRC (**H**ardness **R**ockwell **C**one) hence there is very little if any difference on the material side between the molds fabricated the usual way and the ones we produce. It means that these tools are as close as possible to the production tool but with the decisive advantage of being much cheaper and built much faster. The basic principle is illustrated in Fig. 1.

The starting point is the CAD (Computer Aided Design) file representing the part to be molded. From this file we build, by rapid prototyping techniques, either the part itself or models of the mold elements depending on the part ge-

ometry. These prototypes are then inserted into a standard cavity and MIM material is injected upon it. MIM stands for Metal Injection Molding, it is a technology enabling metal parts to be 'fabricated' by injection molding much like the plastic parts. The MIM process then leads us to a steel insert or mold that can be mounted on an injection molding press in order to produce up to a few hundred thousand polymer parts.

Our technology addresses another issue of the mold making activity. Most of the time, the first mold produced leaves lots of room for improvement. The mold then needs to go through an optimization cycle in order to produce the parts with the desired properties and with a cycle time as short as possible. By multiplying the capabilities of the MIM technology with our Mold In Mold method (hence MIM^2 in Fig. 1) we can shorten this optimization cycle so that the overall time is greatly reduced. The way it works is illustrated in Fig. 2.

Metal injection molding, as for every injection technique, enables the production of several identical parts. The so-called green parts coming directly out of the injection machine are made out of 60% vol. of metal powder and 40% vol. of polymer, which is the composition of the MIM feedstock. By choosing the right polymer, the green parts can be made so strong that they can be easily machined. Once several green parts have been obtained, one is treated through the standard MIM processing and the other ones are saved for later use.

The MIM process is carried out in two steps that eventually turn the mixed material (metal powder and polymer) into a solid steel part.

The first step is called the debinding step. During this stage, most of the polymer (also called binder) used to enable injection of the metal powder is removed. This step is accomplished either thermally by simply heating the green part in the 110 °C to 300 °C range and allowing the liquefied polymer to flow out of the mixture or by a thermochemical process using catalytic degradation of the polymer. The polymers used are polyolefines, waxes, more elaborate products like polyoxymethylene (POM) or a mixture thereof. We use commercially available feedstock from BASF, which is based on POM and other polyolefines. It allows catalytic debinding in which the POM is split by HNO_3 (gas.) at about 130 °C. Fig. 3 describes the process.

The advantage of this process is to speed up the debinding step to about

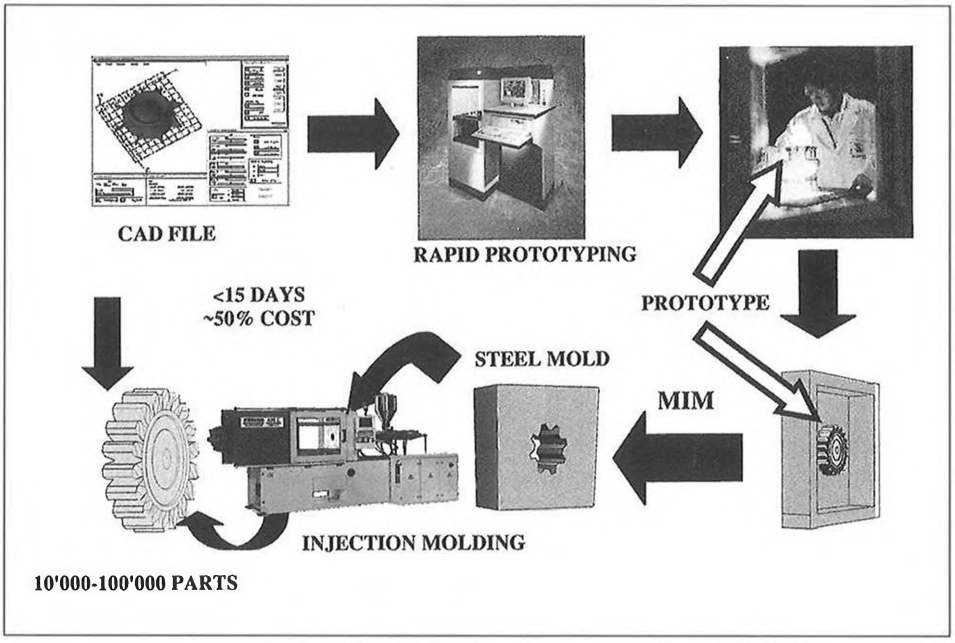

Fig. 1. Working principle of the MIM^2 technology

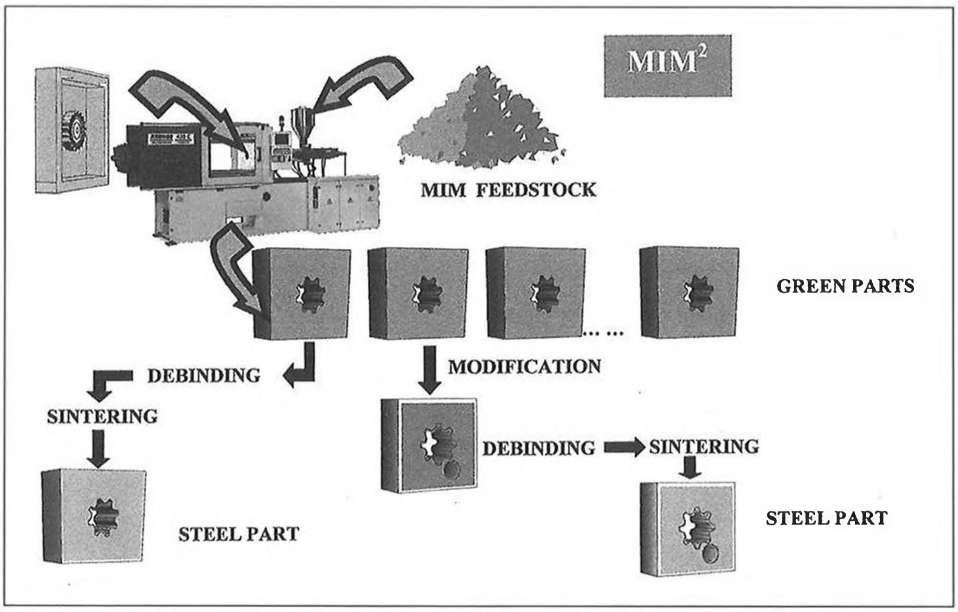

Fig. 2. MIM^2 technology enables fast turn-around time for the mold optimization cycle

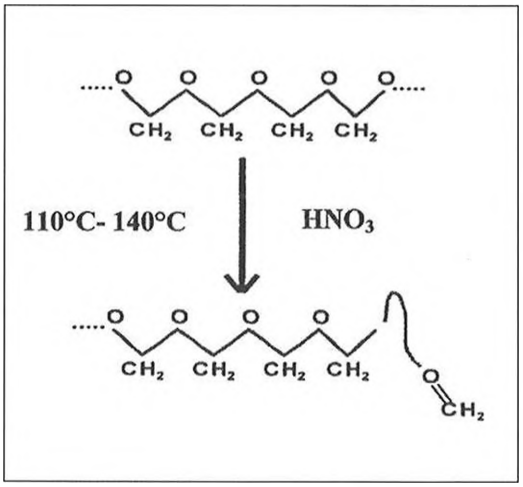

Fig. 3. Catalytic degradation of polyacetal used in the MIM process (after [1])

1mm/h and also to allow debinding of thick parts. The main drawback is the production of formaldehyde in the reaction, which must be disposed of thoroughly.

In the second step, the metal powder, now held together by a minute amount of residual polymer, is sintered at high temperature (1250 °C to 1400 °C for steel parts) in order to reach densities close to bulk steel. During this step, the rest of the polymer is burned and atoms diffuse to fill the voids left by the binder. This step is linked, of course, with a strong size reduction of the parts (in the order of 20%).

Mechanically, the parts after treatments are like machined parts and can be heat treated to give them the desired hardness.

Coming back to the mold improvement cycle that all tooling has to go through, we now have the advantage to be able to produce several identical green parts. After testing the first sintered mold, we apply the required modification very easily to the next green part, which in turn after sintering, will be the new version of the mold. In this way, we can drastically reduce the time needed for mold optimization. Moreover, if a multicavity mold is required, it is quite easy to sinter more than one green part and build a number of identical cavities in this way.

Comparing the total amount of time and money it takes to complete a full cycle from the part CAD file to the preproduction stage, the advantage of our technology over the more traditional ways becomes quite clear as shown in Fig. 4.

Application Domain

The limits of the application domain are not yet defined precisely. At this point, the rapid prototyping method has a practical resolution limit in the order of 0.1 mm. The size of the molds is currently limited by the MIM technology and the available injection molding machines. Moreover, the cascade of shrinkage occurring through the entire process needs to be mastered to reach a reasonable quality level.

Quality is paramount in the injection step of the MIM process. The better the homogeneity of the produced part, the more the shrinkage can be precisely controlled, hence the better the precision of the sintered molds. Of course, the quality of the MIM feedstock is also a key factor to obtain quality in a reliable way.

The shrinkage, although it looks like a limiting factor, contributes to reduce the resolution limitation of the rapid prototyping step. In reducing the overall dimensions by round 20%, it also reduces the minimum feature size from 0.1 mm to about 0.08 mm and less if the molds are used to produce metal parts by the MIM process. In this case the equivalent resolution on the part is about 0.06 mm, which should be sufficient for most applications.

Nowadays the performance of rapid prototyping systems is improving rapidly and it should soon be possible to bring down the resolution limits by a factor of two. The mechanical characteristics and high temperature resistance of the rapid prototyping materials for stereolithography for example are getting into a range where their usability for MIM² technology is much improved.

Conclusion

The flexibility, rapidity and cost reduction that Mold in Mold technology allows open a new route for rapid tooling in metal injection molding. The method cuts the production time of prototype molds by a factor of five to ten and the cost by half compared to production tooling. It bring rapid tools as close to production tools as possible. Thanks to their high mechanical properties, the molds produced by the MIM² technology can be used as a preproduction tool bridging the gap between definitive design and production tooling availability. By reducing drastically the cost of quality tooling, they contribute to make small to middle size part production by injection molding economically feasible.

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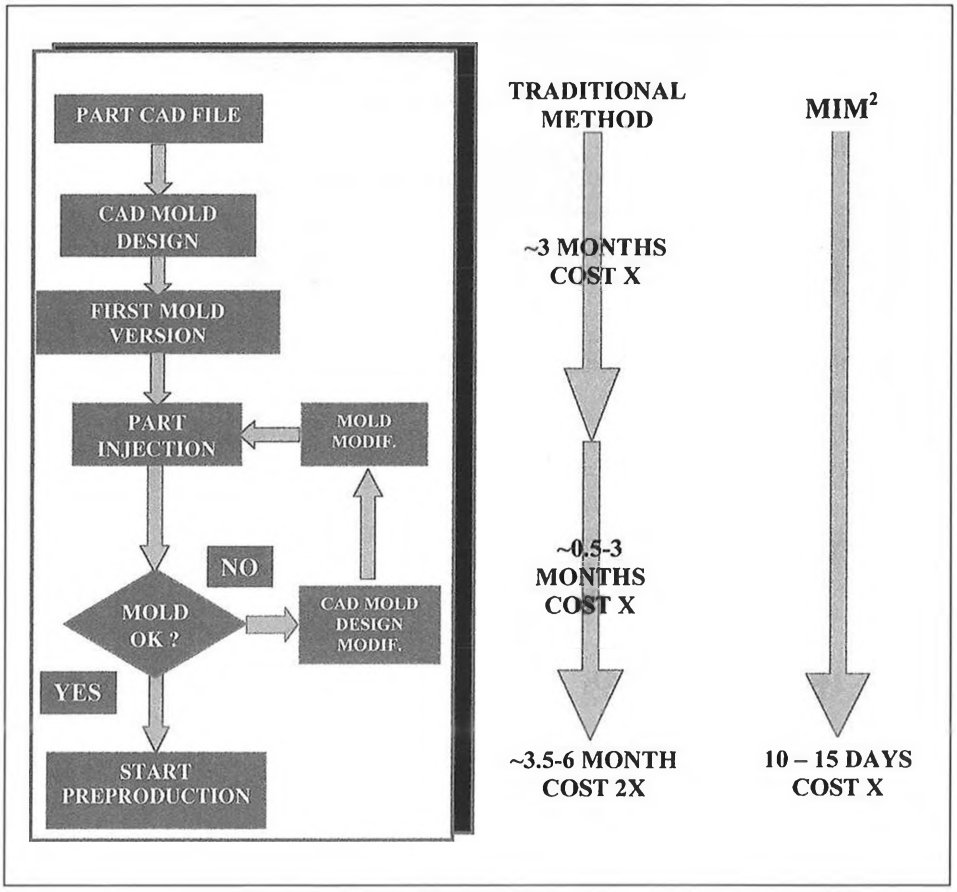

Fig. 4. Comparison of time and cost factors between the traditional method and the MIM² method of building molds

[1] Catamol Feedstock für Pulverspritzguss Technische Information, BASF AG.

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mireco
UMWELTBIOTECHNOLOGIE

Mireco Umweltbiotechnologie
Surface Catalysis for Wastewater Treatment

Nikolaus A.J.M. Gschwind*

Abstract: Mireco was founded as a spin-off company from Ciba-Geigy with the main activity in the field of wastewater treatment. Beside giving support in the optimal application of existing technologies, Mireco develops new procedures for the treatment of wastewater with refractory organics. Starting with the combination of surface catalysis and biodegradation, the work concentrates now on surface-catalyzed wet air oxidation.

Keywords: Surface-catalyzed wet oxidation · Wastewater treatment

Mireco was founded in 1993 as a spin-off company from Ciba-Geigy by a chemist/microbiologist and a microbiologist. The main purpose of this spin-off was the development of new methods for the treatment of wastewaters with refractory (*i.e.* non-biodegradable) organics. Beside the development work we offer support for the characterization of wastewaters, for the optimal choice of treatment combinations (biology, chemical and physical unit operations) to solve wastewater problems and for the optimization of existing treatment facilities. In the following, an overview of the results obtained so far in our development work is given.

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Surface Catalysis and Biodegradation

Laboratory work with the effluent from an extensive biological treatment showed that a substantial percentage of the refractory organics could be removed by biodegradation on catalytically active surfaces [1]. The enrichment of microorganisms for the biodegradation of individual refractory compounds was facilitated by the use of catalytically active surfaces as biofilm supports. Bacteria for the degradation of the herbicide Atrazin and the complexing agent EDTA were enriched [2][3]. Both compounds are of environmental concern and were found in surface water.

A full-scale treatment plant for removal of the refractory organics in a biologically purified landfill leachate was realized as an aerobic filter with a catalytically active filter material. Further work with more active catalysts, different wastewaters and individual refractory compounds showed that in many cases abiotic condensations mediated by molecular oxygen compete with biodegradation. The combination of surface catalysis and biodegradation can therefore not be generally applied for wastewater treatment.

Treatment of Wastewaters on Catalytically Active Surfaces at Elevated Temperatures (<100 °C)

The treatment with catalysts was used as a pretreatment before a biological treatment with the main purpose of increasing the percentage of biodegradable organics. Concentrated wastewaters from the manufacture of pulp, fine chemicals, or chemical intermediates were used for this development step. At temperatures between 80 and 90 °C and hydraulic retention times between 3 and 20 h, the amount of refractory organics could be reduced by 70–85% [4]. This reduction of refractory organics was associated with mineralization (formation of CO_2) to a small percentage only. The main mechanisms seemed to be fragmentation of refractory molecules into biodegradable fragments and condensation to non-soluble macromolecules. Wastewaters with compounds of reduced chemical re-

activity could not be treated with more than 50% reduction of the amount of refractory organic molecules.

Surface-Catalyzed Wet Oxidation

Highly refractory wastewaters from the manufacture of textile dyes and wastewater with sulfonated nitro-aromatics were chosen for further development. With appropriate catalysts, >50% of the refractory organics can be removed at temperatures between 100 and 150 °C and hydraulic retention times below 4 h. Air or oxygen are used as oxidants at a pressure of 5 bar. The organics removed are quantitatively transformed into CO_2. Further development concentrates on the improvement of treatment efficiency to >80% and the increase of catalyst life.

Outlook

The results so far obtained show that surface-catalyzed wet oxidation can be an efficient alternative for the treatment of wastewaters with refractory organics. The use of air as oxidant under relatively mild conditions allows operations at low running costs compared with alternative methods using oxygen, hydrogen peroxide, or ozone. Pilot studies will have to show that loss of catalyst activity has no prohibitive influence on running costs.

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[1] N. Gschwind, *gwf Wasser-Abwasser* **1992**, *133*, 331.
[2] C. Yanze Kontchou, N. Gschwind, *Appl. Environ. Microbiol.* **1994**, *60*, 4297.
[3] N. Gschwind, *gwf Wasser-Abwasser* **1992**, *133*, 546.
[4] N. Gschwind, *WLB Wasser, Luft und Boden* **1998**, *42*, 42.

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MODEX thérapeutiques

Modex thérapeutiques
A T3R Development Company (T3R: Tissue Repair, Replacement & Regeneration)

Jacques Essinger*

Abstract: Founded in 1996, Modex Therapeutics, a Swiss biotech company, focuses on developing technologies related to tissue repair, replacement and regeneration

Keywords: Development · Tissue repair regeneration & replacement

About Modex

Modex' aim is to realize the value potential of tissue repair, replacement and regeneration (T3R) technologies, by developing such technologies from an early stage through to a ROI-optimized mature stage.

Value is created in three successive steps. The first step consists of acquiring, in-licensing T3R technologies, seeking synergies with in-house technologies. The second step consists of developing such technologies using internal and ex-

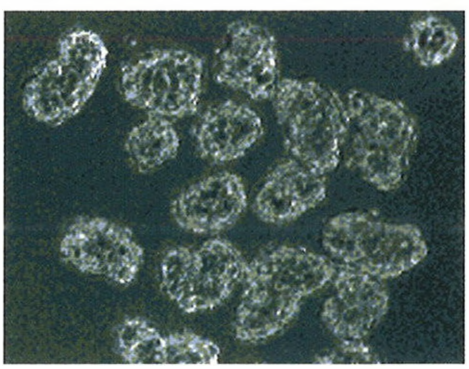

Fig. 1. Islet-like aggregated conditionally-immortalized beta cells

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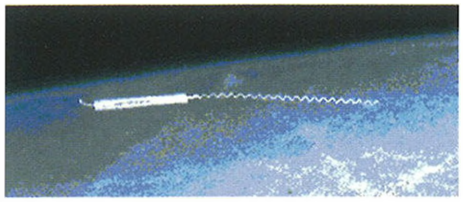

Fig. 2. Radiography of a 3 cm long device implanted below the skin

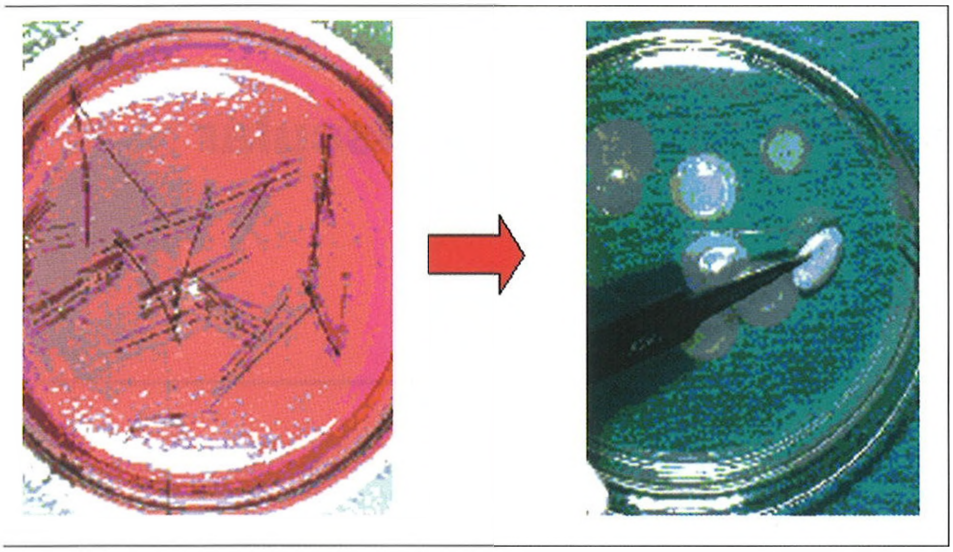

Fig. 3. From hair to skin in four weeks

ternal resources, by supplying scientific, management and business expertise. The development objectives may range from pre-clinical to market launch depending upon the technology. Finally the third step consists of realizing the added value, by licensing out or selling directly or indirectly the developed technology.

A Risk-Balanced Pipeline

Modex' current pipeline contains three T3R projects:

- Development of a diabetes Type I cell-based therapy
- Development of encapsulated cell-based protein delivery
- Development of a non-surgical autologous skin graft for the treatment of chronic wounds

Diabetes Type I

Modex' diabetes Type I project is based on the development of a conditionally-immortalized glucose regulated cell line, in-licensed on an exclusive basis from the Albert Einstein College of Medicine (New York) (Fig. 1). Proof of concept in small and large animals has been achieved. The objective is to bring this technology to a first clinical proof of efficacy.

Encapsulated Cell-Based Protein Delivery

The technology consists of cells containing hollow-fiber devices, designed to produce and deliver peptides or proteins *in vivo* on a continuous long-term basis (Fig. 2). In-licensed from a US biotechnology company for development outside the central nervous system (CNS), this technology is applicable to numerous clinical applications in the fields of infectious diseases, oncology, metabolic, endocrinology and others. A first clinical trial is planned in the field of chronic anemia.

Non-Surgical Autologous Skin Grafts

Initially developed at the University of Bern by Prof. T. Hunziker and Dr. A. Limat and validated in non-controlled clinical trials, the technology consists of producing autologous skin grafts from precursor cells isolated from the outer root sheath of the patient's hairs. About 100 hairs are required to produce fully differentiated epidermal equivalents to treat a 70 cm^2 ulcer (Fig. 3). Modex in-licensed the technology, finalized the product development, and is currently conducting an open multi-center comparative study to establish the product efficacy.

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MYOCONTRACT
Pharmaceutical Research Ltd.

MyoContract
Drug Discovery for Neuromuscular Diseases

Thomas Meier*

Abstract: MyoContract Pharmaceutical Research Ltd. is a University of Basel based pharmaceutical start-up company that focuses its research activities on the discovery and development of novel therapies for several neuromuscular disorders and general muscle wasting seen, for example, during prolonged hospitalization. Currently, MyoContract has launched drug discovery programs for Duchenne Muscular Dystrophy, a progressive and inherited form of muscle wasting, and Friedreich's Ataxia, a neurological disorder resulting from mitochondrial dysfunction. Together with national and international patient organizations and specialized research institutes and clinics, MyoContract forms a strategic alliance for drug discovery for the treatment of neuromuscular diseases and muscle wasting.

Keywords: Drug discovery · Neuromuscular diseases · Orphan drugs · Pharmaceuticals

More than 20 million Americans and probably an equal number of Europeans suffer from one of the 5000 rare diseases known today. Many of these diseases, like the neuromuscular disorders, are life-threatening disabilities often diagnosed already in childhood. Patients with Duchenne Muscular Dystrophy (DMD), for example, suffer from progressive muscle wasting that forces teenaged patients into wheelchairs and culminates in lethal respiratory or cardiac failure at age 20–25. Nevertheless, about 40 000 DMD patients in industrialized countries worldwide are confronted with a current lack of effective treatment strategies. Unfortunately, the majority of the rare diseases, such as the inherited neuromuscular diseases, are not in the focus of the leading pharmaceutical companies. Clearly, there is a gap between the patients' demands and the research and development (R&D) activities by the pharmaceutical industry in any of the orphan indications, despite the increasing publicity generated by alert patient organizations worldwide.

The reason for the unattractiveness of 'orphan drug development' as a business for 'big pharma' is quite obvious. Orphan drug development follows the same rules as major drug R&D: multi-million dollar investments for many years combined with a high risk of failure. But in contrast to the major drug indications, the return of investment (ROI) for a successful 'orphan drug candidate' is comparatively small due to a limited market size. Therefore, it is remarkable that about 85% of new drug applications for rare diseases filed in the US come from biotech companies, as reported by the FDA's Office of Orphan Products Development (see Figure). In fact, the 'orphan drug act' issued in the USA in 1983 encouraged R&D activities in this sector and can be credited with helping to establish the American biotech industry. With regard to the European health care industry, we might also expect our small biotech companies to become the major players in this pharmaceutical sector, especially if they are backed by European orphan drug legislation.

Biotech companies in the field of orphan drug development are confronted with several heavily limiting obstacles when it comes to the question of how to raise sufficient financial support. This holds particularly true for European orphan-drug oriented start-up companies. There is little experience in this field in Europe on both the investor and the biotech industry sides. In particular, early-stage drug R&D by biotech industry is in a rather unfavorable position to compete for venture capital (VC) investments, the 'classical fuel' for embryonic high-tech enterprises like MyoContract. However, once successful drug candidates are identified and ready for clinical trials, the 'orphan drug' status may actually become an advantage. In contrast to classic drugs,

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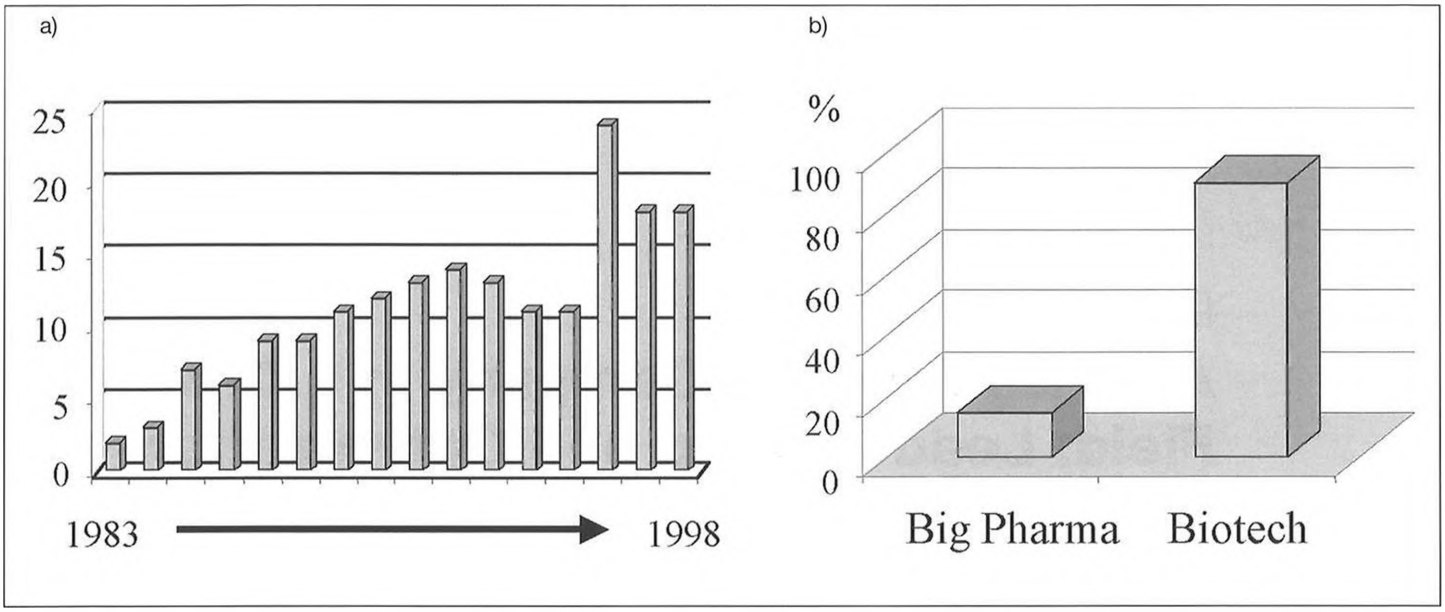

a) Annual distribution of orphan drugs approved by the Food & Drug Administration (FDA) in the USA between 1983 and 1998. The total number is 181. b) Up to 85% of all orphan drugs are currently developed by small- to medium-size biotech companies and only a small proportion by leading pharmaceutical industries. Source: US Food and Drug Administration, USA

comparatively short and therefore less expensive clinical trials are required for the registration of an orphan drug. This will allow VC investors to realize their return of investment within a shorter period of time. The question remains how to find seed-money to exploit breakthroughs of basic research into urgently needed orphan drugs? More precisely, how to finance early orphan-drug discovery programs of start-up companies like MyoContract?

An emerging model is the formation of strategic alliances between national and international patient organizations and the respective Medical Association with biotech companies (see also [1]). Such an alliance could easily fill the initial financial gap for focused industry-style R&D activities to meet the demands of patients with a specific orphan disease. In fact, in the future such a partnership may also enable specialized physicians to contribute to the clinical evaluation of drug candidates and to the improvement of therapy monitoring. In this case, the patient organization together with the specific Medical Association could even adopt the principles of VC investments themselves and provide the necessary seed capital for early-stage R&D activities. This would actually allow patient organizations to control to some extent the research programs of the partnering biotech company *via* their share capital. In case of success the ROI could be reinvested to support the patients and to improve the medical training or to finance additional drug research. Supporting such a promising model, the proposed European orphan drug regulations may become an important legislative framework that will further stimulate such collaborations in the future.

In January 2000, **MyoContract Pharmaceutical Research Ltd.** was formed as a successor company of MyoContract GmbH, which was founded at the University of Basel as a biotech start-up company in June 1998. Since then, MyoContract has launched a drug discovery program for rare neuromuscular disorders, such as Duchenne Muscular Dystrophy and Friedreich's Ataxia, as well as for more general muscle wasting seen in hospitalized patients and as a consequence of diseases such as cancer and AIDS.

The endeavor of MyoContract is to cost-efficiently complement the excellent University-based disease-specific research base with necessary generic key-platform technologies. Core activities are the establishment of molecular, biochemical, and cellular tools and assays that allow the identification of disease-relevant new chemical entities (NCEs) and their evaluation on cultured human cells, in particular using muscle cells. MyoContract expects to employ six scientists by the end of this year and up to twelve scientists (mainly biochemists and cell biologists) by 2002. The company already collaborates with the following biotech companies located in the 'BioValley': Discovery Technologies Ltd. in Allschwil (for large-scale drug compounds screening) and Neurofit S.A. in Strasbourg (for preclinical testing). Paired with senior management expertise from pharmaceutical industry and a world-class scientific advisory board, MyoContract is in a superb strategic position to swiftly implement a R&D program centered on the proof of concept for pharmaceutically active compounds for the treatment of neuromuscular diseases and muscle wasting. Following preclinical evaluation of drug candidates, MyoContract also plans to enter clinical trials with successful drug candidates and ultimately market novel therapies in collaborations with national and international patient organizations and specialized University hospitals and clinics.

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POLYPHOR
Your Partner for Lead Finding

Polyphor Ltd
A Swiss Start-up Company in a Growing Field: Lead Finding and Optimization

Philipp Ermert, Daniel Obrecht*, Jean-Pierre Obrecht*, and Klara Sekanina

Abstract: Polyphor Ltd was founded by Daniel and Jean-Pierre Obrecht in November 1996 and started operations at the Institute of Organic Chemistry of the University of Zürich. In October 1999 the company moved to the Innovation Center in Allschwil where 660 m^2 of new laboratory space was installed especially for parallel and combinatorial chemical synthesis. Polyphor is specialized in the synthesis of high-quality compound libraries for lead finding, validation and optimization using rapid parallel and combinatorial chemistry techniques. The company strives to become an important partner for chemical companies in the search for new products in the fields of pharmaceuticals, agrochemicals, polymers, dyes, cosmetics and catalysts.

Keywords: Lead finding, validation and optimization · Parallel and combinatorial chemistry · Pharmaceuticals and agrochemicals · Protein epitope mimetics · Solid-supported reagents and scavengers

1. Polyphor's History

Daniel and Jean-Pierre Obrecht, two former Roche employees, founded Polyphor Ltd in November 1996. Start of operations was in January 1997 at the Institute of Organic Chemistry of the University of Zürich, where Polyphor rented laboratory space in a scientifically stimulating environment with state-of-the-art infrastructure. Polyphor established early on favorable arrangements with the University to use *e.g.* spectroscopic services and thus avoid costly investments. In return Polyphor employees contribute to the training of students in Chemistry and Pharmacology with lectures and practical courses.

In October 1999 Polyphor moved their laboratories to the Innovation Center of Allschwil, where 660 m^2 of new laboratory space have been installed especially suited for parallel and combinatorial chemical synthesis. As there are options for expansion, the company has found here an ideal place for its further development. While having moved the major operations to Allschwil, Polyphor keeps one laboratory at the University dedicated especially to the Protein Epitope Mimetics (PEM) program which is a joint effort between Prof. Dr. J.A. Robinson's research group and Polyphor and funded partly by KTI.

Polyphor's staff currently comprises 13 highly qualified people with extensive academic and industrial experience in lead discovery and lead optimization; one half are Ph.D. chemists and one half are technicians.

Being chemistry driven, Polyphor serves customers in different fields: In the pharmaceutical sector Boehringer Ingelheim, Roche, Sanofi-synthélabo, Warner-Lambert and a small American biotech company, in agrochemistry AgrEvo and Novartis, in the cosmetics area Wella (hair-dyes) and Givaudan-Roure (flavors & fragrances).

In August 1999 in the course of a capital increase aimed at sustaining Polyphor's ongoing expansion, the Swiss company Bachem, the world leader in manufacturing peptides, took a 31% stake of the voting shares.

2. Introduction

Polyphor Ltd is a company that provides the chemical industry with high-quality compound libraries for lead finding, lead confirmation and optimization using the technologies of *parallel and combinatorial chemistry*. Although these technologies had their origins mainly in the pharmaceutical area, parallel and combinatorial approaches have found widespread applications also in agrochemistry, in the dye industry, flavors and fragrances, in the plastics and polymer industries and more recently in the search for new catalysts and new materials [1].

A common feature for the chemical industry is the fact that the time pressure for development of new products has dramatically increased. *Parallel and combi-*

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natorial chemistry is certainly seen as one of the major drivers to speed up the early phases of product identification and optimization. Polyphor strives with its products, technologies and services to become a major player in providing high-quality compound libraries for lead identification, confirmation and optimization.

3. Company Profile and Products

The early phases of the development of a new chemical product essentially always involves first *identification* followed by *confirmation* and *optimization*. All these steps often require simultaneous variation and optimization of several parameters that in the past has been a long and costly exercise. Parallel and combinatorial approaches are in many cases especially well suited for optimizing multi-parameter systems [2]. In Fig. 1 the different types of compound libraries that are involved in the pharmaceutical lead finding process are shown and serve to characterize Polyphor's products.
The main products comprise:

Focused and customized libraries of small molecules made exclusively for one customer
- Based on customer scaffolds
- Based on scaffolds developed by Polyphor (the Polyphor catalogue of core structures contains currently roughly 700 different scaffolds amenable to parallel synthesis and is available on CD-ROM).

The Polyphor non-exclusive library of small molecules for general and random screening
- Based on 56 highly diverse scaffolds developed by Polyphor. The 15 000 member library is currently synthesized. The structures can be viewed on CD-ROM.

The Protein Epitope Mimetics (PEM) library
- β-Hairpin library (cyclic peptides incorporating 4–12 amino acids and a conformationally stabilizing template) for the identification of hotspots in protein interfaces and validation of biological targets where protein–protein interactions are involved.

Functionalized polymers as reagents and scavengers for library synthesis
- The highly loaded polymer-bound reagents and scavengers developed by Polyphor are used for library synthesis in solution to facilitate work-up and purification. The resins are commercially available at Polyphor.

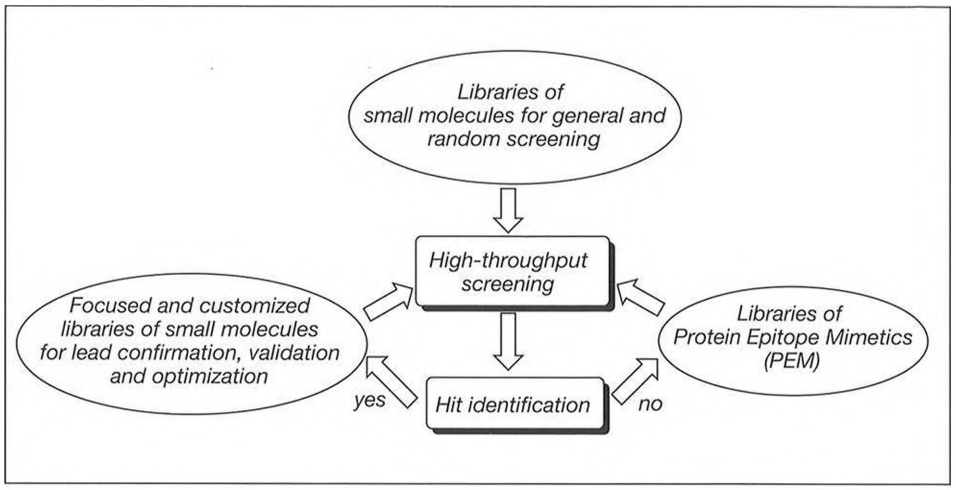


Fig. 1

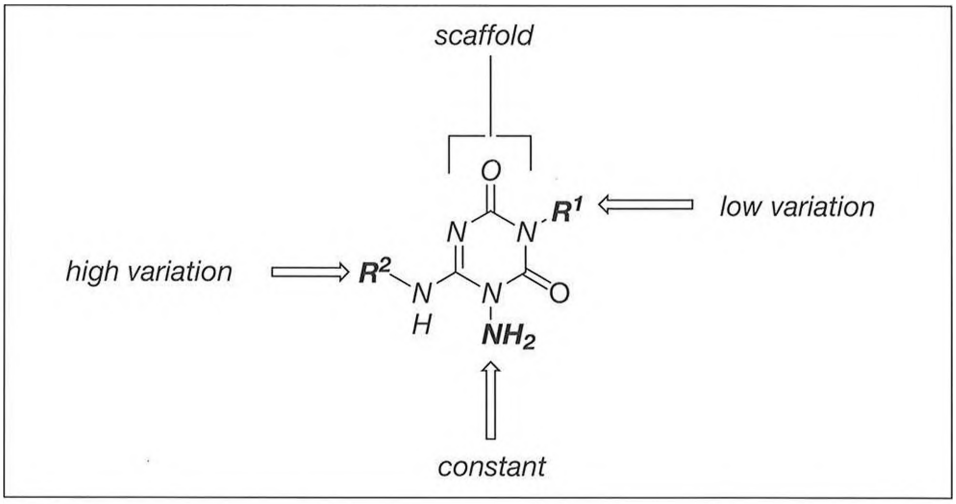


Fig. 2

3.1. *The Polyphor Non-Exclusive Library for General and Random Screening*

In general the lead identification process starts by screening large general or random libraries of preferably small molecules (MG <550) in order to find a hit (Fig. 1). Whereas a few years ago, cocktails of up to 20 compounds were screened as mixtures the trend has shifted towards screening *individual compounds* of good purity.

Polyphor synthesizes only single-compound libraries of good purity (>90%), confirmed structure (MS or NMR) and significant quantities (25 mg for focused libraries, 1–10 mg for general libraries). High-quality libraries offer the following advantages:
- Low false hit rate
- Possibility of long-term storage in compound depositories
- SAR possible
- Lower overall costs

Polyphor is currently building up a highly diverse, non-exclusive library of single small-molecular-weight compounds of high quality and purity for general screening. The library is based on 56 highly diverse scaffolds based on Polyphor's synthesis strategies and comprises roughly 15 000 compounds that are available on CD-ROM. On average, families of 250–300 compounds represent every scaffold. The molecules are based on a three-point pharmacophor model with one substituent being constant (a given functional group, H or a small substituent), one site of low variation and one site of high variation as shown schematically for one scaffold in Fig. 2.

The selection of the 56 scaffolds and the low and high variation substituents was based on the following criteria:
- MW<550; drug-like (following Lipinski's rule of 5)
- High diversity based on the spatial *positioning of the three exit vectors*

- Systematic distribution of *H-bond donors and acceptors* in the scaffolds and the attached substituents
- Systematic distribution of *heteroatoms* within the scaffolds
- Good representation of *lipophilic, polar (acidic and basic) functional groups* in the low and high variation substituents.

The Polyphor library shows a *high scaffold diversity* (based on the positioning of incorporated heteroatoms, H-bond donors, and acceptors) and is furthermore characterized by the fact that the *low and high variation substituents are kept constant* throughout the families which allows hits to be compared in different series. The advantages of the Polyphor library are the following:

- High quality (purity >90%; every compound characterized by MS or NMR)
- Rapid resynthesis of sublibraries for hit validation and optimization on an exclusive basis due to a well-established parallel synthesis approach
- Rapid resynthesis of larger quantities (up to 20 g)
- Customized format (1 mg, 5 mg, or 10 mg)

3.2. *Focused and Customized Libraries Made Exclusively for One Customer*

After a hit or several hits are found in a specific project, the hit confirmation and validation phases usually start by synthesizing focused compound libraries. If such a hit has been generated from a compound made by parallel or combinatorial techniques, this process can be speeded up. After a hit has been validated and turned into a lead compound, several properties have to be optimized by synthesizing more focused libraries. Moreover, such an approach allows several leads to be followed at the same time increasing considerably the chance for finding a development compound more quickly.

Polyphor has specialized in the *rapid synthesis of high-quality focused libraries* for *hit validation* and *lead optimization* using efficient parallel synthesis approaches and offers customers the possibility of outsourcing such programs. These programs can be based on:

- A core structure proposed by the customer
- A core structure based on Polyphor's catalogue of core structures which currently includes roughly 700 different scaffolds. These scaffolds are based on Polyphor's parallel synthesis strategies and can be viewed on CD-ROM

The compounds are designed jointly by the customer and Polyphor and are synthesized exclusively for one customer. The characteristics of these focused libraries are the following:

- 25–50 mg per compound (fixed in advance)
- High quality (purity >90%; every compound characterized by MS or NMR)
- Customized delivery
- Transfer of analytical data possible
- Resynthesis of larger quantities guaranteed
- Resynthesis of sublibraries guaranteed
- Transfer of generic synthetic procedures
- Simple and straightforward payment conditions

3.3. *The Protein Epitope Mimetics (PEM) Library*

An increasing number of biological targets do not yield a small molecule hit in the primary screening even when very large libraries are screened. These targets typically involve large-surface protein–protein interactions [3]. With the advent of genomics it is believed that some 25 000 new targets [3][4] will emerge and many of those will involve surface interactions. Polyphor, in a joint effort with Prof. Dr. J. A. Robinson, embarked in a research program aimed at finding molecules that can interact with these targets. Protein Epitope Mimetics are small template-fixed cyclic peptides of well-defined conformations mimicking the relevant surface areas of protein binding. It has been shown that β-hairpin mimetics [3][5] are especially well suited for this purpose as they are composed of two rather flat surfaces lying opposite to each other joined by a turn-like region as schematically shown in Fig. 3. The templates have been designed to stabilize the β-hairpin conformations [3][5].

The PEM project is partly funded by KTI and has the purpose of synthesizing roughly 10 000 cyclic β-hairpin mimetics incorporating key sequences known for their capability to bind specifically to receptors [3]. Several disulfide-bridged nat-

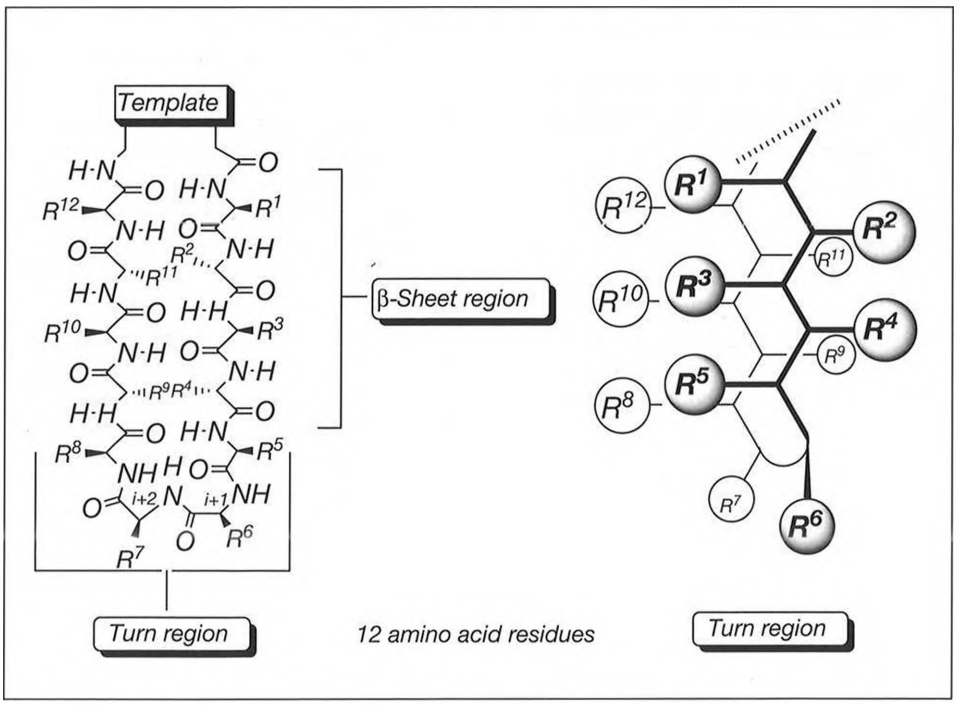


Fig. 3. Representation of β-hairpin mimetics

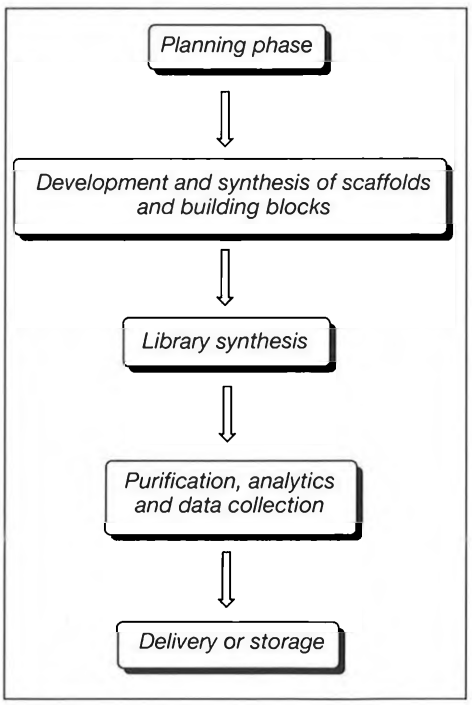


Fig. 4

urally occurring cyclic peptides with β-airpin conformations such as T22-polyphemusin II [6] and derivatives of α-defensins [7] show interesting biological activities as *chemokine CXCR4-antagonists* and *antibacterial agents* underscoring the validity of our approach. Polyphor and the University of Zürich have filed a patent covering the PEM technology.

The unique features of this library are the following:

- Conformational scanning of key sequences
- Detection of hotspots [8]
- 3D information of spatial arrangement of key amino acid residues available
- Design of small molecules based on this information
- Biological validation of targets involving large surface interactions.

4. Technology

Polyphor has specialized in the synthesis of *high-quality compound libraries* using rapid parallel and combinatorial synthesis approaches. The different steps involved in such a program are shown schematically in Fig. 4.

The synthetic techniques and robotic systems applied to a given project depend largely on the following parameters:

- Timeframe of the project
- Physicochemical properties of the final compounds
- Number of compounds

For the synthesis of focused libraries used for hit confirmation and validation and for lead optimization, the average number of compounds per library ranges between 100–1000 compounds with a timeframe for delivery ranging from 2 to 6 months. From experience, the phases of planning, and development and synthesis of scaffolds and building blocks (Fig. 4) usually take 50% of the project timeframe. In these phases Polyphor uses parallel approaches for process development and building block synthesis. For the actual library synthesis Polyphor uses mainly the following two strategies:

- Parallel library synthesis *in solution* using *polymer-bound reagents and scavengers* to ease work-up and purification procedures, followed by rapid parallel flash chromatography, with the advantages of short development time and essentially the whole repertoire of reactions available.
- Parallel library synthesis using a *mixed solution-solid phase strategy*. The synthesis of the scaffolds is usually performed in solution whereas library synthesis occurs on solid support involving typically two to three steps including the release of compounds. The strategy is especially valuable for the synthesis of libraries containing polar functional groups such as carboxylic acids, hydroxamic acids, amines, amidines and guanidines and has the advantage of easy purification of very polar compounds.

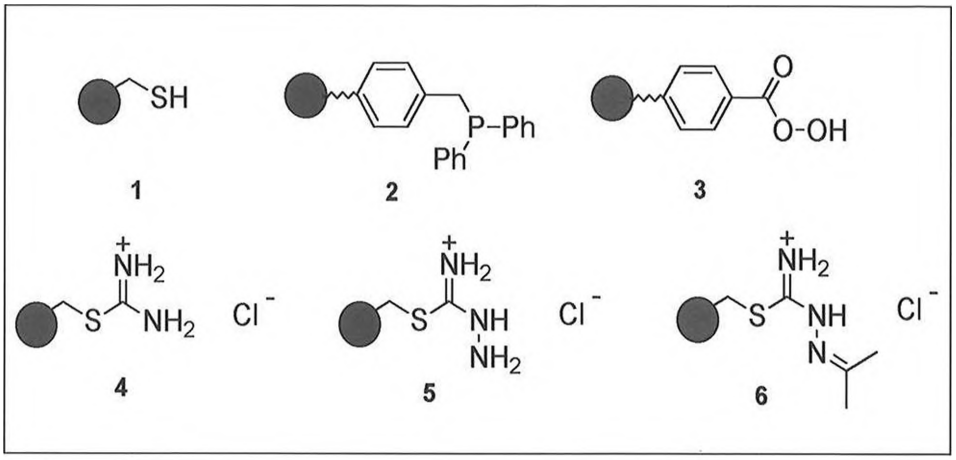
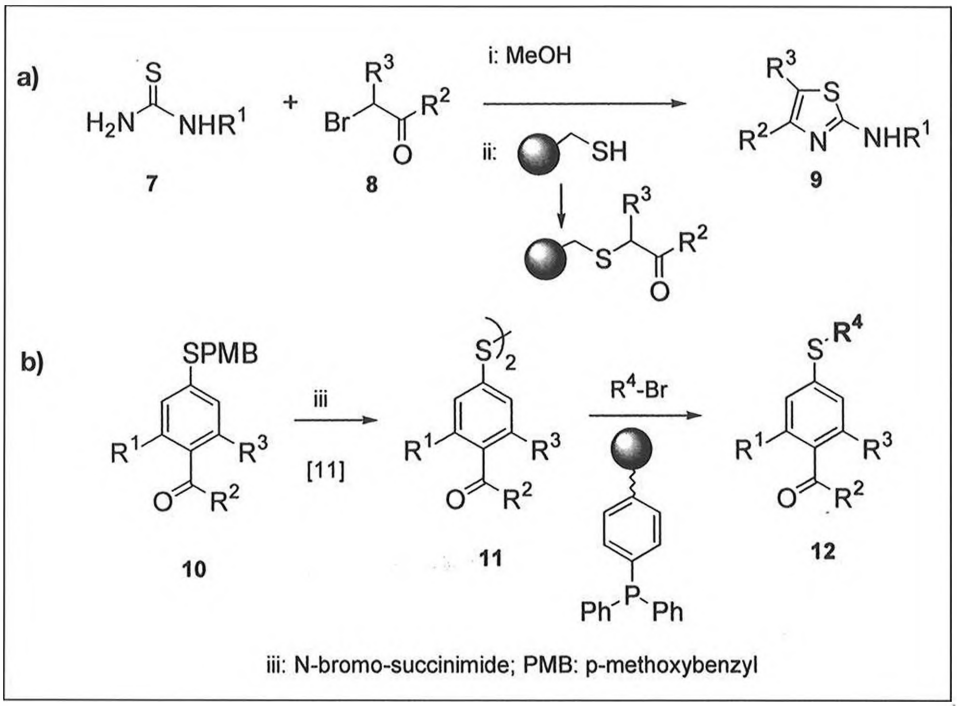


Fig. 5

Scheme 1



In order to achieve the stringent time lines Polyphor uses highly flexible 24 array semi-robotic workstations amenable both to solution- and solid-phase synthesis. For the PEM project Polyphor co-developed a fully automated mixed solution–solid phase process performed on two 96 array robots with Prof. Dr. J. A. Robinson's research group at the University of Zürich.

5. Applications

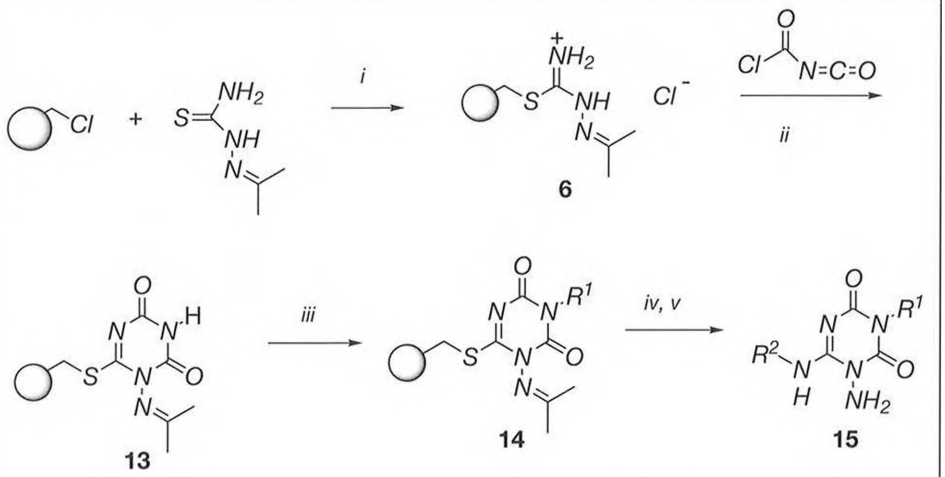
5.1. *Parallel Solution-Phase Synthesis Using Polymer-Bound Scavengers and Reagents*

In order to minimize the effort of work-up and purification procedures in library synthesis, Polyphor has developed a number of polymer-bound reagents, scavengers and novel linker strategies [1]. These polystyrene-derived polymers show the following characteristics:

- High loading (typically 2–3 mmol/g)
- Loading validated by chemical assay (loading based on *reactive* functional groups)

High loading has proven especially valuable for the reactivity of polymer-bound reagents and scavengers. Some typical examples are shown in Fig. 5.

Scheme 2



i: Dioxane, heat; ii: DCM, DIPEA; iii: KOBu^t, DMA, R^1X; iv: p-TsOH, MeOH; v: R^2NH_2, dioxane.

The polymer-bound reagents and scavengers of type **1**, **4**–**6** (Fig. 5) in combination with reactive building blocks such as acetylenic ketones [3][9], α-bromomethylketones [9], 2-azido-benzoic acids [9][10], 2-fluoro-nitrobenzenes and others form the base of Polyphor's capacity to synthesize a multitude of scaffolds from common building blocks ('combinatorics of reactive building blocks'[1]). In Scheme 1 two recent applications of the use of polymer-bound reagents and scavengers are shown.

In entry **a**) a parallel approach towards 2-amino-thiazoles **9** [9] is shown starting from thioureas **7** and bromo-methylketones **8** (Hantzsch synthesis) using a highly loaded thiol-resin to capture excess **8**. Entry **b**) shows the use of a polymer-bound phosphine to initiate reductive disulfide cleavage of **11** and reaction with R^4-Br to yield products **12** in excellent yield after simple filtration of the resin [11].

5.2. *Solid-Phase Synthesis of Heterocycles Using a Sulfur-Based Linker*

Heterocycles play a dominant role in drug discovery. Polyphor has developed several methods for the solid-phase synthesis of heterocycles based on a novel sulfur linker strategy [12]. A recent application towards the synthesis of 1-amino-triazinones **15** is shown in Scheme 2.

Protected thiosemicarbazide was reacted with chloromethyl-polystyrene to yield **6** as a key precursor that was reacted with chlorocarbonylisocyanate to give **13** in a ring-forming reaction. Partitioning of the resin in 24 reaction vessels and alkylation with several reagents R^1-X gave intermediates **14**, which after deprotection and multidirectional resin cleavage with different amines gave the final amino-triazinones **15** in high yield and purities. Similar strategies have been used for the synthesis of pyrimidines [1][3][12], triazines, benzimidazoles and others and serve to highlight Polyphor's synthetic strategies.

6. Outlook

The field of application of parallel and combinatorial chemistry is by no means limited to the pharmaceutical industry as recent applications coming from agrochemistry, dye and polymer chemistry, hair-care industry, and flavors and fragrance companies have shown. Collaborations in the field of combinatorial chemistry have significantly increased over the last five years and it has been argued that some 4.1 billion US dollars will be spent on combinatorial chemistry by 2002 and that 45% of that research will be outsourced [4]. Polyphor strives to become an important partner for chemical companies in the field of discovery of novel products using parallel and combinatorial techniques.

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Prionics AG
Ahead of the Competition in Diagnosing BSE

Markus Moser* and Bruno Oesch

Abstract: In 1999, after 13 years of BSE crisis, Switzerland was the first country to introduce an active surveillance program by screening cattle for BSE infection with a diagnostic BSE test. This program is based on the application of 'Prionics-Check', a BSE test developed by the University spin-off company Prionics AG. Since its incorporation in 1997 Prionics has established itself as a leader in prion diagnostics. Future R&D projects are focused on the development of novel diagnostic and therapeutic strategies for prion diseases and other neurological disorders in animals and humans.

Keywords: Diagnostics · Neurology · Prionics · Prions

BSE (Mad Cow Disease) became a major health concern in Europe when the British Authorities informed the public in spring 1996 of new scientific findings suggesting that the deadly disease can be transmitted to humans. The BSE Advisory Committee of the European Commission urged the development of diagnostic BSE tests as a tool to monitor and fight Mad Cow disease. At that time no suitable BSE test was available despite years of intensive research.

In summer 1996, a research program for the development of a BSE test was launched at the University of Zürich. The project was founded by a special program of the Swiss National Science Foundation devoted to boost applied research in Switzerland. The research was carried out by Dr. Bruno Oesch as project leader, Dr. Carsten Korth, and Dr. Markus Moser. Within only a few months, they succeeded in developing a prototype of a working BSE test.

The three University researchers were faced with the usual choices: leaving the further development and commercialization to an industrial partner or founding a spin-off enterprise by themselves. After a short feasibility study, the three scientists took the second choice and founded the company Prionics AG. The name Prionics comes from 'prion', the infectious agent causing prion diseases such as BSE in cattle, scrapie in sheep, and CJD (Creutzfeldt Jakob Disease) in humans.

Founding Prionics AG was not without obstacles: The legal aspects of the technology transfer from the University to the spin-off company had to be sorted out and suitable investors had to be found. This all happened at a time when the foundation of spin-offs was something new to Swiss Universities and when no experienced technology-transfer consultants were available. And as the foundation of biotech start-up companies in general was a rare event in Switzerland, venture capitalists or other investors were not used to invest in Swiss start-ups but rather allocated their assets overseas.

The first steps in the formation of Prionics was the creation of an extensive business plan and talks with potential investors. After two months it was clear that the start-up capital could be supplied by interested private investors. The negotiations with the Department of Education of the Canton of Zürich regarding the legal aspects of the technology transfer proved to be more tedious than the search for the start-up capital. In 1996, there was no standard procedure for technology transfer from the University to spin-offs or start-ups. Therefore, the process, which involved three institutions, the University of Zürich, the Canton of Zürich and the Swiss National Science Foundation, took many months. Prionics was finally incorporated in February 1997, based on a letter of intention of the Canton of Zürich granting to the company the exclusive rights for the BSE test. A formal agreement for the technology transfer was reached after the foundation of the company.

During 1997, the 'Prionics-Check' BSE test went through several rounds of practical field testing and optimization. Finally the test was subjected to a thorough validation by the Swiss Federal Veterinary Office. Pilot studies carried out in

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Table: Effects of the active BSE-surveillance system using Prionics-Check: Increased discipline of mandatory reporting in 1999 revealed 25 BSE cases, compared to 14 in 1998. Screening for BSE using Prionics-Check was 15 to 80 times more efficient than even the improved mandatory reporting.

Type of surveillance	Swiss dairy cow population	Total (year)	Tested in 1999	BSE	Observed Prevalence	Efficiency Factor
Mandatory reporting	Total cow population older than 24 months of age	901 000		25	0.00003	1
Prionics-Check	Cows older than 24 months disposed as fallen stock	7176	7176	16	0.00223	80
	Cows older than 24 months presented for emergency slaughter	3578	3578	6	0.00167	60
	Cows older than 24 months slaughtered each year	200 000	7138	3	0.00042	15

(Adapted from Doherr *et al.*, *Veterinary Record* **1999**, *145*, 672)

1998 demonstrated that the test can easily be integrated into the normal slaughtering process of an abattoir and that it is effective under field conditions in detecting BSE-infected cattle which show no or no obvious disease symptoms. Since then, the test has been used by the Swiss officials for active BSE surveillance and has enabled the identification of a much higher number of BSE-infected cattle than before. The surveillance system also had the positive side effect of increasing discipline in mandatory reporting of suspect BSE cases by farmers and veterinarians (Table).

The Swiss BSE Surveillance Program is unique in the world and has gained wide recognition especially in the EU member states. In order to establish similar surveillance systems in the EU, the European Commission has recently evaluated several BSE tests. Prionics-Check was the only one of three approved tests which passed the evaluation without showing technical problems and which exhibited an 100% accuracy in distinguishing between normal cattle and clinical BSE cases without the need for retesting.

The test is now also used by several Swiss meat producers to remove apparently healthy but BSE-infected animals, recognized by high prion titers, from entering the food chain. By implementing Prionics-Check, these butchers successfully regained consumer confidence and consequently increased their sales.

Already at the time of its foundation, Prionics diversified its R&D portfolio towards the development of novel diagnostic and therapeutic strategies for prion diseases. In order to mobilize additional funds for its R&D projects, Prionics carried out a very successful private placement in 1999: The share values have increased by a factor of ten since the incorporation of the company. Prionics has steadily increased its staff from the three founder scientists to a present staff of sixteen. Driven by the success story of Prionics, competitors have also entered the field of prion diagnostics. However, thanks to its vast prion expertise and its innovative R&D portfolio, Prionics is destined to stay ahead.

More information on prion diseases and on Prionics is available on the internet: *http://www.prionics.ch/*

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PROVISCO Ltd.
Your Innovative and Reliable Partner for Thickeners and Stabilizers in the Food Industry

Urs M. Domeisen*

Abstract: PROVISCO Ltd. is a producer of guar and locust bean gum (from *Cyamopsis tetragonolobus* and *Ceratonia Siliqua*) with well-defined characteristics such as i) rheological behavior (degraded, low viscosity and high viscosity products), ii) flow properties (granulated products, products with defined particle size distribution), iii) excellent microbiological properties (very low contamination due to hot alcohol extraction). These products are used in the food and pharmaceutical industry for a broad range of applications.

Keywords: Depolymerization · Galactomannan · Pharmaceutical grade · Stabilizers · Thickeners

'ROVISCO Ltd was founded in 1994 as ı producer of food thickeners and stabi-izers. PROVISCO maintains their own ›roduction facilities, pilot plant and QC aboratory, employing twelve qualified ›ersons, in Hauptwil/Canton Thurgau.

Most of the products are based on wa-er-soluble, natural polymers. These are ıatural vegetable gums which come from ources such as seeds (guar, carob bean ;um, cassia, tara, tamarind), plant exu-lates (gum arabic, karaya, tragacanth, ;hatti), plant tissues (pectin, starch, cel-ulose), marine plants (alginate, carrag-enan, agar) and biopolymers (xanthan, ;ellan, pullulan, curdlan). They may be ›lended with other hydrocolloids or food ngredients such as fats or emulsifiers.

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The two main raw materials processed by PROVISCO are guar gum and locust bean gum. Guar gum is obtained from the endosperm of the guar plant (*Cyamopsis tetragonolobus* Lin.) seed. It is a galactomannan, a polysaccharide consisting of a straight chain of D-mannopyranose units joined by β-(1 -4) linkages with a side branching unit of a single α-D-galactopyranose unit joined to every second mannose unit. The raw material is a white to yellowish powder, with a slight odor, and is soluble in hot/cold water. An average quality guar gum contains about 80% galactomannan, 12% water, 5% protein, 2% acid insoluble residue or crude fiber, 0.7% ash, 0.7% fat.

The guar plant has a long history on the Indian subcontinent, where it is an important source of nutrition for animals and humans. It is extremely drought-resistant and grows in semi-arid regions where most other plants perish (India, Pakistan). Guar is the most commonly used natural gum due to its cost-effective thickening. It exhibits synergy with xanthan gum. The gum has a long list of applications in the food industry: stabilizer for dairy food, emulsifier of salts in bakery and baking mixes, cereal stabilizer, cheese/dairy/frozen dessert stabilizer, firming agent in fats and oils, thickener in gravies and sauces, stabilizer in jams and jellies, stabilizer/thickener in processed vegetables and vegetable juices, soups and soup mixes, toppings and syrups, and many other food categories including pet food.

Locust bean gum (LBG or carob bean gum; CBG) is a natural seed gum produced from the fruit of the carob tree (*Ceratonia siliqua* Lin.). The carob bean has been known since biblical times as a source of nutrition. LBG, like guar gum, is a galactomannan. The ratio of mannose/galactose is about 1/4. Prime growing regions for the carob tree include southern Italy, Greece, Spain, Portugal, Morocco, Israel, Turkey and Algeria.

Standard LBG requires heating to 85 °C in order to achieve full viscosity. LBG exhibits synergy with xanthan gum, carrageenan and agar. It can be used with many other hydrocolloids in order to modify the texture of a particular application. It is a highly functional stabilizer and thickener, which imparts a uniquely creamy texture. It is commonly used in

dairy products, such as ice cream (to prevent whey-off); jams, jellies and cream cheese (to improve spreadability), as well as desserts and pet food.

Galactomannanes exhibit pseudoplastic flow behavior, whereby viscosity decreases with shear. Shear thinning is a result of orientation of the extended molecules under the shear gradient – the molecules align themselves parallel to the direction flow. When the speed of the shear increases with respect to the speed of re-entanglement the viscosity falls, but as the shear stops, the original viscosity recovers (Fig. 1).

The wide range of the possible use of thickeners and stabilizers in the food industry requires a broad range of products with different characteristics. Some of the attributes of these products include controlled viscosity, controlled phase separation, prevention of syneresis (watering out), extension of shelf-life, addition of mouth-feel, retardation of crystal growth, suspension of particulate matter, formation of gels, enhancement of spreadability, and creation of formed foods, *etc.*

The quality of unmodified products is often not sufficient to meet all the requirements; the native thickeners have to be modified. PROVISCO prepares a whole range of food-grade tailor-made products with desired rheological properties *i.e.* special, required, even extra-low viscosity (carefully hydrolyzed and depolymerized products with a defined molecular mass and molecular mass distribution), products with very low microbial content (pharmaceutical grade products from selected raw materials and by hot alcohol treatment), non-dusting products and products with special dispersibility and swelling properties, products with minimal lump formation during swelling (by granulation and aggregation to products with defined particle size distribution; defined mesh size, see for example Fig. 2), and odorless/tasteless products (due to washing and extraction with hot alcohol).

Our stabilizers are carefully controlled blends of various food ingredients. They are extremely cost efficient (usually used at levels lower than 1%, and often at levels of less than 0.01%). Although the cost per pound may appear high compared with other stabilizers such as starch or gelatin, the actual use in the product can greatly reduce your cost of formulation.

We look forward to assist you in improving your formulation with our specialty grades or let us take care of your supply needs regarding guar or any other hydrocolloid. You can contact us by telephone, fax, mail, or e-mail.

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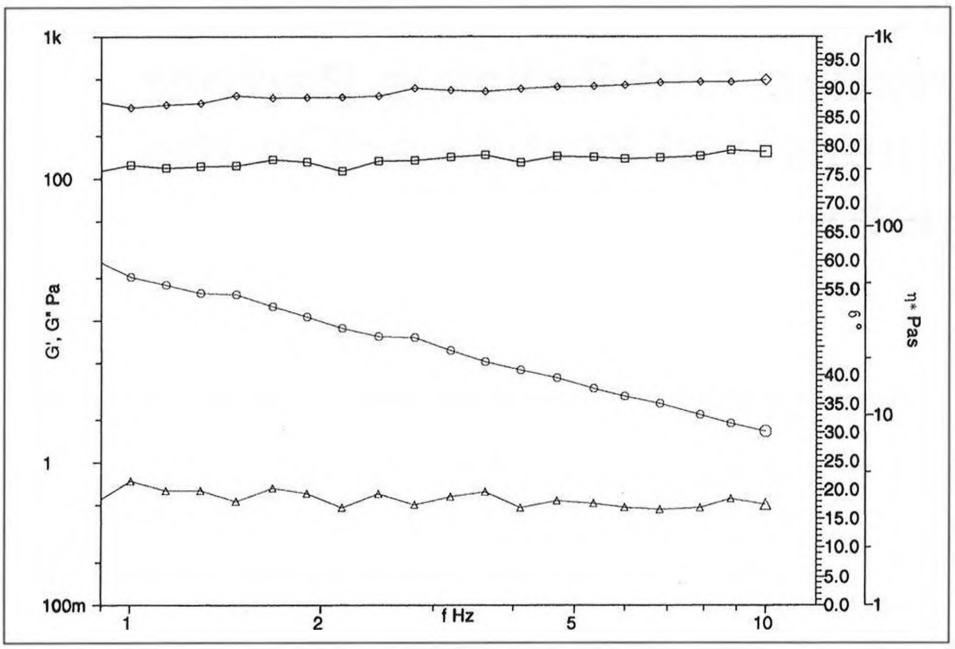

Fig. 1. Typical rheological behavior of PROVIGEL EDG, 4% in H_2O at 23 °C, measured by an oscillation experiment with Bohlin CVO 120 HR in the linear viscoelastic region. G# = storage modulus [Pa], G## = loss modulus [Pa], γ^* = complex viscosity [Pa.s] ($\gamma^* = \gamma' + i.\ \gamma''$ and $\gamma' = G^{\#}/\omega\ \gamma'' = G^{\#\#}/\omega$), δ = phase angle [°] (tan $\delta = G^{\#\#}/G^{\#}$). The order of the curves is, from top to bottom: G#, G##, γ^*, δ

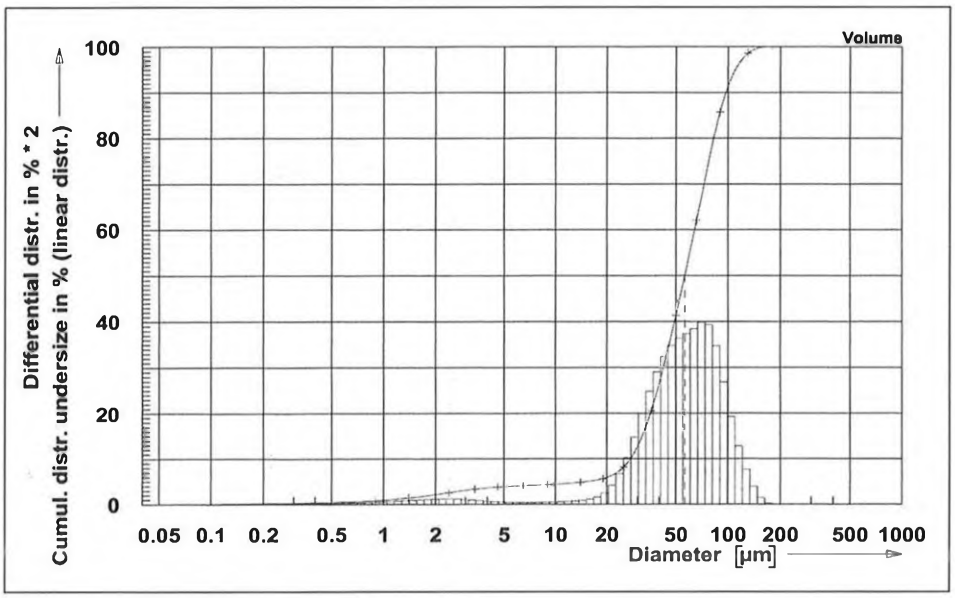

Fig. 2. Particle size distribution of PROVIGEL EDG measured by CILAS 1064. Laser Diffraction Particle Size Analysis is based upon the MIE theory and its Fraunhofer approximation. Each elementary particle of a sample will diffract light, when illuminated by a monochromatic laser beam. For all particles of the sample, the total diffraction is the linear combination of the diffracted intensities. The deconvolution of the pattern and a matrix algorithm will very quickly give the particle size distribution. CILAS 1064's range is 0.04–500 µm.

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PS Prozesstechnik GmbH

PS Prozesstechnik GmbH
Membrane Processes for the Chemical and Pharmaceutical Industry and Optimization of Particulate Processes by Lasentec FBRM

Peter Schirg* and Patrick Wissler

Abstract: PS Prozesstechnik GmbH started operations in January 1997. Lab and pilot facilities are situated on the Novartis Klybeck site in Basel. We are developing membrane processes to customer requirements from the first inception to the operational plant. We have many years of experience with processes such as reverse osmosis, nano-, ultra-, and microfiltration, pervaporation and special membrane processes. Applications are in production and effluent recycling, especially in the chemical and pharmaceutical industry. Our second product is the application of Lasentec FBRM – in-process particle size measurement probes for optimization and control of crystallization, granulation and emulsion processes.

Keywords: Crystallization · Membrane technology · Nanofiltration · Particle size · Reverse osmosis

1. Introduction

PS Prozesstechnik GmbH started operations in January 1997 as a spin-off from the former central process development group of Ciba-Geigy (IVT). The start-up was supported especially with equipment for a membrane process development lab and pilot. We are situated on the Novartis Klybeck site in Basel (Fig. 1 and 2). Our customers are chemical companies such as BASF, Ciba, Fraunhofer Gesellschaft, Hoechst/Axiva, Novartis, and Roche. Our two fields of activity are development of membrane processes to customer requirements and development of in-

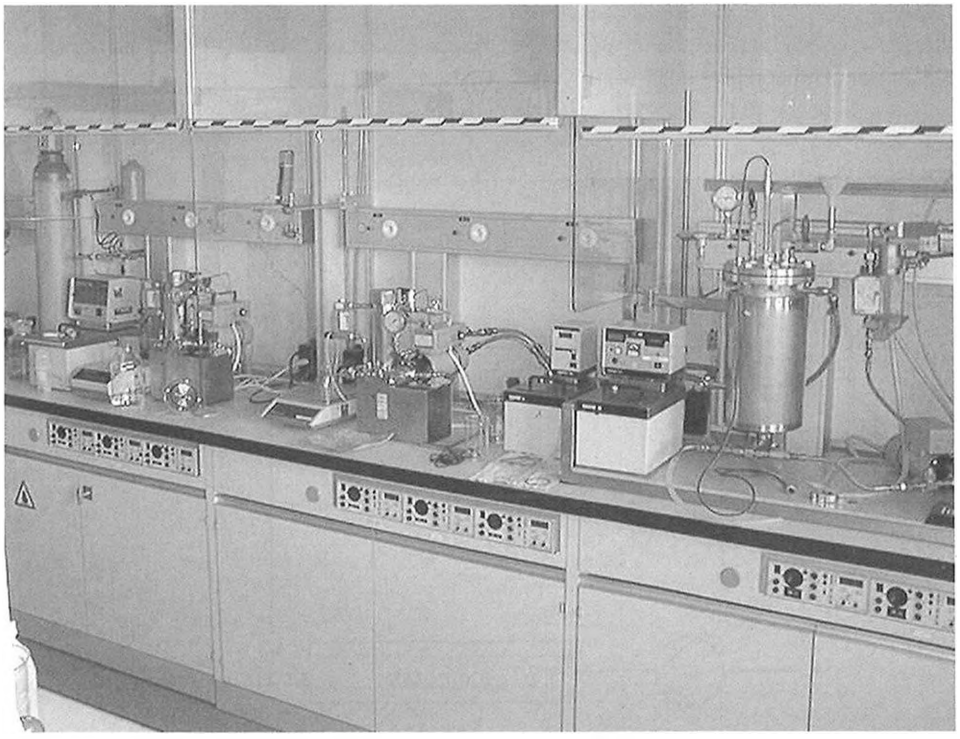

Fig. 1. Membrane process test units

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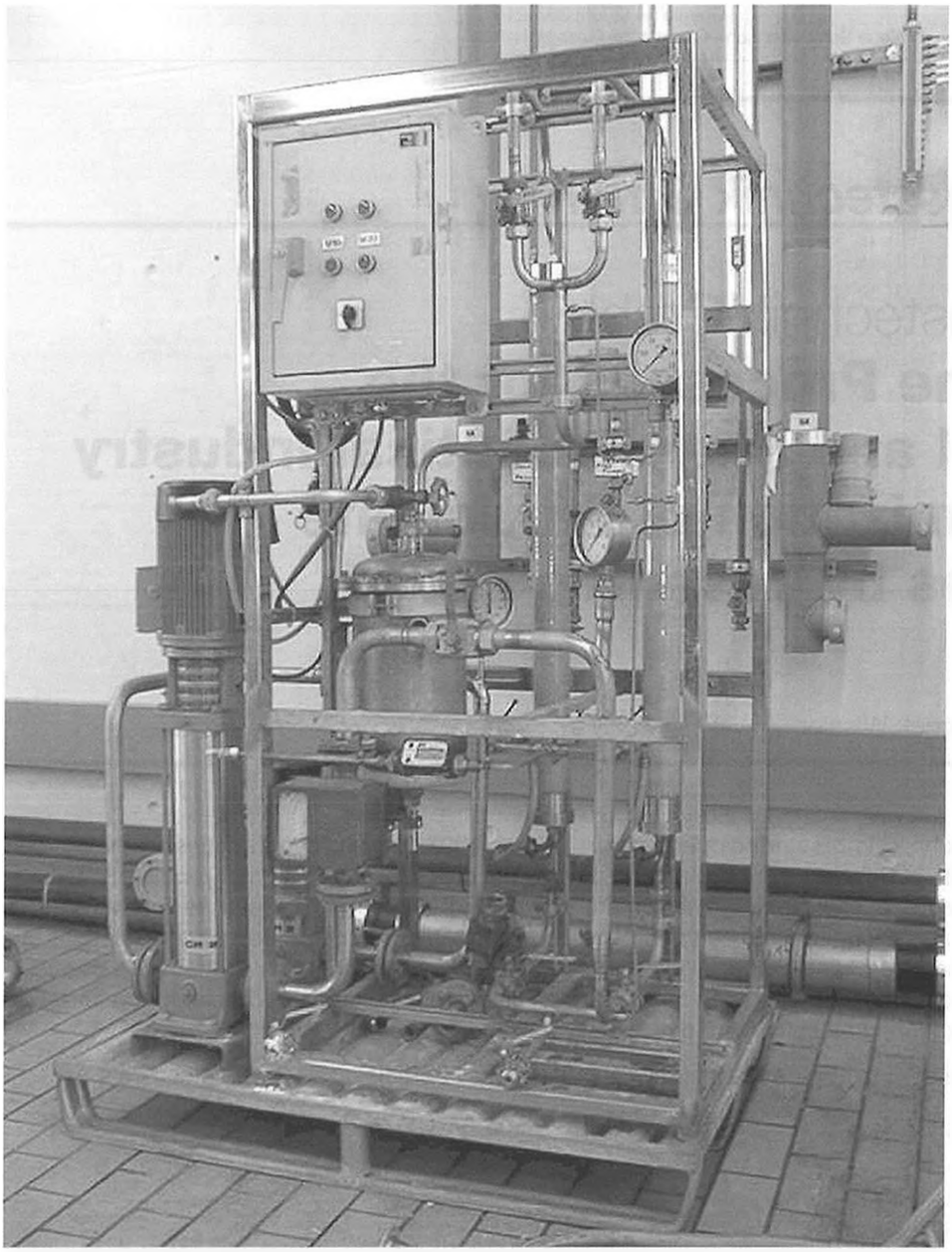

Fig. 2. Nanofiltration pilot unit

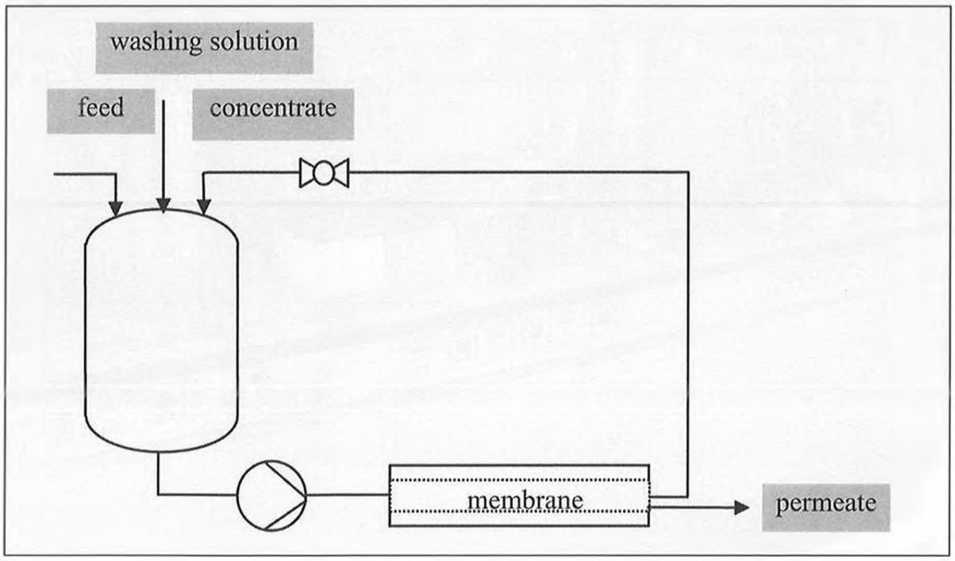

Fig. 3. Membrane process principle (batch)

process particle size measurement applications with Lasentec FBRM.

Our customers are focused on innovation, speed and flexibility and the need to minimize the fixed costs. They are specialized in their core business and involve external specialists when required. PS Prozesstechnik GmbH has many years of practical experience in process engineering and especially membrane technology at its disposal.

Already at the first customer request we can give answers on feasibility and costs. Quick lab tests confirm feasibility, piloting delivers long-term experience data for precise scale-up.

2. Membrane Technology

Membrane technology has progressed from water desalination to process applications over the last two decades. The working principle for batch mode is shown in Fig. 3: feed solution is pumped in crossflow through a membrane module. It is separated in a permeate stream and a retentate stream of different composition depending on the choice of the membrane. Washing solution can be added to the batch to remove lower molecular weight components (diafiltration). The end concentration of product in the feed tank can be 100 times the starting concentration.

The reasons for the increasing use of membrane processes in the chemical and pharmaceutical industry are their broad fields of applications and specific advantages (Table 1). Table 2 lists the ways in which we can ensure advantage is taken quickly of membrane processes.

Table 1. Membrane processes: applications and advantages

Fields of application

- Micro-, ultra-, nanofiltration, reverse osmosis pervaporation, electrodialysis, gas permeation
- Concentrating, cleaning and separation of products in water- and solvent based systems
- Chemical and pharmaceutical production
- Wastewater and air

Advantages

- Modular design
- Closed, sanitary process
- Low energy consumption
- Low operating temperatures for sensitive products
- Total automation including CIP

Three examples of our projects illustrate how membrane technology can help you to make new or higher purity products or decrease your production costs.

Example 1: Closing the loop in extraction. We developed a three-staged membrane plant for separating 30 m^3/day of an alcoholic extraction solution which up to now has been expensive waste (Fig. 4). The plant recovers up to 80% of the total amount for reuse in the extraction. Thus waste is reduced to 20%. Not only are incineration costs dramatically reduced but also valuable raw material is recovered. The plant has been operational since the end of last year and has a very short pay back (membrane rack see Fig. 5).

Example 2: An even shorter pay back is achieved by a *reverse osmosis process to recover a valuable pharmaceutical intermediate from an effluent stream* which had to be treated as waste beforehand. In this example again costs are saved by recovering raw material (up to several 1000 CHF/kg) and eliminating a waste problem. A cost comparison for 1 m^3 of an aqueous waste stream is given in Table 3.

Example 3: We have extensively tested *solvent-stable nanofiltration* membranes for concentrating organic compounds of MW >500. We can offer this process for concentrating a product, reducing a waste stream and gaining a clean permeate *for any solvent*.

Three further examples are given in Table 4.

3. In-Process Measurement of Particle Count and Particle Geometry (Lasentec® FBRM® and PVM®)

In many chemical and pharmaceutical processes, particle shape and dimensions and their change over time have a strong influence on batch time and product quality. Because it is a direct in-process measurement, FBRM can be used to dynamically quantify and control the effect of process variables (temperature, addition rates, residence time, mixing speed, *etc.*) on a particulate system as well as quantify the effect of the particulate system on downstream performance (separation, reactivity, dispersability, *etc.*). The FBRM signal can be correlated directly with any upstream or downstream

Table 2. Our services and equipment

Our services	Our equipment
– Customer consulting independent of membrane supplier – Lab tests – Process development – Piloting – Scale-up and plant design – Construction of complete systems	– Membrane test units for all membrane processes starting in the ml range for expensive products – Pilot units, also for use in Ex-environment, performance several m^3/day – Computer simulation for process optimization – Analytical instruments (UV/VIS spectrometry, chloride-, sulfate-, KF titration, density, viscosity, dry mass)

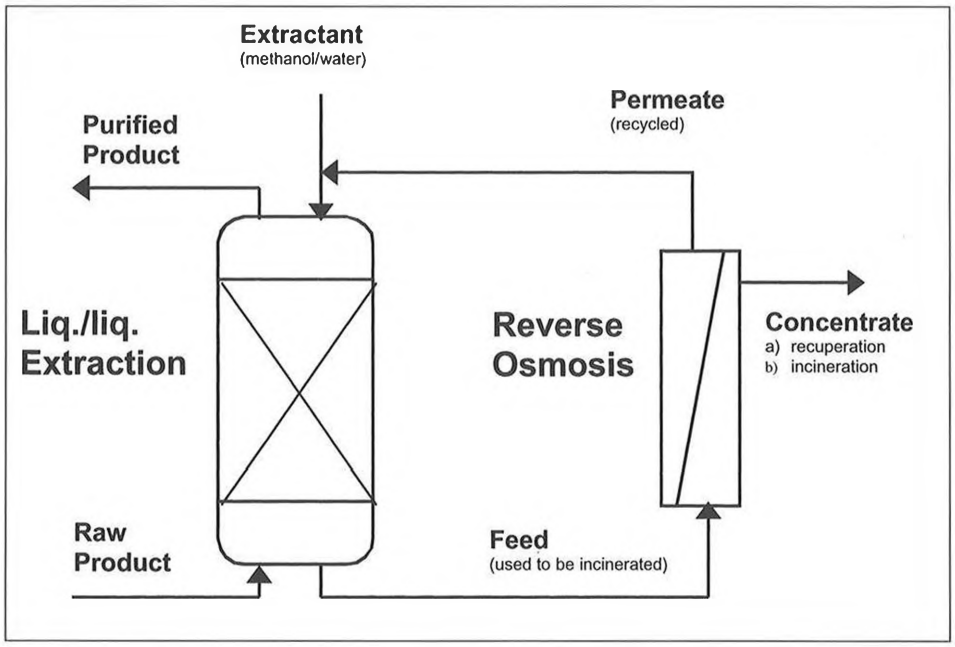

Fig. 4. Combined liquid extraction and reverse osmosis process

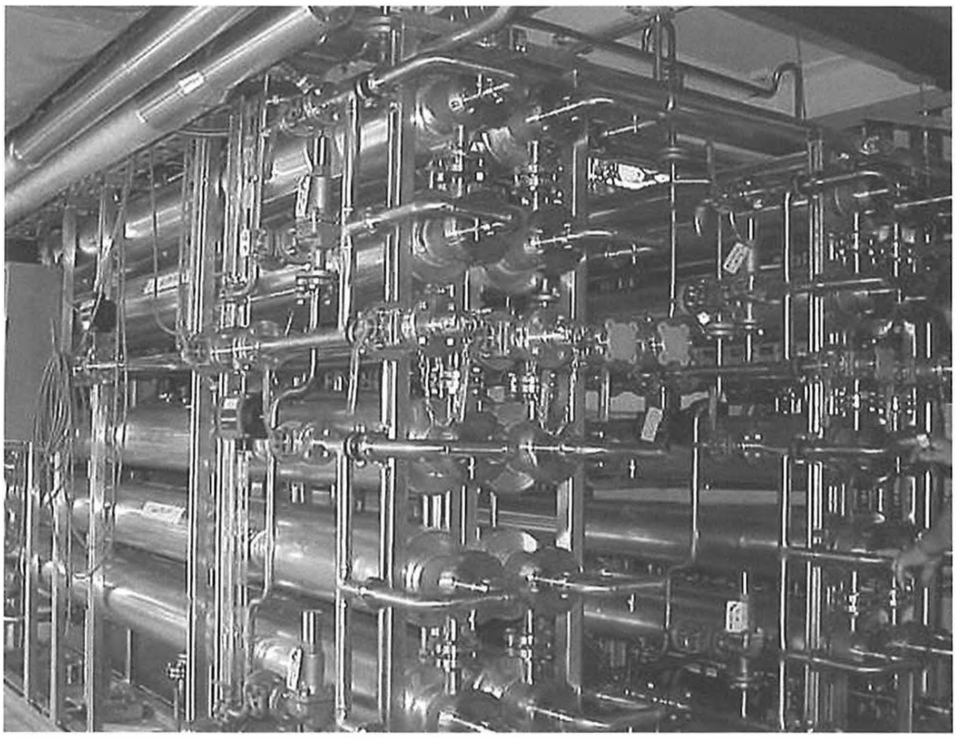

Fig. 5. Membrane rack of extraction solution recovery unit

Table 3. Comparison of costs for treatment of 1 m^3 of aqueous waste

Incineration	700 CHF
Wet air oxidation (limited concentration range)	200 CHF
Membrane process	<10 CHF

Table 4. Other membrane process application examples

Application	**Membrane process**
Effluent containing pesticides	Reverse osmosis
Desalting a product containing high concentrations of sodium chloride	Nanofiltration (in diafiltration mode)
Washing high molecular weight products	Ultrafiltration (in diafiltration mode)

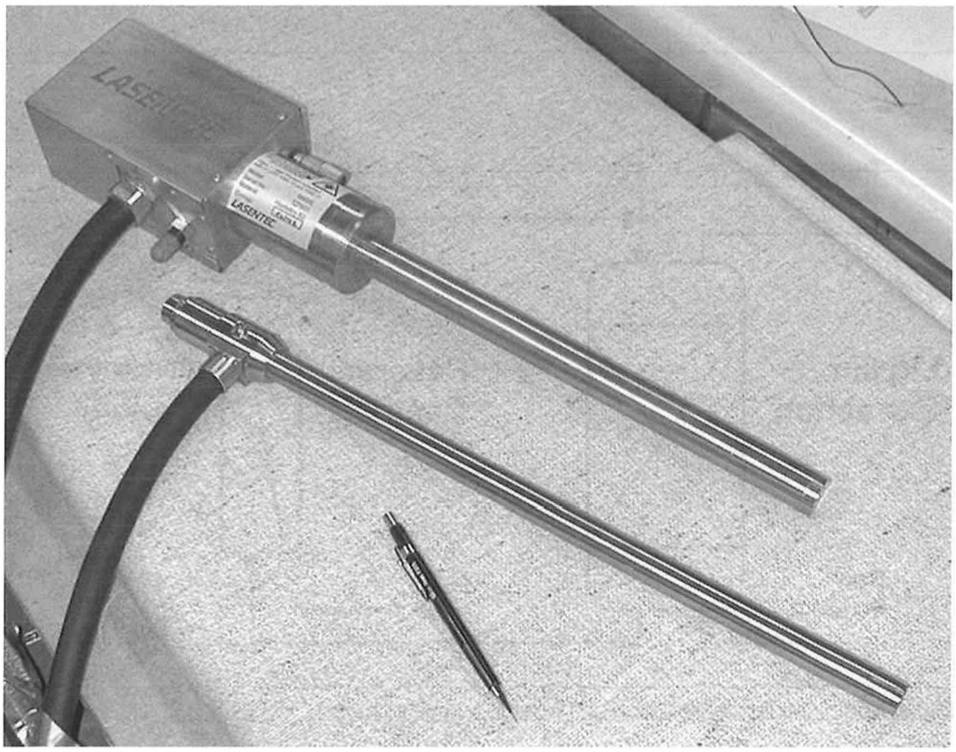

Fig. 6. Two types of Lasentec FBRM probes

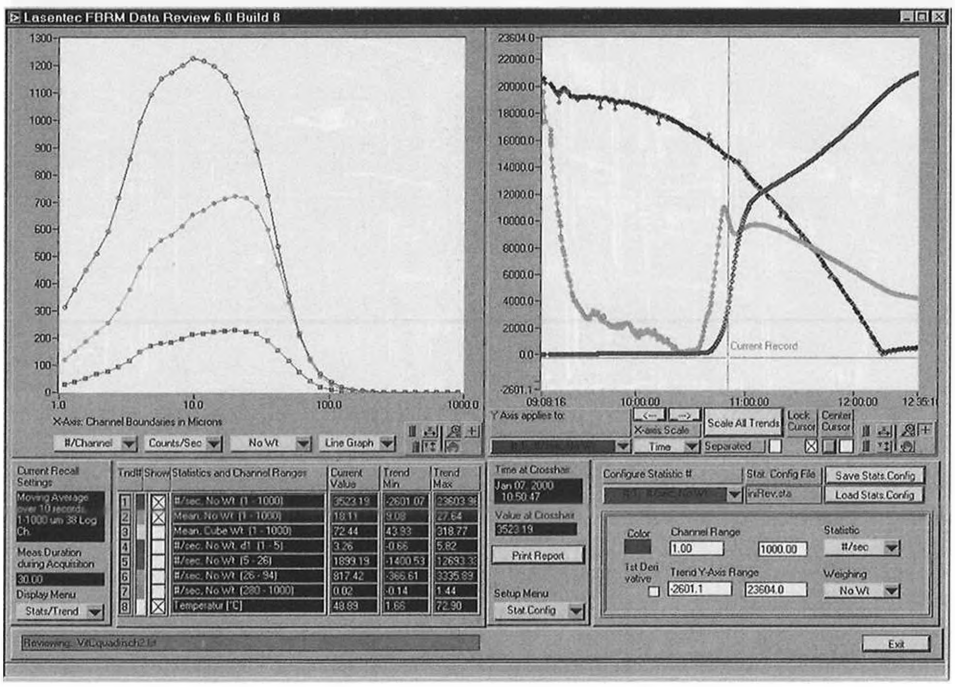

Fig. 7. Screenprint of the Lasentec FBRM software in a crystallization process

process variable or final product specification that is a function of particle shape, dimension and/or number of particles in the particle system.

PS Prozesstechnik GmbH is the representative of Lasentec in Switzerland, Austria, and southern Germany. We offer these systems combined with our knowledge in process optimization.

Measurement principle: The probe (Fig. 6) is inserted into a flowing medium of any particle concentration or viscosity. A highly focused laser beam is projected through the probe window and, at fixed velocity, rapidly scanned across particles and particle structures flowing past the window. The duration of the backscattered light pulses is detected and shown online as a size distribution and trends of user configurable statistics over time (Fig. 7).

Applications:

Crystallization: e.g. in the chemical and pharmaceutical industry. Keywords: crystal modification needles/cubed crystals, filterability, formulation, batch time, crystallization kinetics.

Polymerization: e.g. distribution of starting emulsion

Emulsions: e.g. food industry ('mouth feeling')

Grinding Processes, Granulation Fluidized Beds and other processes where measurement of change over time in the particle system is required.

From process development to continuous control of production

Crystallization Application Example: Optimization of the cooling crystallization process of vitamin C. Different cooling strategies have been tested to reduce overall batch time and reduction of fines. FBRM probes detected primary nucleation (which could be slowed down by optimizing the cooling curve without increasing batch time) and secondary nucleation (abrasion by excessive stirring). It also allowed an optimization of intermediate re-heating.

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RPC AG

Rapid Development of Rapid Prototyping Chemicals

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Abstract: RPC (Rapid Prototyping Chemicals) was founded in 1997 by a group of former collaborators of the Ciba-Geigy research center in Marly. The company is active in the development and fabrication of materials for the rapid prototyping industry and has already commercialized several high-performance resins for stereolithography. These materials are characterized by rapid polymerization by laser light. The development process is based on both the evaluation of resin reactivity and the mechanical properties of the final products. New materials are under development for higher temperature resistance and improved fracture toughness. Production, quality control and distribution are handled from the same location.

Keywords: Crosslinked polymers · Photopolymers · Rapid prototyping · Rapid tooling · Stereolithography

1. Introduction to Rapid Prototyping (RP)

1.1. *Definitions*

RP has become established within the last decade as a group of technologies which combine material processing and handling with computer control to enable virtually automatic production of 3-dimensional objects from computer-generated geometry data. While machine tools (lathes, mills, grinders) with 'numeric control' (NC) had already been developed in the 70's, they have to start cutting into a defined volume of solid material (stock) and require a good deal of machining expertise and geometry dependent 'programming'. Newer generations of control software have automated many of these tasks [1] and even offer a screen-preview of the entire process and threatening tool collisions, but there are still severe limitations on the shapes to be cut (tool access, deep pockets, thin walls, sharp interior angles *etc.*).

1.2. *Commercial RP Systems*

RP technologies, termed by technology experts such as Terry Wohlers or Marshal Burns [2] 'The 3rd Industrial Revolution', have largely overcome many of these problems as material is not cut away (subtractive) but added in the form of strands or layers (additive technologies) combined with a phase change somewhere in the process. Unrestricted access to any geometry is generally achieved by building up any structure layer by layer, whereby some methods and shapes require a removable support structure. In the early phase, applications were rather restricted by the materials available for each process, but continuous development towards better properties and clever application of post-processing or replication methods have broadened the scope into high performance and tooling domains.

A photopolymer-based method called stereolithography (SL) was the first one to be commercially available (Autofact exhibition, 1988) and has since been improved in all aspects [3] from part size to speed to material properties; the basic process was presented in a previous issue of this journal [4] along with a description of the resins which are used in those machines. SL was not only the first, but is still the most popular RP technique based on the number of installed machines; other RP methods are still being developed and a variety of them have appeared on the market, with considerable success. Commercial systems can be grouped according to starting material into liquid (photopolymer), powder/sintering, sheet stock, (liquid) jet and melt extrusion types. The quality of parts, mainly mechanical strength, accuracy and surface finish, is essentially determined by the building technique and the materials, which play an increasingly important role as applications evolve and the methods are taken 'for granted' by modern engineers.

2. RPC Foundation and Collaborators

RPC Ltd. was founded in September 1997 by former collaborators of the Ciba research center in Marly. The closing of the facility and the relocation of the

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whole Additives and Pigment research to Basel had been announced in 1996. As collaborators of the former stereolithography team that had existed in Marly from 1988 to 1995, we saw an opportunity to create our own company that would develop and commercialize materials for rapid prototyping. As mentioned above, there is a need for new materials in this growing market. For each application of rapid prototyping, *e.g.* design verification, functional testing, investment casting, rapid tooling, rapid manufacturing *etc.*, more specific materials have to be developed in order to improve and extend the possibilities of the rapid prototyping technologies. We felt that by coming up with some good, innovative materials, we could become an interesting partner especially for the European prototyping industry.

We started in October 1997 as a team of three collaborators (Manfred Hofmann, Christian Bovet and Bettina Steinmann) to build up the company. An adequate location for RPC's activities was found in the buildings of the former Ciba-Geigy research center in Marly. The infrastructure for product development and quality control consists of a stereolithography machine with different lasers, a vacuum-casting machine and several machines for mechanical testing. For the production of the materials, stirring vessels are available that permit the production of 50 to 250 kg of stereolithography resins per day.

3. Activities

3.1. *Commercial Base*

RPC is active in the development, fabrication and commercialization of materials for the rapid prototyping industry. With our long experience in stereolithography, we concentrated in the start phase almost entirely on the development of high-performance resins for this technology. Our well-equipped laboratories allow an efficient and fast development of new products so that it was possible to commercialize the first two stereolithography resins only a few months after the start of the company. The production of the materials is done in-house, which gives us full control over the quality of the products and makes us flexible with regard to inventory and delivery times.

Customers are mainly so-called service bureaus that use rapid prototyping to produce models for the development departments of *e.g.* automotive, aerospace, electronic or household appliance industries. The Swiss market being rather small (about five service bureaus with stereolithography equipment) we have to focus on the export of our products. In the start phase, we concentrated on the European market. Marketing and sales are undertaken directly from Marly. Meanwhile, some of the biggest service bureaus in Germany, France and England are among our customers. We are now starting to extend our activities also to the American market, which is about twice as large as the whole European market. A distributor has been found for this region and first customers have been acquired.

3.2. *Development*

All the commercial and development products of RPC are based on liquid, reactive polymers and therefore product development concentrates on formulation, curing under process conditions, measurement and testing of materials followed by extensive correlation of composition, processing and finishing with resulting material properties, accuracy and visual aspects.

The main tools for material testing are conventional tensile testers which are also used in bending tests, and an IZOD impact tester. Measurement of fresh samples at fixed intervals reveals a slow postcuring of these 'green parts', whereas chemical reactions are followed with a DSC cell.

Structural aspects over an extended temperature range are observed with a dynamic mechanical analyzer (DMTA), which also reveals postcure effects in a temperature ramp or cure kinetics in isothermal mode.

Collaboration in national and international research projects is an important part of this program.

3.2.1. *Stereolithography Resins*

One of the primary characteristics of a SL resin is a fast and efficient transition from a (low viscosity) liquid to a reasonably stable solid (green body) state, making very efficient use of the 'expensive' laser photons [4].

The very first commercial SL machines all used a HeCd metal vapor laser in UV mode (325 nm). Since then the 'workhorses' of RP have turned to Ar/UV lasers operating at 351 nm with up to tenfold power, and now the industry is turning to solid-state (Nd:YVO) lasers with frequency up-conversion to 355 nm. As photoinitiator absorption and polymerization efficiency significantly depends on wavelength, a distinct set of resins is required for each of these laser types. If we keep in mind that current SL materials comprise two different reactive systems – a cationically polymerizing epoxy and a radically reacting acrylate system – each with its photoinitiator and stabilizer set, then this 'wavelength tuning' is not a trivial approach.

On the materials properties side, a long-standing wish is to have a tough, thermoplastic-like polymer with a heat deflection temperature well above 100°C. No color, essentially no moisture sensitivity and resistance towards commodity solvents and lubricants are also considered essential for a 'general purpose' material.

New formulations are therefore developed on experience with existing components, consideration of structure and reactivity and then tested in a hierarchical order; most crucial is photospeed, expressed as cure depth for a given energy and mechanical (green) strength, expressed as the modulus of a multilayer beam under defined curing conditions. Only those formulations which meet our standards are then UV 'postcured' and tested for other material properties.

All the measurements combined give us a feedback on the formulation and our structure model, and input for further refinements.

3.2.2. *Casting Resins (Thermal Cure)*

SL can be seen as just one link in a chain to rapid prototyping or, in a broader context, rapid product development. SL prototypes are in fact often used, after some traditional hand finishing, as master patterns for a range of molding and duplication techniques. Two of them, which are also based on reactive resins, have drawn our interest, as their development also relies on the correlation of formulation and structure with reactivity and thermomechanical properties. A very popular method to make several precise, durable copies of an SL master is to pour a silicone rubber (RTV) mold and then cast individual polyurethane parts (up to about 50 per mold). These reactive polyurethane formulations with well-defined properties in a given temperature range are an interesting development field.

The second application is the rapid path 'from SL master to injection molding tool'; research institutes and the industry are working on a plethora of different processes towards this goal, each one with its niche of accuracy, tool life, cost, speed and ease of manufacture, as well as claims to yield 'production-like' castings. Mold inserts with reasonable thermal stability and useful life of several

Table: RP*Cure* resins for stereolithography

	RP*Cure* 100 HC	RP*Cure* 100 AR	RP*Cure* 100 ND	RP*Cure* 200 HC	RP*Cure* 200 AR	RP*Cure* 200 ND	RP*Cure* 300 HC	RP*Cure* 300 AR	RP*Cure* 300 ND	RP*Cure* 550 HC
Laser-Type	He/Cd (325 nm)	AR/UV (351 nm)	Solid State (355 nm)	He/Cd (325 nm)	Ar/UV (351 nm)	Solid State (355 nm)	He/Cd (325 nm)	AR/UV (351 nm)	Solid State (355 nm)	He/Cd (325 nm)
		Epoxy based			Epoxy based			Epoxy based		Acrylate
Dp, mils	4.4	4.86	4.6	4.88	4.58	4.2	5	4.8	4.8	5.2
Dp, mm	0.11	0.12	0.12	0.12	0.12	0.11	0.13	0.12	0.12	0.13
Ec, mJ/cm^2	10	7.7	10.6	8.3	7.8	10.2	10.5	10.1	10.8	5.4
Viscosity (30 °C), cps	650	540	520	480	440	450	530	500	540	1370
Post-Cured Resin										
Tensile modulus, MPa	3210	3020	3000	2000	2000	2000	3000	3000	3000	1300
Tensile strength, MPa	67	75	75	50	50	50	67	60	60	35
Elongation to break, %	4	9	9	17	17	15	3	3.5	3.5	9
Shore D	85	83	82	82	80	80	86	85	84	80
Impact resistance, unnotched part, kJ/m^2	21	30	30	No break	No break	No break	7	15	12	18
Impact resistance, notched part, kJ/m^2				2.2	2.2	3.8				
Glass transition (DSC) °C	81	81	81	60	60	60	120 (DMA Peak E'')	120 (DMA Peak E'')	120 (DMA Peak E'')	92
Characteristics	Very high resolution Smooth surfaces, Fast High water resistance			High impact Flexible Very fast Water resistant			Smooth surfaces High temperature resistance Good mechanical properties			Temperature resistant Can be sterilized
Application	General applications Quick cast Parts with fine details Small spot laser			Snap fits Quick cast			High temperature testing Rapid tooling			Medical parts Concept models

hundred to thousands of shots, depending on the polymer injected and mold complexity, can be cast from high-T_g epoxies which are reinforced with metal powder. These resins provide again a challenge in formulation, mechanical testing at melt temperatures and in realistic mold applications.

3.3. *Fabrication and Quality Control*

As mentioned above, stereolithography resins are blends of different reactive monomers and polymers with a photoinitiator that makes them UV sensitive. The resins are produced in vessels by stirring the components at about 60 °C under exclusion of UV light. For the quality control, viscosity and reactivity are tested. The reactivity test is the establishment of the so-called working curve, which shows the thickness of a laser-polymerized layer (the cure depth), as function of the logarithm of the incident energy. Criteria for the quality control are the slope of the curve (so-called D_p) and the critical energy, the intersection of the curve with the x-axis [4].

Stability tests are also performed to determine the vat life of a resin which is guaranteed for one year without an increase of viscosity beyond the specifications.

4. The Products

At the end of 1999, three types of epoxy-based stereolithography resins were on the market, each of which is available for the three different laser types. This gives a range of nine different epoxy resins. In addition, a fast acrylate resin that can be used for concept models or medical applications is available (Table).

1) The **RP*Cure* 100** series for general applications and for parts with fine details and small spot laser applications ('micro-stereolithography'). The resins have high photospeed and give parts with very good surface finish, low curl and high resolution. After post-curing, a tensile modulus of 3000 MPa is obtained, a tensile strength of about 70 MPa and an elongation to break of 4 to 9%. The glass transition temperature is at 80 °C.
2) The **RP*Cure* 200** family for applications which need more flexible, but not too soft materials for snap fittings *etc.* The post-cured material has a tensile modulus of about 2000 MPa and an elongation to break of 17%. The T_g is at 60 °C.
3) The **RP*Cure*** 300 series with high temperature stability. The glass transition temperature of about 120 °C makes them suitable for functional testing at higher temperatures, rapid tooling *etc.*
4) The **RP*Cure* 550** type with very high photospeed for medical applications and big parts. The parts can be sterilized.

For vacuum casting, one product,

RP*Cast* 1000, has been commercialized so far. It is a transparent, slightly yellow urethane resin with good impact resistance and a temperature stability of 80–90 °C.

Our first rapid tooling resin, **RP*Cast* 5000**, is being commercialized in the first quarter of 2000. It is an aluminum-filled, two-component epoxy resin that can be used for the production of prototype mould inserts for injection molding. With these moulds, pre-series of up to 1000 plastic parts can be produced.

5. Projects

If an engineer is asked about his 'ideal' RP material, he often quotes 'like ABS or a similar engineering plastic' with a high fracture toughness, temperature resistance (or in engineering terms, heat deflection temperature) well above 100 °C, elastic modulus around 2000 MPa, colorless, transparent *etc.*, *i.e.* a range of properties which is difficult to mimic with a crosslinked photopolymer. While we optimize some material properties, we may have to compromise on others, or the processing conditions, but can then satisfy different application niches.

- In a current development for a resin with a significantly higher T_g, target markets are in the automotive industry (engine compartment), aerospace (turbine components) and general plastic molding, where short-run mold inserts made of SL resin are still reaching their limits.
- Dimensional accuracy and stability are basic requirements for SL resins in technical applications, but similar to other epoxies, these materials absorb some moisture from the ambient air. The challenge is therefore to find new components, which reduce this water affinity, especially for the range of 'flexible' materials.
- Mechanical properties at elevated temperatures are frequently improved by adding some (mineral) filler to the base polymer. As the resulting increase in viscosity deteriorates the required recoating properties, no commercial SL resins with fillers are in use. But as a French manufacturer now offers a similar machine with a different coating concept, highly filled materials can be processed, and we are pursuing this development.

Besides these active projects with a defined product target, a continuous search for new compounds which can enhance product properties is an essential part of our product development. On the other hand, a close watch on new RP technologies is vital, as new processes can be a threat to the established business or also open a new market for specific tailored materials.

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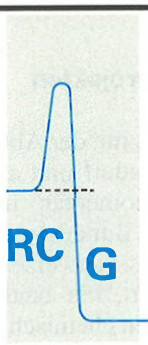

ReseaChem GmbH
Chemical Research Laboratory

ReseaChem GmbH

Die Vernetzung von Synthese, Analytik und Informatik

Stefan Berger*

Combination of Synthesis, Analytics, and Information Science

Abstract: ReseaChem GmbH was established in 1996 in Burgdorf. The objective was to give small and middle companies without any chemical equipment in the region of Burgdorf the chance to have a partner in chemical questions. Since then the company has grown constantly and employs at present three chemical engineers, an information scientist and a Ph.D. chemist as a consultant. Today we operate worldwide and the field of activities covers:

- Custom synthesis of chemical intermediate products or reference materials
- General chemical analysis, *e.g.* analysis of tea, or microscopy
- Determination of chemical structures *e.g.* 24 h NMR services, mass spectroscopy
- Chemical information services *e.g.* development of databases (PPS LIMS) or literature searches
- Work on combined projects

Keywords: Analytics · Chemical information services · Custom synthesis · Microscopy · 24 h NMR services · Reference materials

Firmenporträt

Die ReseaChem GmbH mit Sitz in Burgdorf ist ein junges Dienstleistungsunternehmen in den Bereichen der chemischen Analytik, der Synthetik sowie der chemischen Informatik. Gegründet wurde sie anfangs 1996 und beschäftigt zur Zeit einen promovierten Chemiker als Berater, drei Chemiker HTL, sowie einen Informatiker.

Hintergund für die Firmengründung waren die immer häufiger an die Abteilung Chemie der Hochschule für Technik und Architektur (HTA) Burgdorf (früher Ingenieurschule Burgdorf) gestellten Anfragen nach Dienstleistungen im Bereich der instrumentellen Analytik. Aufgrund der permanent prekären Situation im personellen Bereich der HTA Burgdorf konnten diese häufig nicht mehr in den von den Auftraggebern gewünschten Zeitrahmen erledigt werden. Dieser Umstand einerseits, sowie die mangelhafte Auslastung der Geräteinfrastruktur an der HTA Burgdorf anderseits, liessen uns einen ungewöhnlichen Weg gehen: Die Dienstleistungen wurden in ein eigenständiges Dienstleistungslabor ausgegliedert. In Zusammenarbeit mit dem Kanton Bern wurde ein Mietvertrag ausgearbeitet. Dieser regelt die Benutzung der Räumlichkeiten und der Geräteinfrastruktur an der HTA Burgdorf durch die ReseaChem GmbH sowie die finanzielle Abgeltung an den Kanton Bern. Damit ergeben sich für beide Vertragspartner echte Win-win-Situationen. Die ReseaChem GmbH profitiert von der guten Geräteinfrastruktur, der Kanton generiert Mietzinseinnahmen und profitiert von der guten Gerätewartung. Dieser Weg setzt neue Massstäbe in der Zusammenarbeit zwischen einem Dienstleistungsunternehmen und einer Ausbildungsstätte und soll kreative Problemlösungen für KMU ermöglichen. Die ReseaChem GmbH strebt in Zukunft eine Akkreditierung nach EN 45001 oder nach der in Vorbereitung stehenden ISO Norm 17025 an.

Unsere Dienstleistungen

Ziel unseres Strebens sind nicht die Lösung eines einzelnen Problemes, sondern vielmehr die ganzheitliche, interdisziplinäre Lösungsfindung, das heisst Beratung, Durchführung von Analysen, Resultatebeurteilung und die Mithilfe bei der Umsetzung neuer Erkenntnisse. Un-

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ser breites Know-how in den Bereichen chemische Analytik und Synthetik und das Vorhandensein eines modernen Geräteparks erlauben uns schnelle und effiziente Lösungsfindungen auch in Spezialanalytik wie NMR, MALDI-TOF, uam. Unsere Dienstleistungen umfassen:

- allgemeine chemische Analytik
- Strukturaufklärung
- Synthesedienstleistungen
- Durchführung und Betreuung chemisch-technischer Projekte
- chemische Informatik (Recherchen, Chemometrie, Datenbanklösungen (PPS, LIMS))

Allgemeine chemische Analytik

Wir verfügen über ein modern ausgerüstetes Laboratorium, in welchem wir Arbeiten und Projekte durchführen. Den Kundenaufträgen entsprechend sind wir bestrebt, stets die der Problemlösung optimal angepasste Analysenmethode zu wählen. Es kommen sowohl nass-chemische als auch instrumentelle Methoden zum Einsatz.

Strukturaufklärung

Die gängigsten spektroskopischen Untersuchungsmethoden wie NMR-Spektroskopie (alle gängigen Kerne und Methoden), IR-Spektroskopie und Massenspektrometrie (EI, CI, MALDI-TOF) bieten wir standardmässig in unserem Programm an. Zu unseren diesbezüglichen Kunden zählen sowohl Forschungslaboratorien wie auch Entwicklungsabteilungen in der Industrie. Mit unserem 24-Stunden-NMR-Service (Spektren innerhalb von 24 h) bieten wir unseren Kunden eine gute Möglichkeit, Ihre NMR-Analytik an einen kompetenten Partner auszulagern.

Abgesehen von der routinemässigen Spektrenaufnahme werten wir auf Wunsch diese auch aus und erstellen mögliche Strukturvorschläge. Bei Bedarf werden postulierte Strukturen anhand von Referenzsubstanzen verifiziert.

Synthesedienstleistungen

In unserem Labor verfügen wir über die notwendige Infrastruktur, um die meisten organischen Synthesen bis zu einer Ansatzgrösse von *ca.* 1 kg durchzuführen. Reaktionsverlauf und Beurteilung der Qualität werden im Hause durchgeführt. Neben der Synthese von Zwischenprodukten stellen wir Referenzmaterialien für die chemische Analytik her und/oder optimieren bestehende Synthesen. So wurden beispielsweise nichtkäufliche Tee-Inhaltsstoffe, welche einen positiven Effekt auf koronare Herzkrankheiten aufweisen, in unserem Labor synthetisiert und anschliessend in einem Projekt zur Teeanalytik eingesetzt.

Durchführung von Projekten

In Zusammenarbeit mit der Abteilung Chemie der HTA Burgdorf und anderen Partnern sind wir momentan in Forschungsprojekte des Bundesamtes für Energie (BFE) und des Schweizerischen Nationalfond involviert. Für beide Projekte bearbeiten wir den chemisch analytischen Teil.

Chemische Informatik

Mit der Entwicklung der modernen Analytik hat auch die Informatik vermehrt in analytischen Laboratorien und in der angrenzenden Probenadministration Einzug gehalten. Dabei spielen insbesondere Datenbanken und Informationsmanagement eine sehr wichtige Rolle. Eine zielgerichtete Forschung und Entwicklung ist auf verlässliche Daten angewiesen und nutzt diese als Wissensvorsprung aus. Als innovatives Unternehmen sind Sie für Ihre Arbeiten auf Informationen zum Stand der Technik oder vorhandenen Synthesemethoden (Literaturhinweise) angewiesen. Diese beschaffen wir über Literaturrecherchen bei diversen Datenbankanbietern und stellen unser Know-how auch unseren Kunden zur Verfügung. Im Bereich Informationsmanagement sind wir auf die Erstellung (Datendesign) und Ausführung von Datenbanken (PPS, LIMS, Wartungs- und Instandhaltung) spezialisiert.

Die enge Vernetzung von Analytik, Synthese und Informatik erlauben es uns, individuelle Problemlösungen in den verschiedensten Gebieten der Chemie zu finden und auf Kundenwünsche gezielt einzutreten.

Eingegangen am 1. Februar 2000

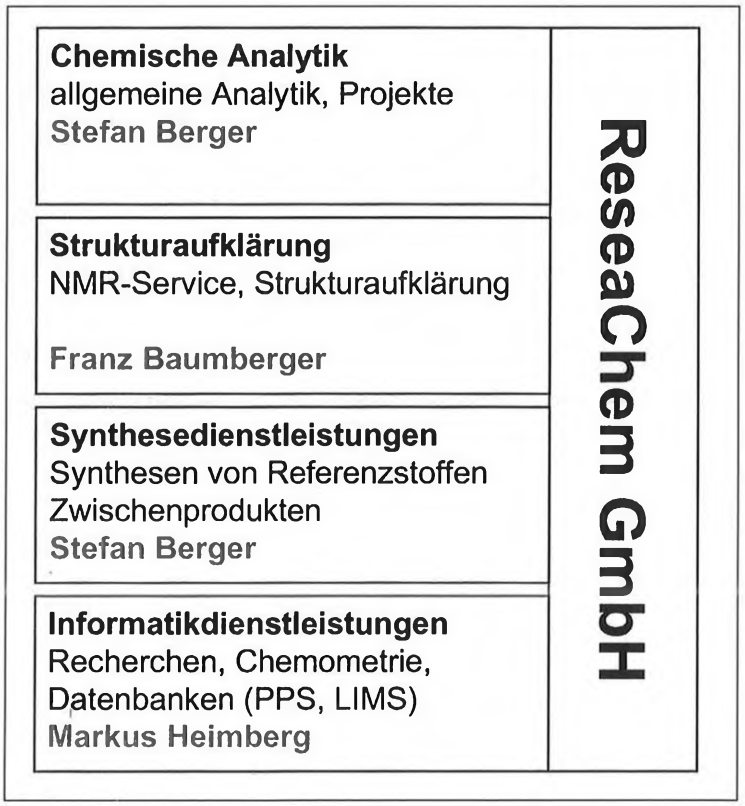

Fig. Struktur und Verantwortlichkeiten der ReseaChem GmbH

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SENSORIX

SENSORIX
ANTRIS™: A Flexible Multiparameter Sensor System for Process Control

Markus Rothmaier* and Fritz Tschopp

Abstract: The ETH Zürich spin-off company SENSORIX is focused on the development and distribution of analytical instruments based on chemical sensor and biosensor technology for online process analysis. Its first product, ANTRIS™, is a flexible platform for amperometric, potentiometric, and optical sensors. ANTRIS™ is primarily positioned in the biotechnology, fermentation, and food technology markets for continuous and simultaneous measurements of glucose, lactate, ethanol, and other nutrients and metabolites.

Keywords: ANTRIS™ · Biosensors · Chemical sensors · Multiparameter measuring systems · Online process analysis

Introduction

Chemical sensors and biosensors offer a great opportunity to monitor online processes without the need for extensive sample preparation. They are easily miniaturizable and can therefore be placed close to or, under certain circumstances, into the process. Nowadays, three types of chemical sensors can be distinguished by their signal transduction principle. As a result of the chemical recognition process the sensors deliver either a change in current, potential or in light absorbance. However, analytical instruments that can embody several sensor transduction principles for online analysis are not yet commercially available. ANTRIS™, a flexible sensor conception for multiparameter measuring systems in process control, has been developed by the start-up company SENSORIX. It offers a platform for amperometric, potentiometric and optical biosensors and chemical sensors for online process analysis in food technology, biotechnology, and water management.

History

SENSORIX is a spin-off company from the Swiss Federal Institute of Technology in Zürich (ETH), where chemical sensor technology has been investigated for over 30 years. It was the late Prof. Wilhelm Simon [1] who started with the development of cation-selective sensors soon after the discovery of the ion-binding capabilities of nonactin and valinomycin. Initially the main focus was on clinical and diagnostic applications in blood, urine and other biological matrices, and led to several patents. In 1994, on the initiative of Prof. Ursula Spichiger-Keller, a new research group at ETH was established (Center for Chemical Sensors, CCS [2]) dealing mainly with applied research in the field of chemical sensors and biosensors. At CCS early prototypes of flow-through sensor modules have been developed and an award from 'Technologie-Standort Schweiz' was received in 1996. In order to commercialize these developments into industrial products, SENSORIX was established on March 1st, 1999. SENSORIX was founded by five individual partners from ETH and industry and is today located in the Technopark Zürich.

The Product

SENSORIX' business is based on the development of a modular sensor system (ANTRIS™, see Figure) and on an applications laboratory for its customers, where solutions for specific measurement problems are developed. ANTRIS™ is a platform for setting up all three sensor transduction principles: amperometric, potentiometric and optical chemical sensors or biosensors. The core of the product consists of a small disposable flow-through cell, which incorporates a thin channel to transport the sample solution, a sensitive membrane for the chemical recognition process and a connector to optical fibers or the amplifier

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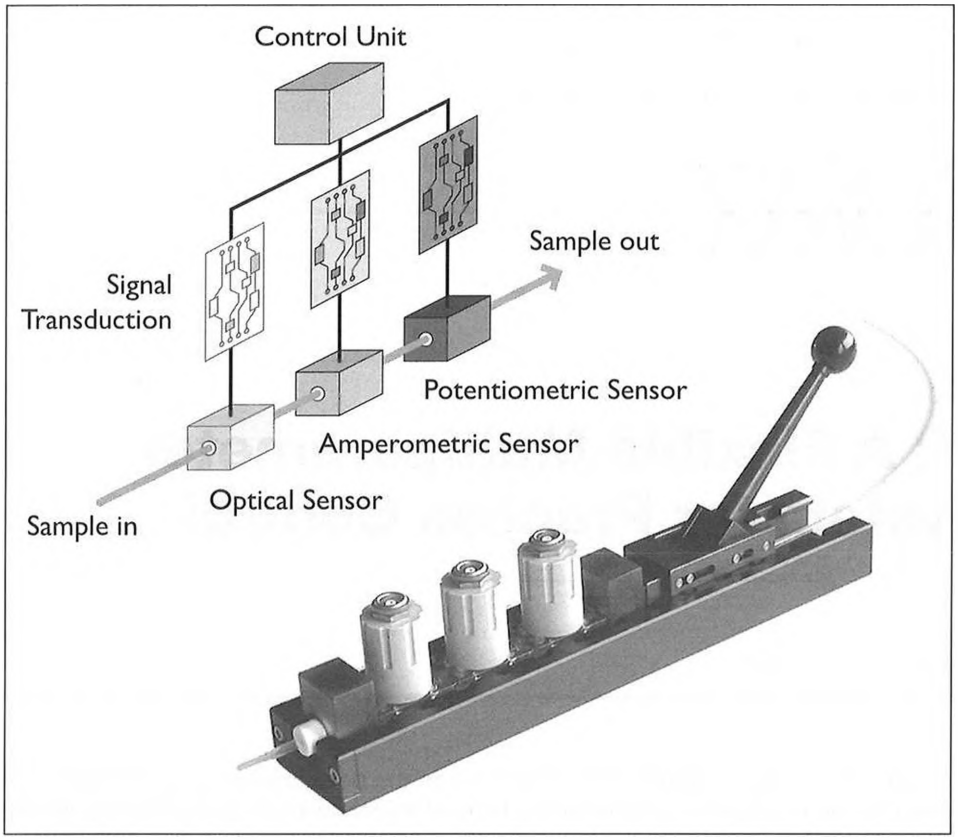

General scheme and flow-through sensor modules of the ANTRIS™ measuring system

electronics. Several of these modules can be assembled in series or parallel, giving the user highest flexibility and allowing the operation of completely new combinations of sensors with different transduction principles inside one analytical device at the same time. A maximum of three parallel channels can be placed in the basic system resulting in many advantages over state-of-the-art instruments:

a) every channel has an independent liquid control unit, which allows several buffer combinations (biosensors and optical sensors often require precise pH control);
b) extended measuring range by using several sample dilution factors;
c) increased precision (crosschecking);
d) reduced failure risk (backup sensor).

ANTRIS™ operates in three different modes. To control threshold values, upper and lower concentration limits can be entered and an alert is transmitted over its interface (*e.g.* to the process control software). For quality control reasons ANTRIS™ is equipped with data logger functions to record critical quality parameters over several weeks or months. The most advantageous operation mode is certainly the ability to measure and control in process technology where the reading of the sensors will trigger an action. Although ANTRIS™ conception is committed to continuous measurements it can be setup for batch analysis of individual samples as well.

Markets

Customers with the need for continuous monitoring of sensitive process data are the first to utilize novel instruments technology. SENSORIX is entering primarily the biotechnology, fermentation, and food technology markets with its first products (ethanol, glucose, and lactate sensors). In all these instances continuous analysis is fundamental, either to shorten process time, display real-time information for critical process parameters, for concentration determination of in- or outgoing products, quality control or to monitor the living conditions of the microorganisms involved (*e.g.* their carbon and nitrogen sources).

Chemical sensors to measure pH, O_2 and CO_2 concentrations have been developed in the past and are used routinely in every biotechnological process. In most cases they give sufficient information about the progress of a fermentation as soon as the process is running under stable conditions. However, in the development phase of a new bioprocess, an increased amount of information is needed to establish a well-working environment but little online sensor technology is as yet available. In general, disposable photometric tests are used or HPLC and GC methods, which are time consuming, costly and require personnel resources. ANTRIS™ is designed to be connected to the fermentation process through a small sampling system providing the required sample flow. The sampling system either delivers a particle and cell-free solution or it extracts the analyte by means of dialysis (no sample loss in process). Minimum sample volumes of 1 ml/h can be analyzed continuously. Therefore, ANTRIS™ is privileged also to monitor small reactors used in the development phase of a new process. Due to a sterile barrier between the instrument and the process, contamination is virtually impossible.

Another extensive business for SENSORIX products is the water management market, *e.g.* wastewater treatment, industrial process water monitoring, and hydroponics. All these fields need reliable quality management combined with control engineering. The ANTRIS™ system offers at this point a perfect tool to match individual needs for diverse industries. By combining multiple sensors it controls continuously the elimination of harmful substances, the regulation of sewage treatment or the mixing of the accurate concentration of fertilizers in hydroponic plants.

The process industry must improve its online analysis in order to ensure the quality of the products and to speed-up processes at reduced costs without cutting back on safety. The SENSORIX flexible multiparameter sensor system offers an ideal tool for this industry to reach these lasting challenges.

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solvias

Solvias AG
A Direct Way for Solving Synthetic and Analytical Problems

Hans-Ulrich Blaser, Dieter Plogmann*, and Martin Studer

Abstract: Solvias, formerly part of Novartis Services, is a new independent technology company with 200 employees located in Basel. It offers an exceptionally wide range of services for the chemical and nutritional industries in the areas of synthesis, especially using catalytic methods, and chemical, physical and biological analytics. Its major strength is the ability to offer packages comprising any desired combination of highly sophisticated services.

Keywords: Analytics · Catalysis · Chirotechnology · Optical Probes · Polymorphism · Reference Compounds · Regulatory Affairs · Separation · Software Development · Surface Technologies · Synthesis.

Who is Solvias?

Solvias AG evolved from a center of scientific expertise at Novartis. Its roots go back to the central research department of the former Ciba-Geigy AG, which merged with Sandoz to form Novartis in 1996. An increased focus on core businesses presented an opportunity to spin-off our services and make them available to a larger circle of customers. Since October 1st 1999, Solvias AG is an independent company with some 200 highly qualified people. Our aspiration is to contribute to the success of our customers by developing solutions that best fit the needs of our customers in the shortest possible time – regardless of whether the task at hand is a standard analysis, a simple step in a chemical synthesis or a complex integrated solution.

Solvias employs top chemists, physicists, biologists, biochemists, molecular and microbiologists, pharmacists, crystallographers, and engineers. They are backed up by IT specialists, technicians, lab assistants and other back-office staff. The acknowledged quality of our people is reflected by the number of university teaching assignments, publications in scientific journals and invitations to conferences. Furthermore, our scientific network and participation in international working groups ensures access to the latest scientific developments and technologies. This enables us to play an active part in pioneering scientific advances and making them accessible to our clients.

Solvias Offers A Wide Range of Services

Solvias offers an exceptionally wide range of services in the areas of synthesis, especially using catalytic methods, and chemical, physical, and biological analytics. Our expertise has been developed over decades in the Scientific Services of Ciba-Geigy/Novartis and therefore our teams have extensive experience and an unusual track record in solving industrially relevant problems in an efficient and cost effective man-

Solvias at a Glance

- Independent spin-off company from Novartis Scientific Services; with a staff of 200
- Headquarters in Basel, with sites in Basel and Muttenz
- Services in the areas of
  - chemical, physical and biological analytics
  - synthesis with emphasis on selective catalysis
  - service-related products
- Main customers
  - pharmaceutical, agrochemical, fine chemicals and nutrition companies (biotechnology, biochemistry, molecular biology, medicine, formulation, purity guidelines)
  - Start-up and virtual companies with little or no chemical infrastructure
  - Regulatory authorities, environmental departments, local governments, administration of sewage and waste-treatment plants
- Board of Directors: Dr. Peter Loew (President), Dr. Fritz Thommen (CEO and delegate), Dr. François L'Eplattenier, and Dr. Roland Haag.
- Executive Committee: Dr. Fritz Thommen (CEO), Peter Baumeister, Dr. Hans-Ulrich Blaser, Daniel Hüsser (CFO), and Dr. Hansjörg Walther.

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ner. *In short: Over the whole life cycle of a molecule, Solvias can help its customers to achieve a prompt, technically up-to-date solution for problems at all stages of the development of an intermediate, an active compound or a material.*

In the *early phases (first synthesis, identification)* Solvias offers preparative hydrogenation and high-pressure services, synthesis design (see detailed descriptions A–P below), determination of elemental composition (B) and support with separation and by-product identification (C).

In the *development phase (technical synthesis, scale-up, toxicity, physical properties)* Solvias offers synthesis design with emphasis on catalytic methods, custom synthesis of up to kg amounts, development and piloting of catalytic steps (A), microanalytical services, trace analysis (B), preparative separation and quantification of product mixtures (C), the determination of physicochemical parameters and modeling of properties (E), and polymorphism studies to obtain optimal solid forms and crystallization processes (G).

In the *commercial phase (production process, registration, environmental impact)* Solvias offers development and implementation of catalytic production processes and trouble shooting (A), online technologies and fiber-optic probes for process control of synthetic and separation steps in chemical production (O, P), quality control with analytical tools (B, E, G), isolation, production, certification, and supply of reference substances (H), analysis of trace compounds in air, water and soil (I), ecotoxology and water analysis (impact of chemicals) (J), ambient-air monitors to assure work safety (K), support with regulatory affairs (notification of chemicals and registration of drug products) (L), and release analytics for excipients, active substances, and end products (M).

In addition, Solvias has expertise in and offers services for nucleic acid analysis for molecular biology, biochemistry, medicine and nutrition (D), surface technologies for analyzing and treating surfaces of materials (F) and software engineering and consulting for analytics (custom-made solutions for complex analytical problems from laboratory to production) (N).

Who are Solvias' Customers?

Solvias has experience working for a wide range of customers:

- Research, development, production and quality assurance departments in pharmaceutical, agrochemical, fine chemicals and nutrition companies (biotechnology, biochemistry, molecular biology, medicine, formulation, purity guidelines)
- Start-up and virtual companies with little or no chemical infrastructure
- Universities, clinics and technical colleges
- Regulatory authorities, environmental departments, local governments, administration of sewage and waste-treatment plants
- Engineering companies in connection with site remediation and landfill monitoring

How do we support our customers?

Our full-service capacity offers the shortest possible route to a specific goal. Our customers can get everything they need from a single source: Our services range from single synthesis or analytical services to the development of special methods, processes and products and whole service packages. We are a reliable partner whether a customer needs back-up with routine operations or support for an ambitious development project or even when the outsourcing of a whole department is planned.

What are the benefits for Solvias' customers?

Outsourcing peripheral activities can increase the profitability and efficiency of a core business. It is an effective form of partnership and very often a superior way of reaching ambitious goals. By providing back-up for routine operations our customer can cope better with 'work overload'. Working with Solvias puts the kind of resources only major companies can usually afford within everybody's reach. Customers can deploy new technologies, call on the services of highly qualified scientists and other experts for solving a broad variety of synthetic and analytical problems without tying up their own capacities.

In short: Concentrate on the core business – we'll take care of the scientific services: competent, dependable and conscious of the great responsibility entrusted to us.

Quality Standards and Confidentiality

Quality Standards

In our view, quality is not something one can dilute. Our performance can be measured in absolute terms by clearly defined criteria included in project specifications. We are committed to fulfilling every detail. Through consistent quality management we are constantly fine-tuning our processes and structures in an ongoing effort to improve efficiency. Our process-oriented quality management system ensures that our clients receive services and products of the highest quality standards.

Solvias' quality management system is based on the ISO 9001 international standard and certified by Swiss Association for Quality and Management Systems (SQS).

On request, investigations are carried out under cGMP (RFS-recognized contract laboratory for drug analysis according to IKS guidelines), GLP (official endorsement of compliance with the OECD principles of GLP) or according to USP or ICH guidelines.

In the final analysis, quality is also a measure of attitude. That's why the responsibility for implementing our quality concept is part of the personal mission of every single staff member. Quality should be apparent in everything we do and experienced in every contact with our company.

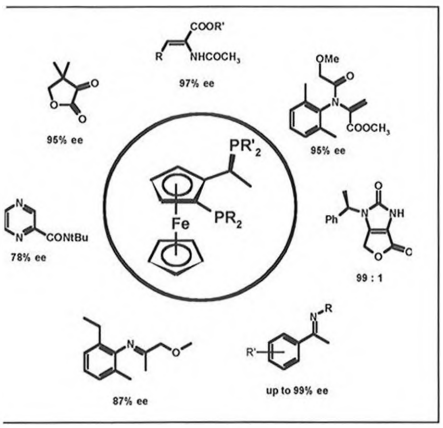
Confidentiality

Our independence, the way we have organized our processes and our handling of data and information allow us to guarantee absolute confidentiality to all our customers.

Detailed Description of Solvias' Services

A. Catalysis, Contract Synthesis, Hydrogenation, and High-Pressure Services

For solving complex synthetic problems we have an experienced network of organic and catalytic chemists and patent specialists with a proven track record in organic – especially stereoselective – synthesis. Central to our expertise are modern catalytic methods as well as high-pressure and fluorination reactions. We can offer our customers an efficient and fast service with a high success rate, due to experience handling problems in the life sciences and an extensive assortment of tested heterogeneous and homogeneous catalysts and ligands. Thanks to our sizable research efforts and several collaborations with university laboratories, our customers have access to a broad, proprietary catalysis technology (a number of patents in specific areas) and to extensive



g. 1. Enantioselective Hydrogenation with siphos Ligands

ocumentation and in-house reaction data ses. Our development teams have scale- and production experience, know-how designing and maintaining high-presure uipment and work in close cooperation ith catalyst manufacturers.

ervices

onsulting

Synthesis planning and synthesis optimization

Feasibility studies on synthesis steps and routes as well as on hydrogenation and high-pressure reactions

Advice on planning and improving chemical processes and synthetic routes

ustom Synthesis and Single Orders

Evaluation of experimental procedures, conducting catalytic and high pressure reactions as well as fluorinations on a mg to kg scale

Preparation of demanding target compounds in mg to kg amounts according to existing procedures

ynthesis Design and Optimization

Developing new synthesis strategies and routes for specific target compounds

Optimization of selected single steps, partial and total syntheses

Development of laboratory procedures

rocess Development and Implementation n a Pilot and/or Production Scale

Method screening to evaluate chemical feasibility

Optimization of catalytic processes

Elaboration and implementation of laboratory and pilot processes (including process safety, ecology, economy, quality-risk analysis, and analytics)

Producing, optimizing, and characterizing homogeneous and heterogeneous catalysts

Support for pilot studies and the introduction of processes into production

Production of kg and pilot amounts according to catalytic procedures provided by the customer or developed in-house

Process Maintenance, Trouble-shooting, and Other Services

- Trouble shooting, fine tuning, and redesigning of catalytic processes
- Metal removal after catalytic processes
- Safe and environmentally sound disposal of pressure gases

Future-Oriented Catalysis Research

- New chiral ligands and auxiliaries for enantio- and chemoselective hydrogenation
- Separation methods for soluble metal compounds (metal adsorbers, immobilized and water-soluble ligands)
- Selective catalytic oxidations for industrial application
- Catalytic C–C, C–O and C–N coupling reactions

Products

- Highly selective, chiral ferrocenyl diphosphine ligands with tunable steric and electronic properties on a gram to multi-kilogram scale (see Fig. 1)

Specialized Equipment

- Stirred autoclaves from 50 ml to 50 l (see Fig. 2). Materials: glass, enameled steel, stainless steel, Hastelloy B and C, Inconel 686, Monel and tantalum
- Equipment for filtering and dosing under pressure

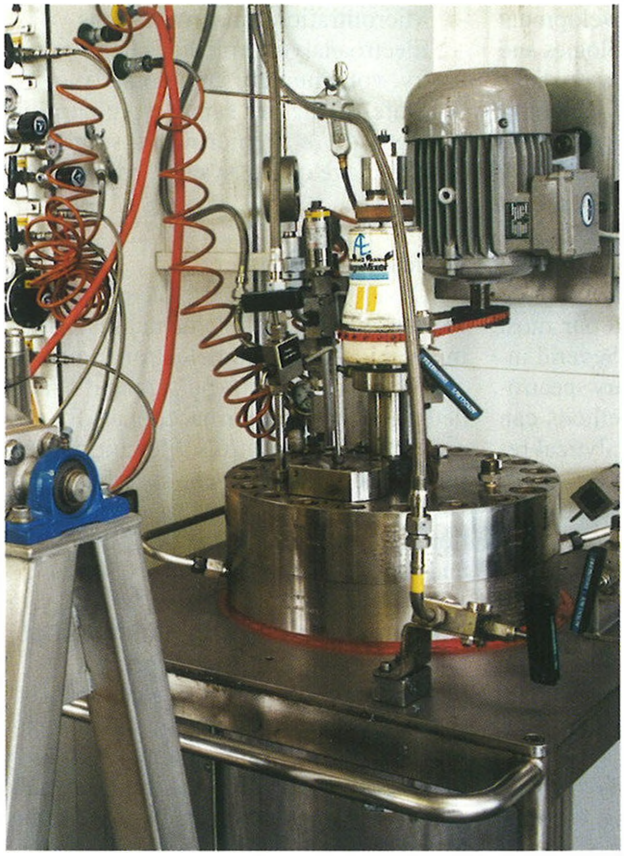


Fig. 2

- Heat-flow calorimeter (0.8 l, 250 °C, 1–50 bar); TPR catalyst characterization; TPD–MS coupling
- Chemspeed synthesis robot for fast catalyst screening, high-pressure parallel reactor

Typical Examples

Evaluation of a selective fluorination method for the preparation of 3,5-bis(trifluoromethyl)toluene. Carbonylation of a chloropyridine derivative on the kilogram scale. Design and implementation of a new low-cost total synthesis of a chiral pharmaceutical intermediate or of a novel synthesis strategy for the synthesis of a complex pharmaceutical with four stereogenic centers. The development of a Matsuda–Heck reaction with consecutive catalytic hydrogenation for the alkylation of an aromatic sulfonic acid derivative. Development of a modified platinum catalyst for the selective hydrogenation of a wide variety of functionalized nitroarenes. The development of a new enantioselective iridium catalyst for the large-scale production of a chiral herbicide.

B. Elemental and Microanalytical Services

We offer our customers a fast and reliable analytical service for the determination of elements, ions and functional groups in a broad range of products and

materials, including method development and validation. The latest technologies and methods are applied covering a wide range of concentrations starting from ultratraces up to percentage amounts. Specialized in microanalytical methods, we are able to conduct most of the classical and instrumental analytical tasks using extremely low amounts of sample. Analyses in the ultratrace range (clean room, ICP–MS, TXRF, ETAAS, IC) belong to our most important core competencies. Several independent and/or complementary spectroscopic and microanalytical methods can be used in parallel to assure analytical reliability and to choose an optimum method for a specific matrix and/or problem.

Services

Elemental Composition

- Quantitative determination of chemical elements, inorganic and organic ions and functional groups, as well as water content in all concentration ranges
- Overview analyses to identify samples of unknown composition (*e.g.* customer compliance, marketing support, process residues, forensic problems)

Quality Control of

- Pharmaceutical drug substances, excipients, drug products, and packaging materials
- Ultrapure materials (photosensitive polymers, high purity chemicals, solvents, and water)
- Organic and inorganic pigments and dyestuffs
- Polymers and polymer additives
- Cosmetics

Development and Validation of Analytical Methods for

- Toxicological and clinical studies
- Pharmaceutical research and development as well as quality control
- Biotechnology

Specialized Equipment

- X-ray fluorescence spectrometry (XRF)
- Total reflection X-ray fluorescence spectrometry (TXRF)
- Inductively coupled plasma mass spectrometry (ICP–MS)
- Optical emission spectrometry methods (ICP–OES, DC-Arc-OES)
- Flame and flameless atomic absorption spectrometry (FAAS, ETAAS)
- Ion chromatography (isocratic and gradient systems)
- Microanalytical combustion methods (C, H, N, O, S, halogens)
- Micromethods for the determination of water content
- Microtitrations, macrotitrations
- Electroanalytical methods (tensammetry, voltammetry, amperometry)
- State-of-the-art sample preparation methods (*e.g.* microwave supported ultraclave quartz system, cold plasma ashers)

Typical Examples

Development of a reliable method for the determination of elemental impurities in chemicals for microelectronic materials down to the 5–10 pg/g range. Water determination in pharmaceuticals for the routine stability controls. Flexible and reliable method for element-specific analysis of heavy metals in a broad concentration range for pharmaceutical, cosmetic, and food products.

C. Separation and Quantification of Complex Product Mixtures

Using chromatographic, electrophoretic, spectroscopic and hyphenated techniques we develop the optimal solutions for specific problems in the fields of qualitative and quantitative analyses covering a broad range of compounds such as pharmaceutical substances, agrochemicals, small organic molecules, inorganic ions, amino acids, peptides, glycoproteins, carbohydrates, synthetic polymers and biopolymers, additives, fluorescent whitening agents (FWA), natural compounds, surfactants, lipids, plant ingredients, and others. Our services consist of single measurements, complex analysis and preparative purification as well as scientific project management and technical consulting for research, development, and production.

Services

Analytical Method Development and Validation

- Method development for qualitative and quantitative analysis and for release testing. Method validation including accuracy, linearity, specificity, robustness, intermediate precision, LOD, LOQ, *etc.*

Quality Control and Release Analytics

- Active substance and by-product (purity) assay (see Fig. 3)
- Reference batch certification
- Analysis of intermediates, by- and degradation products
- Amino acid and peptide analysis
- Determination of residual solvents
- Analysis of environmental samples
- Stability studies

Analytical Support for Projects

- Product development
- Pilot campaigns
- Product plant introduction

Purification, Characterization/Certification of Substances

- Providing reference material for release analytics
- Isolation of unknown compounds, *e.g.* from chemical/pharmaceutical production
- Structure elucidation of unknown compounds using hyphenated techniques
- Isolation and characterization of by-products *e.g.* for registration purposes

Specialized Equipment

- Chromatography (HPLC, GC, TLC, preparative LC, IEC, SEC and many special detectors)
- Electrophoresis (IEF, SDS–PAGE, FFE)

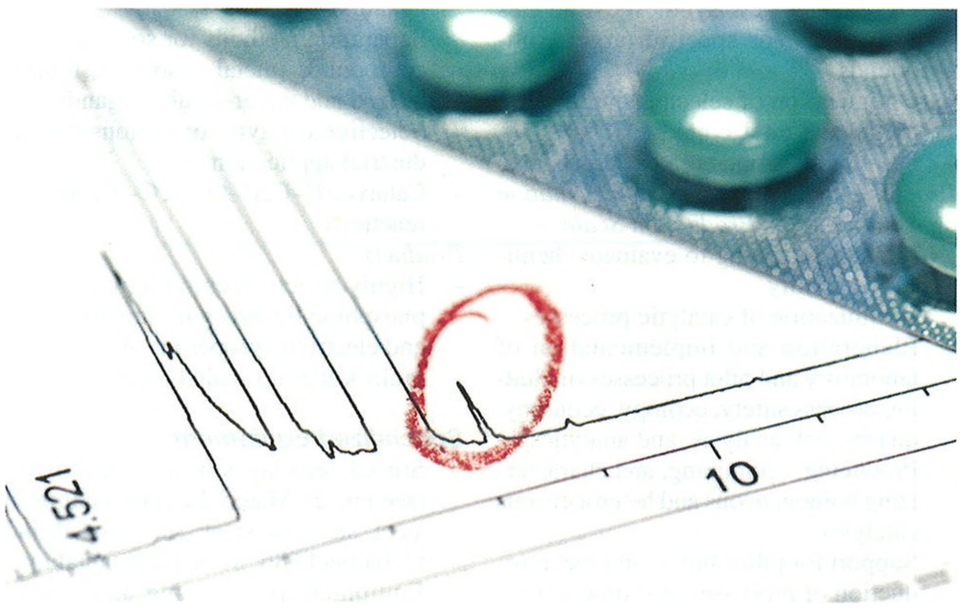


Fig. 3

- Capillary electrophoresis (UV and LIF detection)
- Mass spectroscopy (ESI, APCI, MS^n, MALDI–TOF–MS)
- Hyphenated techniques (LC–MS, GC–MS, GC–IR, TLC–IR, TLC–MS, LC–AMD)

Typical Examples

Scale up of an efficient RP–HPLC method from analytical to preparative dimensions for an unknown impurity. Development of robust, validated chromatographic methods for quality control under GMP. Development and implementation of a custom-made analytical concept for an active compound.

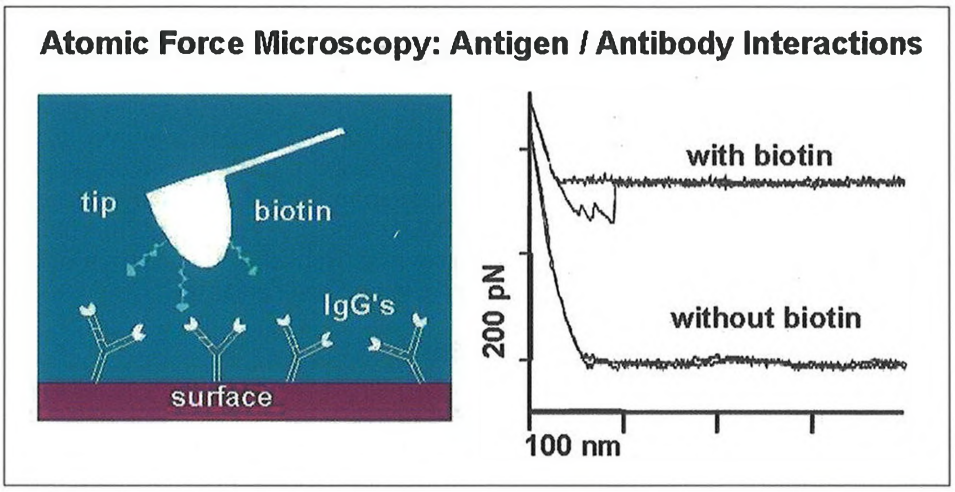


Fig. 4

D. Nucleic Acid Analysis

Using state-of-the-art technologies and the latest hardware, we provide interdisciplinary know-how in nucleic acid analysis to customers in diverse fields of the life sciences. We are recognized experts in DNA sequencing and PCR technology (amplifications and combined applications, mutant screening, genotyping), in lab automation and information technology, and we offer our customers a broad spectrum of services from comprehensive consulting to the development of individual solutions, including method optimization and validation.

Services

Molecular Biology Support
- Primer design and purchasing
- Transformation
- Automated template isolation for PCR products, plasmids, cosmids, and BACs
- Isolation of genomic DNA from tissue biopsies and blood

DNA Sequencing
- DNA sequencing of PCR products, plasmids, and BACs
- Primer extension, EST sequencing
- Sequence confirmation and determination of unknown sequences
- Mutation detection and characterization by sequencing
- Large-scale sequencing projects (*e.g.* cosmids, BACs)

PCR Technology
- Consulting on experimental strategy and the use of high-throughput tools
- PCR amplification (method optimization and validation, routine measurements)
- Genotyping, heterozygosity assays
- Real-time and quantitative PCR

Contract R&D (examples)
- Subcloning projects
- Site-directed mutagenesis and applications of GPS (genome priming system)
- Production of reference materials (*e.g.* control templates for PCR) and hybridization probes (*e.g.* for Southern blotting)

Specialized Equipment
- State-of-the-art hardware park, *e.g.* ABI PRISM 3700, ABI PRISM 7700, Real-time PCR, Robots, Peltier-based and gradient thermocyclers
- Custom-built integrated solutions for IT and automation needs on a high-throughput scale

Typical Examples

Direct sequencing of bacterial artificial chromosomes (BACs). Quantitative PCR (Real-time PCR) using the state-of-the-art ABI PRISM 7700 sequence detection system.

E. Physical Chemistry

We can support our customers in all areas of physical chemistry, biological–pharmaceuticals, and optics. Our experts with a broad know-how and a complete methodology are available to conduct single measurements as well as to develop complete solutions, plan and conduct studies and to carry out contract research.

Services
- Characterization and determination of substance data in general physical chemistry (*e.g.* preformulation characterization)
- Integral solutions based on the properties of the substances involved, polymorphism studies
- Stability studies of active substances and formulations
- Process optimization: distillation, crystallization, drying, lyophilization
- Formulation development
- Quality control
- Binding studies and kinetic analyses
- Modeling and simulation of processes that are not directly accessible
- Representation of cells, molecules, crystals, inhomogeneities and impurities
- Determination of properties of biological and technical macromolecules
- Characterization and quantification of surfaces, particles, and dispersions
- Contract research and consulting

Specialized Equipment

In our well-equipped laboratories, we work with all current physicochemical methods as well as special methods such as:
- Atomic force microscopy, also in aqueous systems
- Scanning electron microscopy with electron dispersive X-ray analysis
- Analytical ultracentrifugation
- Coupled thermal/spectroscopic methods
- X-ray diffraction at controlled temperature and atmosphere
- Ellipsometry and radiometry

Typical Example

Increase in low-temperature stability of a formulation by identification of the triggering crystal compound, and avoiding its formation by a slight change in composition.

F. Surface Technologies

Our scientists have a broad knowledge in the qualitative and quantitative analysis of surfaces, interfaces, and thin films of industrial importance. Using up-to-date methods and technologies, we analyze and treat surfaces according to the criteria of physics, material sciences, (bio)chemistry, medical, and biotechnology.

Services

Microscopic Surface Analysis
- Roughness and morphology analysis
- Analysis of micro- and nanostructures
- Quantitative particle analysis (size, shape, size distribution)
- Determination of coating thickness (Å to mm)
- Biophysics – quantitative determination of single macromolecule structure and interaction properties (see Fig. 4)

Surface Energies
- Wetting properties of solid-state surfaces
- Stability of formulations

Surface Treatment
- Physical and biochemical surface treatment (cleaning/coating/functionalization/patterning)

Chemical Surface Analysis
- Elemental microanalysis (mapping)
- Optical spectroscopy for chemical analysis

Technical Consulting
- Feasibility studies and consulting on materials and processes for surfaces
- Trouble-shooting and support in research, development, and production

Specialized Equipment
- Light and laser scanning microscopy (LM & LSM)
- Infrared and Raman microscopy
- Electron microscopy (SEM & TEM)
- Scanning probe microscopy (STM & AFM)
- Ellipsometry
- Elemental microanalysis mapping (EDX)
- Photo-electron spectroscopy (ESCA/XPS) (*via* third parties)
- Time-of-flight mass spectrometry (TOF–SIMS) (*via* third parties)

Typical Examples

Analyzing the homogeneity, roughness, morphology, and thickness of contact lens coatings with atomic force microscopy under physiological buffer conditions on the nanometer scale. Documentation of asbestos in buildings and ventilation systems using scanning electron microscopy (SEM) allowing the classification of different types of asbestos. Characterization of micro- and nanostructured surfaces such as semiconductor chips or diagnostic biosensors down to the molecular level without destroying the surfaces. Direct examination of the structural and functional properties of single biological macromolecules or other biosystems like cells or tissue using the appropriate labeling procedures (*e.g.* fluorescence or immunolabeling).

G. Polymorphism Studies

We offer our customers an internal network of specialists and state-of-the-art equipment and technologies to analyze organic solids. Our services cover an extensive range of methods and encompass the determination of simple physicochemical parameters, entire polymorphism studies as well as the preparation of expert reports and patent specifications.

Services

Solid-State Characterization of Organic Substances
- Determination of simple physical parameters
- Complete characterization of substances
- Evaluation and optimization of crystallization processes for the requested polymorphic form

Expert Reports, Registrations, and Patenting
- Composing registration documents and patent specifications
- Composing expert reports, such as patent litigations

Specialized Equipment
- Hot-stage Raman microscopy
- Hot-stage X-ray diffraction analysis
- Coupled thermal and spectroscopic methods, *e.g.* TG–FTIR

Typical Examples

Identification and determination of the pharmaceutical relevance of different crystal forms. Development of a robust crystallization procedure to obtain a defined metastable form with superior characteristics.

H. Production, Isolation, Certifiction and Supply of Reference Substances

We provide our customers with support in isolating chemical and biological by- and degradation products using synthesis, separation, purification, and analysis including several combinations of chromatographic and spectroscopic techniques. We offer a range of services, including characterization, production, certification, stocking and delivery of reference compounds including the adaptation of methods to individual customer needs. We also determine compliance with threshold values for our customers, if this information is required to certify an active substance for further processing or sale.

Services
- Production, isolation, and characterization of minor constituents, degradation- and by-products
- Purification, certification, and re-certification of active substances and by-products
- Full service for stocking and delivery of reference substances (with certificate of analysis on request)

Specialized Equipment
- Automated high-throughput laboratory for preparative separations
- Free-flow electrophoresis (FFE)
- Equipment according to state-of-the-art development including all chromatographic methods (HPLC, CE, GC, HPTLC) with a series of detectors
- Spectroscopic technologies (mass spectroscopy, infrared spectroscopy, MALDI–TOFMS *etc.*)
- Various hyphenated technologies (such as HPLC–MS, GC–MS)

Typical Examples

Fast development of a preparative isolation method for a reference substance. Solving a quality problem with a pharmaceutical intermediate by isolating and identifying unknown impurities.

I. Analysis of Trace Compounds in Air, Water, and Soil

We develop integrated solutions (analysis, project management and consulting) and research new methods to help our customers locate and prevent potential environmental impacts. Using state-of-the-art technologies and procedures, an interdisciplinary team of specialists with experience in environmental problems analyses toxic substances in air, water, and soil.

Services

General Water Analysis
- Chemical analysis of ground, surface and wastewater
- Quality control of drinking water
- Microbiological water analysis

Air and Waste Air Analysis
- Measurement of emissions from combustion gases and waste air
- Air pollution control measurements for 'Clean Air Acts'
- Development of concepts to improve air and waste air quality
- Monitoring room air for industrial hygiene

Examination of Waste and Soil
- Soil analysis
- Analysis of contaminated sites according to regulations
- Landfill monitoring and collaboration in site remediation

Specialized Equipment
- Mobile labs

- Solvent-free laboratories to determine solvents in the ultra-trace range
- Enrichment systems for measuring dioxins
- Liquid chromatography/mass spectrometry
- Gas chromatography/mass spectrometry
- Thin-layer chromatography
- Ion chromatography

Typical Examples

Application of the Head-Space Technique to determine volatile organic solvents in soil down to concentrations of 50 µg/kg. Accredited measuring agent for periodic air pollution control measures.

J. Ecotoxicology and Water Analysis

Our expert staff of chemists, biologists and microbiologists has a broad know-how in handling industrial and agricultural chemicals as well as pharmaceutical active substances. We support our customer to register substances, conduct risk analyses and process data in compliance with regulatory requirements. We assess the impact of chemical substances on water and soil organisms, design studies to estimate their biodegradability and bacterial toxicology, and conduct microbiological and chemical analyses of drinking and ultrapure water.

Fig. 5

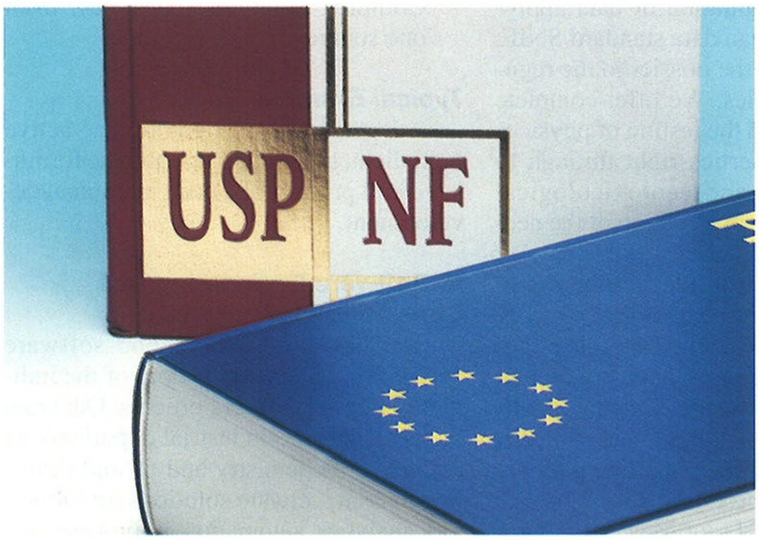


Fig. 6

Services

- Studies for the registration of new chemical substances
- Analyses of wastewater and contents of wastewater
- Impact assessment of chemicals in water and soil ecosystems
- Analyses of drinking and ultrapure water
- Determination of acute and chronic toxicity to algae, daphnia (see Fig. 5), fish, earthworms and plants
- Diverse range of tests for degradability and bacterial toxicology
- Measurement of BOD, COD, TOC, and other special parameters
- Microbiological analyses, such as determination of *E. coli*, *Enterococcae* and the total sum of aerobic microbes
- Determination of endotoxins

Specialized Equipment

- Newest generation of TOC analyzers for the determination of TOC in ppb range

Typical Examples

Determination of aquatic toxicity with algae, daphnia, and fish. Biodegradation tests with substances and wastewaters using activated sludge. Quality control of ultrapure water for pharmaceutical production.

K. Ambient-Air Monitors

The use of highly toxic or carcinogenic compounds often cannot be avoided. Techniques to handle such compounds have been established. Nevertheless, a certain risk remains that at some critical point, *e.g.* a valve, an invisible leak occurs and toxic fumes in amounts injurious to the health escape. Consequently, appropriate precautions need to be taken to assure work safety. Our monitors enable our customers to take care of this task and comply with legal requirements.

Services

- Complete systems for monitoring ambient-air and wastewater including service contracts, personnel training, and adaptation of control software
- Permanent as well as time-limited installations, *e.g.* limited to a pilot phase
- Consulting and development of safety concepts

Important Applications

Monitoring of compounds with MAK values (Maximale Arbeitsplatzkonzentration, maximum workplace concentration, 1997 Swiss regulation) from the lower ppm range (*e.g.* acrylonitrile, 2 ppm; epichlorohydrine, 2 ppm) down to the lower ppb range (*e.g.* dimethyl sulfate, 20 ppb; bis(chloromethyl) ether, 1 ppb). Typically, detection limits are 100 times smaller than the corresponding MAK values (*e.g.* <1 ppb for dimethyl sulfate, <0.01 ppb for bis(chloromethyl)ether). Analysis times are between 2 and 12 min.

Important Features of our Ambient-Air Monitors

- Guaranteed specificity; detection limit normally 1/100 of MAK value
- Up to 15 sampling points, each up to 150 m apart; parallel monitoring of several compounds
- Permanent operation (auto-calibration/auto-function control)
- Parallel screen display of latest analysis results for all sampling points
- Storage of all alarm chromatograms, printing of all relevant results, statistical reports

L. Regulatory Affairs

Thanks to close interdisciplinary collaboration between our regulatory affairs specialists, our in-house analytical scientists and carefully selected outside companies, we can prepare registration dossiers for drug products and chemicals that are tailored to the specific needs of our customers.

Services

- Advisory support for the notification of chemicals in accordance with the EC Directive 92/32/EEC (7th Amendment); elaboration of the registration dossier; consolidation of data applying the European data standard SNIF; submission of the dossier to the regulatory authorities. We offer complete solutions, from the testing of physicochemical properties right through to toxicological and ecotoxicological studies and the preparation of the necessary documentation.
- Preparation of full registration dossiers for drug products as well as consulting and documentation for re-registration procedures (*e.g.* production site transfers, changes in manufacturing process)
- Support during the registration procedure for drug products
- Preparation of Drug Master Files for the registration of drug substances both in the USA (Type II DMF) and Europe and for manufacturing sites and facilities (Type I DMF for USA). Together with our Catalysis Department we can help to develop and register new methods of synthesis with a view to substantially reducing production costs. Preparation of the technical dossier for medical devices according to the European requirements (93/42/EEC)
- Development of Change Control Systems

Skills and Experience

- International experience in registration of drug products, drug substances, medical devices, and chemicals
- Thorough understanding of the laws governing the registration of drug products, drug substances, medical devices, and chemicals

M. Release Analytics

We conduct release analytics for raw materials, excipients, active substances and end products, also providing the necessary methods and validations where required. Our experts carry out these analyses either as partial or entire packages, as agreed upon with the customer. A broad variety of methods ensures quick results in the case of unexpected additional investigations (such as in case of OOS results)

Services

- Release analytics for excipients, active substances, and end products as well as for intermediates or starting materials from external providers
- Development and validation of new methods and testing procedures
- Retrospective validation of existing methods and testing procedures
- Complete solutions (packages) from one source

Typical Example

Adaptation of methods for the active ingredient, two excipients, and the formulated end product of a drug in clinical development.

N. Software Engineering and Consulting for Analytics

The development of good software begins with an understanding of the individual steps in the work process. Our team of specialists has industrial experience in the areas of chemistry and IT and develops custom software solutions for laboratory analytics, automation, in-process control and monitoring. We are skilled in integrating our customers' specific knowledge as well in providing extensive consulting.

Services

General Solutions

- Analysis of business processes
- Software design and implementation
- Project management
- Quality assurance

Custom Software Development

- C++, Java
- Databases
- Windows NT and LINUX

Specialization

- Chemometrics
- Colorimetry
- Numerical simulation and mathematical algorithms
- Matlab application programming

Validation

- Software development based on a lifecycle model according to ISO 9001 standards, enabling FDA-conform validation.
- Creating SOPs according to specifications, including validation documentation for IQ, OQ and PQ
- Analysis of existing systems
- Consulting for new projects

Technology Basis

Our software is based on a modular package. Modules for data analysis (such as chemometrics, colorimetry), drivers for connecting instrumentation (such as spectrometers, balances, diluters, auto samplers, barcode readers) and client-specific modules are combined individually.

Typical Examples

In-process quality control by optimal coordination of analytical sequences in the plant. Control of laboratory instruments in a GMP Lab. Development of expert software as application and sales support for the formulation of dye formulations.

O. Online Technologies

Through the implementation of online analytics, our customers are able to optimize processes and determine important process decision points, leading to reduced production costs and increased product quality. Employee and environmental safety are also noticeably improved. Our services include consulting, concept development and evaluation as well as the technical implementation and customer training. We have successfully installed more than 240 applications on both the production and laboratory scale; over 1000 of our process probes are in use today.

Services

Projects in Online Analytics

- Distillation and reaction (start and endpoint, intermediates) monitoring
- Control of specific chemical processes (such as bromination, hydrogenation, Grignard reaction)
- Crystallization monitoring (polymorphism)
- Control of mixing processes (powder, liquids, gases)
- Turbidity measurement in the fermenter
- Monitoring of separation and filter devices
- Wastewater and air monitoring
- Quality control and raw material identification (QC/QA), product identity
- Determination of water content, OH^-, iodine and acid values
- Measurement of fat and dry substance content (dairy products)

Process Optimization

- Determination of process kinetics
- Process modeling
- Identification of relevant process parameters

Ambient-Air Monitoring for Exposure Limit Compliance

- Detection of hazardous substances (*e.g.* dimethylsulfate, bischloromethylether)

- Detection limits: typically $^1/_{100}$ of exposure limits

Specialized Equipment

- Spectroscopic methods: UV/VIS, NIR, IR and Raman
- Fiber optics and sensors
- Data analysis: chemometrics and other computer-based methods
- Laboratory analytics and automated reactors

Typical Example

Saving costs in a distillation process by continuous online monitoring in NIR range.

P. Fiber-Optic Probes for Chemical Process Technology

Solvias offers both a range of standard probes as well as a broad selection of custom designs. Fiber-optic probes allow online and inline measurements in laboratories and production plants while the analysis device stays in a protected environment (explosion-proof installation). Complex sample extraction devices and bypass-systems involving long distances are avoided leading to better cost efficiency and higher plant safety. Through direct dialog with users we continuously improve our products and adapt them to changing needs.

Our standard probes can be used up to 16 bar and 140 °C. Custom-made probes for usage up to 100 bar and 280 °C are available. Materials used for probe construction: Glass, quartz, sapphire, high-grade steel, titanium, Hastelloy, PTFE, PVDF and perfluoro elastomers.

Transmission Probes

Probes for Installation into Pipelines

- Variable thickness, up to 20 mm, reproducibly adjustable
- Probe consists of an optical part and a tube adapter for any tube dimension and flange combination
- Material: standard steel 1.4571; other materials available on request
- Pressure load: standard 16 bar or 40 bar; probes for 63 bar and 100 bar are available
- All commercial devices that measure in the UV, visible, and NIR spectral regions and that can be connected to an optical fiber are suitable for use as photometers.

Transmission Immersion Probes

- Different models for laboratory and production facilities are available
- Variable layer thickness from 0 mm to approx. 5 mm through adjustment of mirror position

Fig. 7

Diffuse Reflection Probes

Diffuse Reflection – Back Scattering (Immersion Probes)

This type of probe measures the light scattered back from suspensions, emulsions, powders and surfaces. The probes are available in a range of different sizes, and are therefore easily integrated into existing facilities (*e.g.* through an Ingold fitting). Operational range: pressure 40 bar, temperature 140 °C (standard); custom-made devices up to 500 bar and 280 °C are available.

Typical Applications: Turbidity, reflection and Raman measurements

Diffuse Reflection – Forward Scattering

These probes are suited for installations in pipes for measuring small turbidities (measurement range from *ca.* 0.1 NTU); the form is similar to transmission probes (available as DN40 and DN50 adapter).

ATR (Attenuated Total Reflection) Probes (see Fig. 7)

Total reflection occurs at the transition from an optically dense to an optically less dense medium. The light enters the optically less dense material through the boundary layer to approximately one fourth its wavelength where it can be absorbed. In our probes, the denser medium is sapphire-crystal; the optically less dense medium is the sample to be tested. Typically, layer thickness is in the sub-micrometer range; therefore good measurement results are to be expected for extinctions $<10^5$/cm.

One Last Comment

Undoubtedly, a major strength of Solvias is its exceptionally wide range of services in the areas of synthesis, especially using catalytic methods, and chemical, physical, and biological analytics. However, even more important will be our ability to offer service packages comprising any desired combination of our competencies from one single partner within Solvias. These combinations and their efficient handling allow us not just to solve smaller and bigger problems but to come up with major contributions to enhance the success of our customers.

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Speedel

Speedel Pharma Inc.

A New Company for Fast-track and Efficient Development of Cardiovascular Drugs

Alice Huxley, Chris Jensen, and Dietrich W. Scholer*

Abstract: Speedel Pharma was established at the end of 1998 in Basel, Switzerland, with the goal of contributing – with a new business concept – to the fast and efficient development of innovative cardiovascular drugs. The company's business objective is to acquire, finance, and develop innovative molecules for the treatment of cardiovascular and metabolic disorders and to unlock their value through:
• Fast-track clinical development programs emphasizing clinical proof of concept and indication targeting,
• Innovative technical problem solving (*e.g.* synthesis improvements, galenic formulations)
Speedel was founded by a group of Pharma managers and scientific experts with long-standing R&D experience. This core team is supported by a Medical Advisory Board and a Scientific-Technical Advisory Board. Speedel has raised over 20 million Swiss francs in private financing.
The front-runner of Speedel's development portfolio is SPP 100, an orally active renin inhibitor, licensed from Novartis Pharma AG, for the treatment of hypertension, chronic renal disease, and congestive heart failure. SPP 100 represents a breakthrough in an effort lasting more than two decades to find a suitable renin inhibitor with high potency, specificity, and oral bioavailability.
Since licensing this compound from Novartis Pharma in 1999, Speedel has established an ambitious fast-track program and driven the development of SPP 100 from Phase I testing in volunteers to the successful start of patient studies in Phase II.
Speedel is confident that its business concept and operational approach can accelerate drug development. Speedel is now interested in broadening its pipeline to additional compounds, which could take advantage of Speedel's strengths in efficient concept testing and innovative technical development.

Keywords: Cardiovascular innovation · Fast-track development · Pharma R&D start-up · Renin inhibitor

Speedel Pharma Inc. was established at the end of 1998 in Basel, Switzerland, with the goal of contributing – with a new business concept – to the fast and efficient development of innovative cardiovascular drugs. Speedel Pharma identified smart design and speedy development as key success factors for swiftly turning research progress into patient benefit.

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Concept and Business Objectives

As a highly specialized and focused company, Speedel is driven by a synergistic team of experienced Pharma managers and experts, supported by opinion leaders in the field as advisers, and acts as an independent turnkey operation with a network of leading development facilities. The company's business objective is to acquire, finance, and develop innovative molecules for the treatment of cardiovascular and metabolic disorders and to unlock their value through:

- Fast-track clinical development programs emphasizing clinical proof of concept and indication targeting,
- Innovative technical problem solving (*e.g.* synthesis improvements, galenic formulations)

'Speedel's ambition is', as Alice Huxley, President and CEO, explains, 'to design and implement the most efficient strategy – like in a chess game – for pushing innovative compounds through the initial phases of the clinical and technical development process. Recognizing the profound changes of Pharma R&D, we felt that there is an increasing need to concentrate on these critical development steps. With this goal in mind, we have built a dynamic and flexible organization, able to provide a full package of development activities from a com-

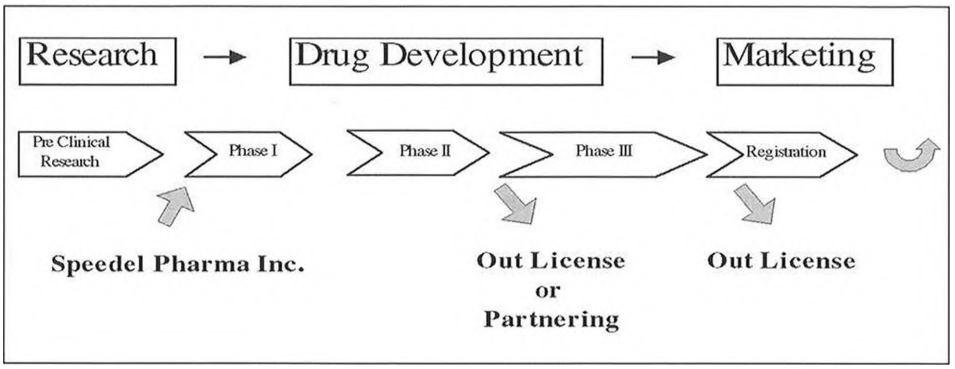
pound's early clinical development through registration'.

The company does not pursue its own discovery research or marketing. It concentrates on development activities; from early clinical development through Phase II/III leading to registration. Speedel addresses the strategic needs of its partners, these being fully integrated pharmaceutical companies (interested in licensing-out certain projects for strategic or resource reasons), or research start-up companies and research institutes lacking development experience.

Speedel's concept is different from that of CROs (Clinical Research Organizations) since Speedel acquires the compounds, owns their intellectual property rights, finances the development and participates in the commercial success of marketed products.

Speedel develops in-licensed compounds for its partners, without burdening them with the utilization of their development resources (management resources, manpower, and financial resources) against adequate compensation (Scheme). Compensation is defined case-by-case, taking into account the value-added contributions made by Speedel, and will usually include significant milestone payments and royalties on the marketed products. The partners may have the right of first negotiation upon successful completion of an agreed development stage (usually end of Phase II).

Scheme



Focused Project Management

Speedel operates with a core team of specialists who design and manage the development projects by outsourcing selected development activities. Speedel's managers and experts evaluate and engage the best subcontractors and closely supervise the execution of a given task in terms of results, timing and costs.

CVS Focus and Portfolio

The company's initial focus is treatments for cardiovascular and metabolic disorders, indications which account for 25% of the global pharmaceutical market.

Speedel's first compound in development is SPP 100, an orally active renin inhibitor for the treatment of hypertension, congestive heart failure and chronic renal diseases. SPP 100 is currently in Phase II clinical trials. SPP 100 was licensed from Novartis Pharma AG and represents a breakthrough in an over two decades-long effort to find a suitable renin inhibitor with high potency, specificity, and oral bioavailability.

Other potential in-licensing candidates have been identified from different companies and are in pre-negotiation phases.

The Management Team

Speedel's key strength is the people involved, their previous professional experience and track records in the drug development process.

Alice Huxley, Ph.D., founder, CEO and President, previously a global project manager at Novartis Pharma AG leads the Management Team.

The team includes:

- Dietrich W. Scholer, M.D., Chief Operating Officer, was previously the Head of CVS and CNS Drug Discovery at Ciba-Geigy Pharmaceuticals Division
- Chris Jensen, Ph.D., Director of Clinical Operations, has extensive international clinical research experience at Sandoz Pharma AG, as COO of BioClin, a Clinical Research Organization, and President of International Services at Chrysalis
- Erich Widmer, Ph.D., Director of Chemical Synthesis, is an expert in process development and optimization
- Satish Khanna, Ph.D., Director of Drug Delivery, brings expertise and a track record of patents of sophisticated oral dosage forms
- Judith Dubach, Ph.D., Head of Pharmacokinetics and Toxicology, has experience in large pharmaceutical companies and contract Toxicology Institute
- Roland Tschannen, Ph.D., Director of Licensing, is an experienced licensing executive

The Board of Directors

The Board of Directors embraces persons with long-standing, diversified experience in pharma businesses:

- Martin Kuhn, JD, is the previous Head of New Businesses Department at Ciba-Geigy Pharmaceuticals Division, Chairman of the Board
- Georges Haas, Ph.D., is the previous worldwide Head of Research and Pre-Clinical Development of Ciba-Geigy Pharmaceuticals Division
- Alice Huxley, Ph.D., CEO and President of Speedel
- Fritz Kunz, Ph.D., previously headed various pharmaceutical R&D functions including a special project development unit at Sandoz Pharma, and has experience as CEO and CFO of two mid-sized medical technology companies
- Marius Sutter, Ph.D., has extensive experience in Investor Relations and Strategic Planning.

Speedel enjoys the support of its strategic advisors and business lawyers, Viren Mehta from Mehta Partners LLC (New York) and Thomas Rinderknecht and Ralf Rosenow from Rinderknecht, Klein and Stadelhofer Law Company, (Zürich), respectively.

Medical Advisory Board

- Hans R. Brunner, the Chairman of Speedel's Medical Advisory Board, is a Professor of Medicine at the University of Lausanne, Switzerland, and is Head of Division of Hypertension and Vascular Medicine. He has been at the forefront of research on the role of renin and the renin-angiotensin system in blood pressure regulation. He has been involved in the development of such drugs as ACE-inhibitors and angiotensin-II-receptor-antagonists. He was, together with H. P. Gavras, the first to introduce the use of angio-

tensin-converting enzyme inhibitors in the treatment of hypertension and congestive heart failure.

- Haralambos 'Harry' P. Gavras, a Professor of Medicine at Boston University, is the Head of the Hypertension Section. He served on the NIH Cardiovascular Renal Study Section and serves on the Advisory Committee for Hypertension and Atherosclerosis at the NHLBI. He is the past president of the Inter-American Society of Hypertension. His research has led to major contributions to the understanding of the role of the renin-angiotensin system in the pathogenesis of hypertension and heart disease. He was, together with H.R. Brunner, the first to introduce the use of angiotensin converting enzyme inhibitors in the treatment of hypertension and congestive heart failure.
- Albert Mimran, is a Professor of Medicine and Head of the Group Renin and Hypertension at the Institute of Clinical Research, University of Montpellier, France. He is the president elect of the International Society of Hypertension. His research focuses on experimental models of hypertension and the renal microcirculation. He has been instrumental in showing the role of renin and the RAS in the progression of renal disease.
- Jürg Nussberger, is a Privat Dozent of Medicine at the University of Lausanne and a member of the Department of Hypertension and Vascular Medicine. He has been at the forefront of development of bioanalytical methods for the determination of renin, angiotensin I and II and bradykinin.
- Michael Weber, is a Professor and the Chairman of Medicine at Brookdale University Hospital, Brooklyn, N.Y. He is the president of the American Society of Hypertension and editor of the American Journal of Hypertension. He also serves on the Food and Drug Administration (FDA) Cardiovascular and Renal Drugs Advisory Committee. He has been instrumental in the development and evaluation of many of the drugs used in hypertension today.

Company Milestones

Since its foundation in late 1998, Speedel has successfully:

- Licensed a first compound (SPP 100), an oral renin inhibitor for the treatment of arterial hypertension, congestive heart failure and chronic renal failure, from Novartis Pharma AG
- Raised over 20 million Swiss francs in private financing
- Assembled a diversified, experienced Management Team and Board of Directors as well as Medical and Scientific/Technical Advisory Boards
- Completed the Phase I program of SPP 100
- Started treatment of patients in Phase II
- Concluded an agreement with Novartis Pharma AG for financing the fast-track development of SPP 100 throughout Phase II in two indications and a call-back option for Novartis at the completion of Phase II studies in hypertensive patients
- Established and scaled-up a new synthesis for SPP 100 and has filed two patent applications for the new process
- Developed a solid dosage form of SPP 100 for clinical studies
- Identified additional licensing candidates

Speedel is confident that its business concept and operational approach can accelerate drug development. Speedel is now interested in broadening its financial basis and pipeline by integrating additional compounds, which could take advantage of Speedel's strengths in efficient concept testing and innovative technical development.

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Syndeco GmbH
Your Chance to Outsource Your Projects

Andreas Gugger* and Philipp Wettstein*

Abstract: The outsourcing of projects within the chemical and pharmaceutical industries has become an important factor in modern management strategies. The reasons for outsourcing are manifold. As a CRO start-up company, Syndeco GmbH is filling a gap in the market, specializing in custom synthesis and synthetic development combined with a hi-tech analytical service.

Keywords: Contract Research Organization (CRO) · Custom Analysis · Custom Synthesis · Organic Synthesis · Outsourcing · Research and Development

Over the last few years, many companies within the chemical and pharmaceutical industries have begun to outsource projects. This outsourcing ranges from single studies or synthetic steps through to complete drug development. These projects are undertaken at contract research organizations (CRO) for many reasons [1], however, cost considerations are often the underlying factor. A further advantage for the customer is the transfer of development and production risks.

Syndeco GmbH is a start-up company specializing in custom synthesis and synthetic development. Our expertise lies in the area of organic and bio-organic chemistry, involving the synthesis of intermediates, drugs, metabolites and other reference compounds for chemical research.

The synthetic projects and the corresponding analytics are carried out according to the wishes of the individual customer with a high degree of interaction between Syndeco and our clients.

At Syndeco we have the hi-tech analytical facilities which are not normally available to companies of a similar size. We know no boundaries with regard to the amounts of compound we can prepare (1 milligram to hundreds of kilograms) and can therefore offer our services at any stage of the development process. This combination of synthetic flexibility and in-house analytics, together with our close customer relations, is unique.

Our customer base forms a broad section of companies from the chemical and pharmaceutical industries. Companies in need of complex chemicals and/or analytics, who are without the capacity, time, or for financial reasons need to outsource, are our potential clients.

Syndeco is, after only a short time, known worldwide. We have clients and partners in both Europe and North America. We are proud to count among our customers some of the most well-known and respected chemical and pharmaceutical companies in the world.

If you are in need of the services which we offer and require a fast and efficient partner, please contact us for a quotation.

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How we work:

briefing session
(Phase 1)
↓
non-disclosure agreement
(Phase 2)
↓
elaboration of individual customer package
(Phase 3)
↓
offer submission
(Phase 4)
↓
contract finalization
(Phase 5)
↓
project realization
(Phase 6)
↓
intermediate customer orientation
(Phase 7)
↓
product/service delivery
(Phase 8)

our chemistry:

- nucleosides and nucleotides
- peptides
- carbohydrates
- aromatics
- aliphatic compounds
- cyclizations
- hydrations
- reactions under pressure

we are:

- customer-orientated
- competent
- fast and efficient
- versatile and cooperative

our analytical services:

- NMR (300 MHz to 600 MHz)
- various MS methods
- FT-IR
- UV/VIS
- GC
- MPLC/HPLC
- combustion analysis (C,H,N,O)

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[1] For more information on custom synthesis, see *Chimia* **1998**, *52*, 241.

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Thales Technologies AG
Mechanism-Based High-Throughput Screening of Catalysts

Christian Hinderling[a,b], Christian Adlhart[a], and Peter Chen[a,b*]

Abstract: Thales Technologies, a spin-off company of the ETH Zürich, applies an unique technological position to the design, discovery, and optimization of organometallic catalysts for the chemical industry. The methodology and the initial focus on polymerization reactions is illustrated in this report by examples on several classes of organometallic catalysts. The combination of preparative, mechanistic, and analytical expertise offers particular advantages to new catalyst discovery, especially for catalysts that are either prepared as mixtures of components or are transformed into mixtures upon activation.

Keywords: Catalysis · Combinatorial libraries · High-throughput screening · Mass spectrometry

The Market

Approximately 80% of the processes in the chemical industry involve at least one catalyzed step. Within certain sectors, such as the polymer industry, the fraction is 100%, with optimization of the catalytic step constituting the primary technical challenge in new product development. The recent introduction of 'single-site' catalysts has revolutionized polyolefin production. The first commercial polyolefin material produced with a metallocene-based single-site Ziegler-Natta catalyst appeared in 1991 using the Exxpol catalyst system from Exxon. By 1996, approximately one dozen manufacturers produced just under 1 million tons of metallocene-based polymers worldwide, corresponding to about 2.5% of the total production of Ziegler-Natta-based polymers. The cumulative research effort up to 1996 totaled about US$ 3 billion. By the year 2000, the estimated annual production of metallocene-based polymers will total 20 million tons worldwide, comprising more than 10% of the global thermoplastic and elastomer market, with the share exceeding 50% by 2010 [1]. In 1998, annual R&D expenditures of approximately US$ 1 billion on metallocene-based systems comprised 75% of the total research effort in polyolefins [2]. Moreover, single-site catalysts of comparable sophistication are beginning to appear for other classes of polymers as well [3]. The reasons for the dramatic change in a once 'mature' industry are the superior physical properties, *e.g.* from crystalline to elastomeric, high impact strength and toughness, improved processing, optical clarity, *etc.* available at low cost in the polymers produced with the new catalysts. Because the materials themselves are still simply polymers of ethylene, propylene, and other inexpensive vinyl monomers, the improved properties derive from changes in the polymer microstructure, which, in turn are controlled by the physicochemical properties of the catalysts themselves. New metallocene polyolefins that have successfully entered the market are an isotactic polypropylene [4] from BASF whose superior mechanical and optical properties make it an alternative to more expensive polyethylene-terephthalate (PET) resins, and Engage®, a polyolefin elastomer from Dupont Dow Elastomers which processes like a thermoplastic but performs like a rubber. Engage® is the fastest-growing product in Dupont Dow, which has announced plans to triple annual production to 225 000 metric tons within the next three years [5]. The market for the new polymers, and, consequently, for new catalysts, is clearly demonstrated.

Thales Technologies AG

Thales Technologies AG, a spin-off company of the ETH Zürich founded in 1999 by Prof. Dr. Peter Chen of the Laboratory for Organic Chemistry, will fill a market need by design, discovery, and optimization of new catalysts. Services include:

i) discovery of new and/or improved polymerization catalysts by high-throughput screening of combinatorial libraries of potentially catalytic organometallic complexes for activity of the catalyst, molecular weight of the polymer, and molecular weight distribution,
ii) assay of the probable selectivity of new catalysts, *e.g.* tacticity, linear *vs.* branched polymer formation, homo- *vs.* copolymerization activity, on the mg scale without scale-up or bulk polymerization or characterization,
iii) extension of patent coverage on existing catalysts by rapid assay of functionalized complexes in the same structural class, and
iv) protection of patented catalysts by direct determination of the active catalytic species and mechanisms of catalysis.

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The Method

The core technology at Thales is an adaptation of electrospray ionization tandem mass spectrometry to organometallic reactive intermediates, combined with preparative and mechanistic expertise. The methodology has been developed in the research group of Prof. Dr. Peter Chen in the Laboratory for Organic Chemistry at the Swiss Federal Institute of Technology (ETH Zürich) [6–8]. The process of discovery and optimization occurs in several phases, each of which is illustrated below with an example.

Identification of Catalytically-Active Species in Solution

All competing methods for screening rely on rapid identification of *products* on the microscale using miniaturized and/or automated analytical methods. The methodology employed by Thales is a screen that relies on detection of active *catalytic species in situ*. Among the many other advantages offered by catalyst, as opposed to product, detection is the ability to work with catalytic formulations that are themselves mixtures of components under the reaction conditions. While many catalyst formulations in industrial applications are inherently mixtures, even well-defined complexes can produce multiple active species upon activation in solution. For example, even the Grubbs-type ruthenium carbene complexes [9], while prepared as a pure substance and characterized by X-ray crystallography, can generate (depending on conditions) more than one metathesis-active species in solution [10]. In a much more complicated example, a highly active ROMP catalyst prepared according to the procedure disclosed in a BF-Goodrich patent [11], and described as a 'dark orange syrup', clearly shows at least seven molybdenum complexes in high abundance and many more as trace components [10]. Activation by Et_2AlCl produces yet more species. Screens that function by product detection will have difficulty deconvoluting activity arising from multiple species, or from minor components in a complicated mixture.

For Thales, it should also be emphasized that the catalytically active lead structures need not come from existing structures. While the examples in this report detail studies on published catalysts, the mechanistic information gained from the experiments on organometallic reactive intermediates lead to novel lead structures, some of which are under development as new catalysts.

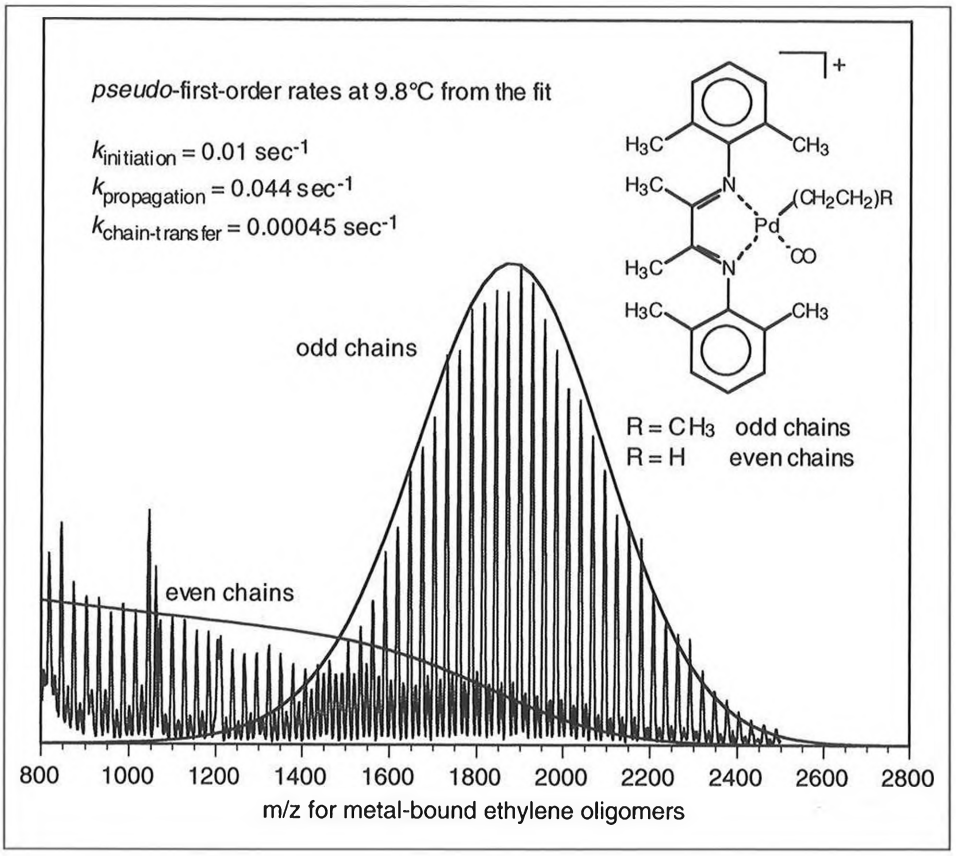


Fig. 1. Electrospray mass spectrum of catalyst-bound ethylene oligomers, after activation of catalyst, reaction with ethylene, and quenching with CO. The expanded region shows the odd and even chain distributions. The fit to the integrated kinetic scheme from ref. [14] yields the initiation, propagation, and chain-transfer rates. Further integration yields the prediction that the weight-average molecular weight (M_w) of bulk polyethylene formed from this catalyst will be about 5400. From ref. [8].

Construction of a Mechanism-Based Screen

The fundamental problem in high-throughput screening is to obtain the answers to complicated questions from simple measurements. While overall rate of a reaction can be measured in library screens by means of simple physical measurements such as heat release, *i.e.* the thermographic method [12], or changes in refractive index, the important questions in a complicated process such as polymerization require a more complicated probe. Even the most basic figure-of-merit in a polymerization reaction, the average molecular weight of polymer formed by a given catalyst, is itself a composite property with many inputs. To achieve rapid assay of a complicated property, one must put into the screen some sort of information content that encompasses the complexity of the problem.

For the Thales approach, this added information content is mechanism. Although it cannot be guaranteed that any given reaction has a mechanism which can be easily worked out, the mechanism provides the necessary link between what can be quickly measured and the needed complex material properties of a product. As a concrete example, we have reported [8] a high-throughput method for determination of the molecular weight and molecular weight distribution of polyethylene from a palladium-based catalyst reported by Brookhart and coworkers [13]. The assay was done on 2 mg catalyst in 5 ml CH_2Cl_2, and apart from a reaction time of ~1/2 h, required only minutes of measuring time on the instrument. Further data processing could be done offline. In the experiment, the solution of catalyst and ethylene was activated, allowed to react for a defined period at a set temperature, and then quenched with a two-electron neutral donor ligand, CO in the present example. The quenched solution was then diluted fifty-fold and electrosprayed into the mass spectrometer. Fig. 1 shows a portion of the mass spectrum in which are visible two series of catalyst-bound ethylene oligomers. The two observed series are consistent with the mechanism proposed by Ziegler and coworkers [14]: the 'odd chains' correspond to propagating oligomer chains which have not undergone associative

chain transfer, while the 'even chains' are propagating oligomers which have undergone chain transfer at least once. The kinetic scheme from Ziegler was numerically integrated, with the *pseudo*-first-order rates as fitting parameters. The fit and the corresponding rates are shown in Fig. 1. Variable temperature measurements allow extraction of Arrhenius parameters. With the rates and their temperature dependence, the kinetic scheme can be further integrated to yield the ethylene uptake rate and average molecular weight of polyethylene for the particular catalyst and conditions. It should be emphasized that the mass spectrometric measurement of relatively short metal-bound oligomers is translated by the mechanistic analysis to the molecular weight of metal-free polymer, in this case M_w ~5400. Of particular note is that bulk polymer, with its attendant problems of diffusion, precipitation, and isolation, was never actually produced. Nevertheless, the final result of the assay compares well with results from conventional bulk polymerization and gpc analysis, but has the advantage of working in minutes on the mg scale.

Screening of a Library

While an interface of the mechanism-based screening described above to a parallel reactor system is certainly possible, the catalyst-based assay offers the particular advantage that a pooled library can be screened. Moreover, while a pooled library may be deliberately constructed by a combinatorial synthesis of multiple catalysts in one-pot, the library could also be a catalytic formulation comprised of multiple components. Thales has a particular advantage in this case, in that product-based assays would be unable to handle a mixture. As an illustrative example [7], a mixture of eight palladium complexes was activated in ethylene-saturated solution, allowed to react for a time at a set temperature, and then quenched with a neutral donor, DMSO in this case. The solution was then diluted and electrosprayed. The upper panel of Fig. 2 shows the resulting mass spectrum, with multiple distributions of catalyst-bound ethylene oligomers evident. If all ions below a certain cutoff, m/z = 2200 in the example, are rejected, and the remaining ions subjected to collision-induced dissociation (CID with xenon), the resulting β-hydride elimination cleaves off the oligomer chain and leaves a palladium hydride complex corresponding to that catalyst within the mixture that gave the high-mass oligomeric ions. In the lower panel of Fig. 2, it is clearly seen that only one of the eight catalysts was responsible for the high molecular weight oligomers. The particular catalyst had also been identified as the most effective in the group by conventional methods. Connecting the qualitative result of Fig. 2 – one catalyst is better than the others – with bulk polymer properties is done *via* a parent ion scan. In a parent ion scan, a mass spectrometric detector is set to monitor a particular product of an ion–molecule reaction or CID event. A scan for ions that produce the particular product then deconvolutes contributions from different components of a mixture. Fig. 3 shows two parent ions scans [15], taken with the mixture of eight catalysts (Scheme), **1a–h**, activated to cationic complexes **2a–h**, reacted with ethylene to make a mixture of eight catalyst-bound oligomer populations, **3a–h**, each with its own distribution, and finally, subjected to CID to make the hydrides **4a–h**. In parent ion scans monitoring the hydride derived from either a moderately good catalyst, **4b**, or that from the best one, **4c**, the original catalyst-bound oligomer distributions are recovered. They can be subsequently analyzed as shown in the previous section to give the bulk polymer properties expected for these two catalysts. The bulk polymer properties are obtained in this fashion, not only without preparing bulk polymer, but also without ever separating the individual catalysts.

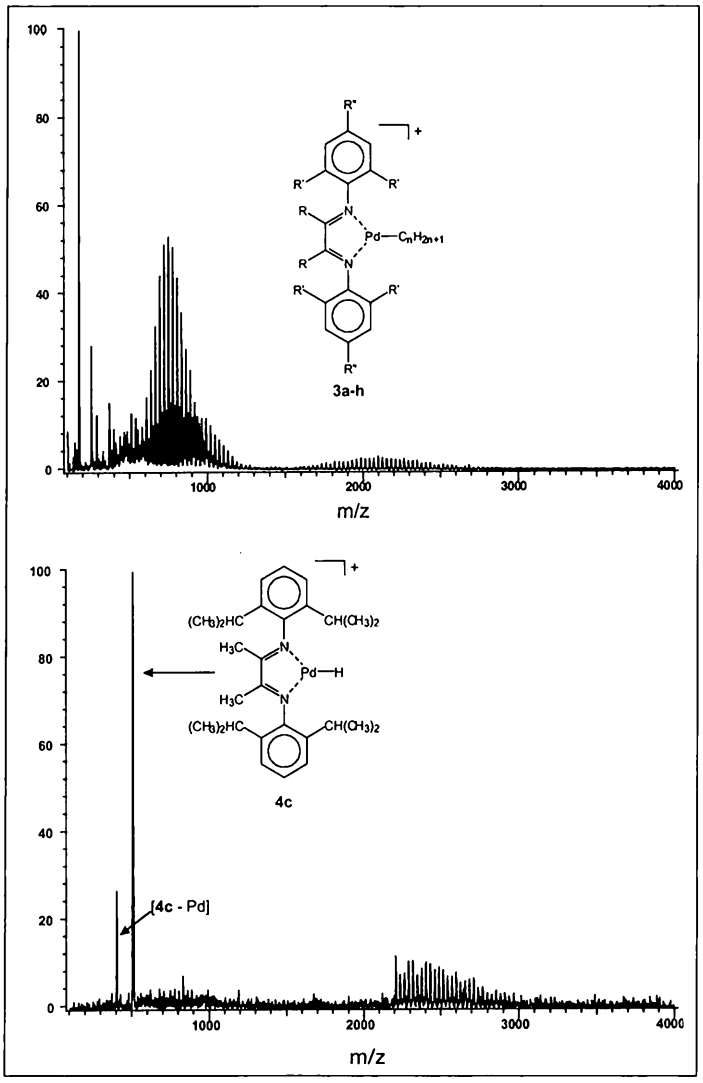


Fig. 2. Electrospray ionization mass spectrum (top trace) of the mixture of oligomeric/polymeric ions **3a–h** after reaction of **1a–h** with ethylene and quenching with DMSO. After selection of ions with m/z > 2200 and CID with Xe to induce β-hydride elimination (bottom trace), the daughter ion spectrum shows a predominant peak(s) at m/z ~511 (multiple Pd isotopes) and a smaller peak at m/z = 405. The former peak corresponds to **4c**; the latter to a secondary fragment [**4c**–Pd], identifying the best catalyst for high molecular weight polymerization within the library of eight catalysts. From ref. [7].

Summary

Thales Technologies AG combines an unique technological position in catalyst screening with the preparative and mechanistic expertise to design, discover, and optimize new catalysts. While the initial focus as demonstrated in the published examples is on polymerization, many of the techniques are more general. Under development are not only novel lead structures, but also new analytical techniques which will allow assays according to stereochemical or other structural properties.

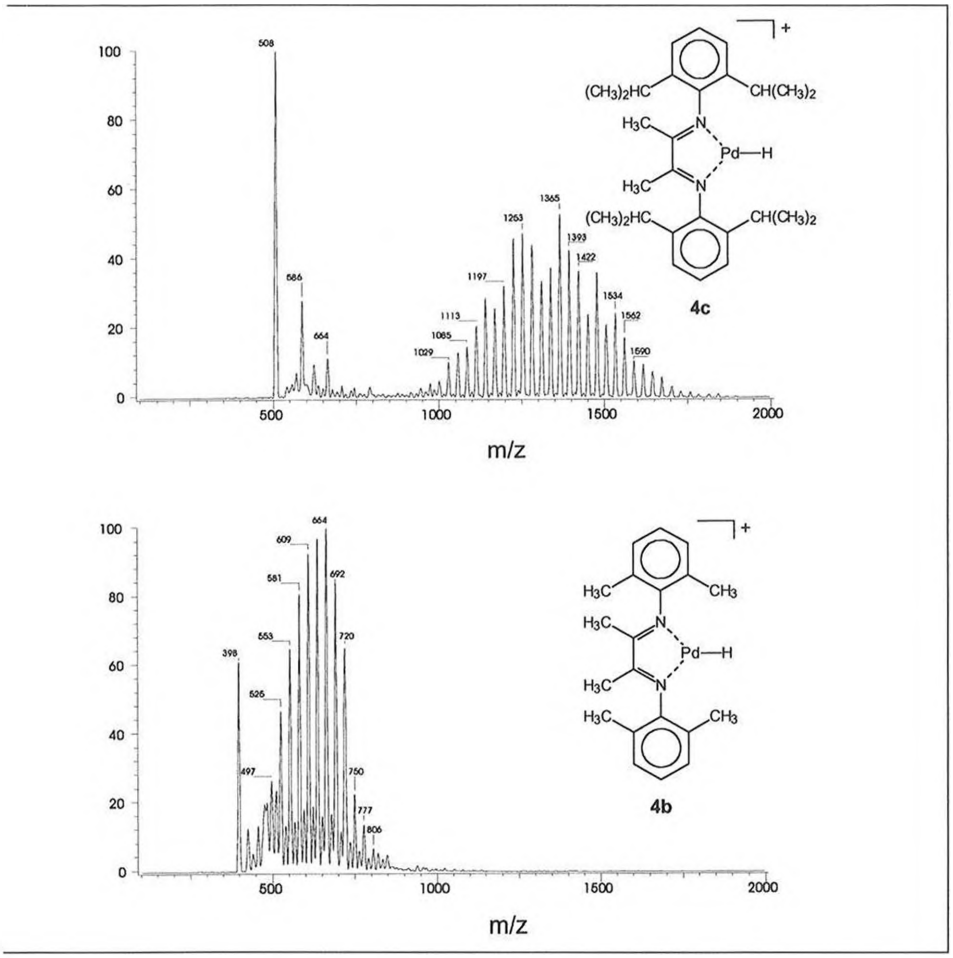
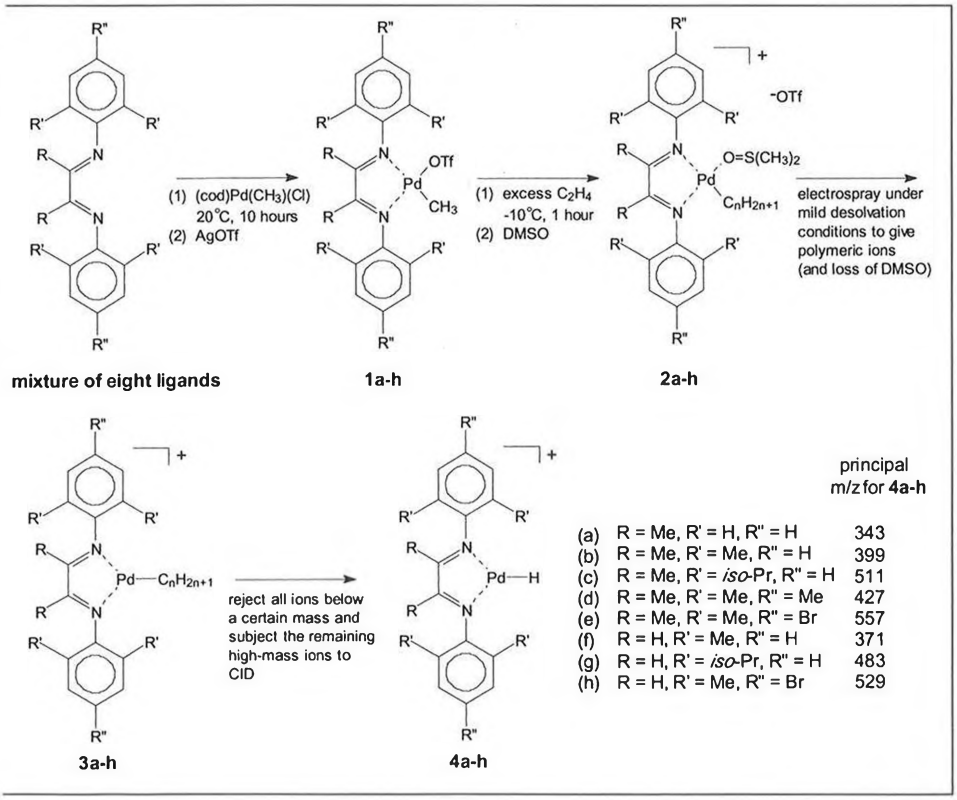


Fig. 3. Mass spectra from the mixture of eight catalysts **1a–h**, activated, reacted with ethylene at –15 °C for one hour, quenched, electrosprayed, and then subjected to CID. Top trace: Parent ion scan taken for m/z = 509, corresponding to **4c**. Bottom trace: Parent ion scan taken for m/z = 399, corresponding to **4b**. Each parent scan shows those ions, which upon CID, produce the selected daughter ion.

Scheme



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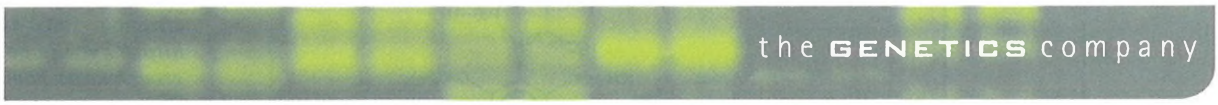

The Genetics Company, Inc.
A Newly Founded Swiss Biotech Company

Mario Jenni*[a], Konrad Basler[b], Ernst Hafen[c], and Michel Aguet[d]

Abstract: Morphogenetic pathways govern the processes that underlie embryonic development as well as self-renewal and homeostasis in adult tissues. The Genetics Company (TGC) exploits the untapped potential of morphogenetic pathways to develop new therapeutic approaches to human diseases with an initial focus on cancer and type-2 diabetes.

TGC has established Morphogenetics™ as a proprietary strategy:

- To identify and validate novel modulators of tissue and organ development for new therapeutic applications, ranging from the morphogenetic remodeling of tumors to *in vitro* tissue engineering and organ regeneration
- To identify new drug targets through *in vivo* saturation mutagenesis in *Drosophila*
- To identify small compounds by means of an innovative *in vivo* screening technology in *Drosophila* (InvoScreen™).

Keywords: Cancer · Diabetes · *Drosophila* · Functional genomics · Mouse

Introduction

Developmental genetics has brought light to one of life's deepest mysteries: how complex organisms develop from a simple egg. It has also inspired new approaches to the treatment of multifactorial diseases such as cancer and diabetes. Because of the stunning similarities of biological processes in individuals as different as a fruitfly and a man, organisms such as *Drosophila* or the mouse can serve as relevant, functional *in vivo* systems for the generation of new drugs.

Novel Concepts for Cancer Therapy

Tumors arise from accumulated mutations that corrupt the equilibrium between cell division, specification of cell fate, cell survival and programmed cell death. Over the past years, a large number of such molecular defects were identified. The advent of novel technologies allows the exploitation of these molecular defects as new molecular markers, and the improvement of both the sensitivity and the specificity of early detection and diagnosis. Numerous promising studies are underway to explore new therapies resulting from these discoveries, however, the impressive advancement in basic research has not yet translated into commensurate therapeutic progress.

Tumor cells not only grow, but also behave abnormally. Later stages of tumorigenesis involve invasion and metastasis, the consequences of a lack of proper observance of signals that govern cellular integration into the normal tissue architecture. In the last years, our understanding of the processes of cell fate specification and morphogenesis has progressed primarily through the genetic analysis of the development of model organisms such as the fruitfly *Drosophila melanogaster*. Strikingly, these developmental pathways prove highly conserved between *Drosophila* and man.

It is becoming increasingly evident that morphogenetic pathways are dysregulated in many tumors. Still, many tumors, including colon, breast and prostate carcinomas, retain an intriguing ability to differentiate, at least in local areas (microheterogeneity). The molecules that govern this behavior, presumably through direct cell-to-cell contact, are largely unknown.

TGC will combine *Drosophila* genetics and large-scale gene cloning in mammalian cells to discover and develop new pharmaceuticals that are able to attenuate the malignant behavior of tumor cells through modulation of morphogenetic pathways.

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Genetic approaches in *Drosophila* allow the identification of biologically relevant new drug targets in oncogenic signaling pathways (Fig. 1). TGC will set up large-scale saturation screens for mutations that revert the activity of cancer-promoting genes. TGC has developed several *Drosophila* tumor models, some of which are based on the concomitant activation of more than one pathway (oncogene cooperation), in analogy to most human tumors.

TGC will further characterize and validate recently identified, proprietary signaling components that suppress the activity of the oncogenes Wnt, Hh or D-Raf which are frequently activated in human tumors. These new signaling components are prime candidates as new therapeutic targets.

Cancer treatment is likely to rely increasingly on a combination of therapeutic strategies that affect different biological functions such as cell growth, programmed cell death, cell invasion, angiogenesis, or immune responses. It is our vision to exploit morphogenetic pathways to render tumor cells less aggressive through modulation of their microenvironment, with the aim, for example, to establish pre-surgical treatment protocols. Prior to surgical removal, solid tumors and/or metastases would be locally infiltrated with morphogenetic modifiers to induce a more differentiated tissue architecture and/or stimulate tumor encapsulation. This treatment would result in attenuated malignancy and significantly reduce the risk of tumor cell dissemination.

A *Drosophila* Model for Type-2 Diabetes (NIDDM)

Diabetes mellitus is the most common metabolic disease worldwide. Type-2 or non-insulin-dependent diabetes mellitus (NIDDM) accounts for >90% of cases. Owing to the lack of suitable model systems, it has been impossible to systematically screen for suitable drug targets or small molecules that attenuate or cure this disease. One of the TGC's founders has recently demonstrated that the insulin signal transduction pathway, which is affected in NIDDM, is structurally and functionally conserved between *Drosophila* and man (Fig. 2).

TGC has identified a genetically sensitized condition (patent application) that allows for the systematic identification of new genes which play critical roles in insulin signaling in *Drosophila* and thus provide putative drug targets.

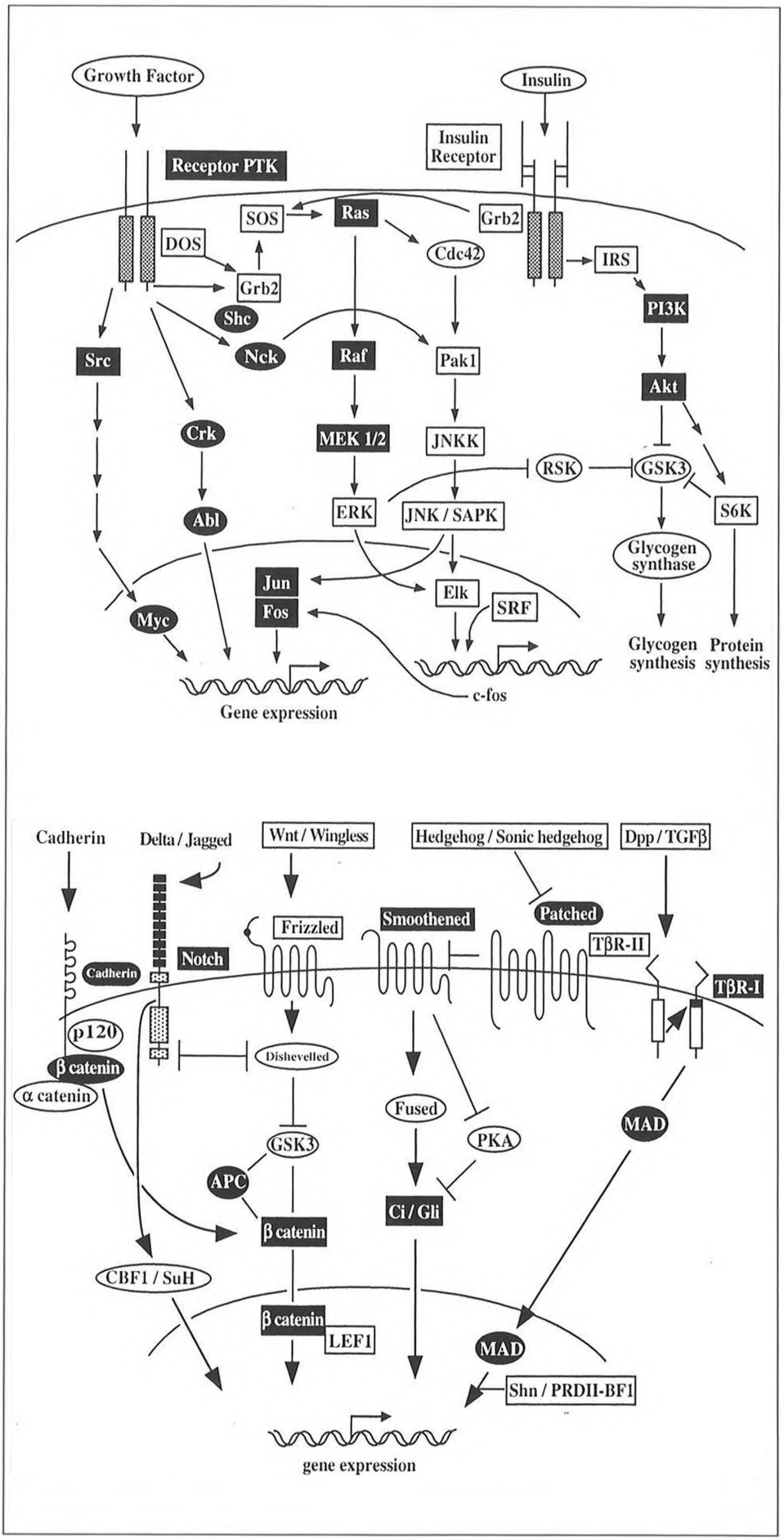

Fig. 1. Oncogenic signaling pathways in *Drosophila*
Black: Proteins implicated as oncoproteins or tumor suppressor proteins
Rectangles: Components identified or characterized by TGC founders

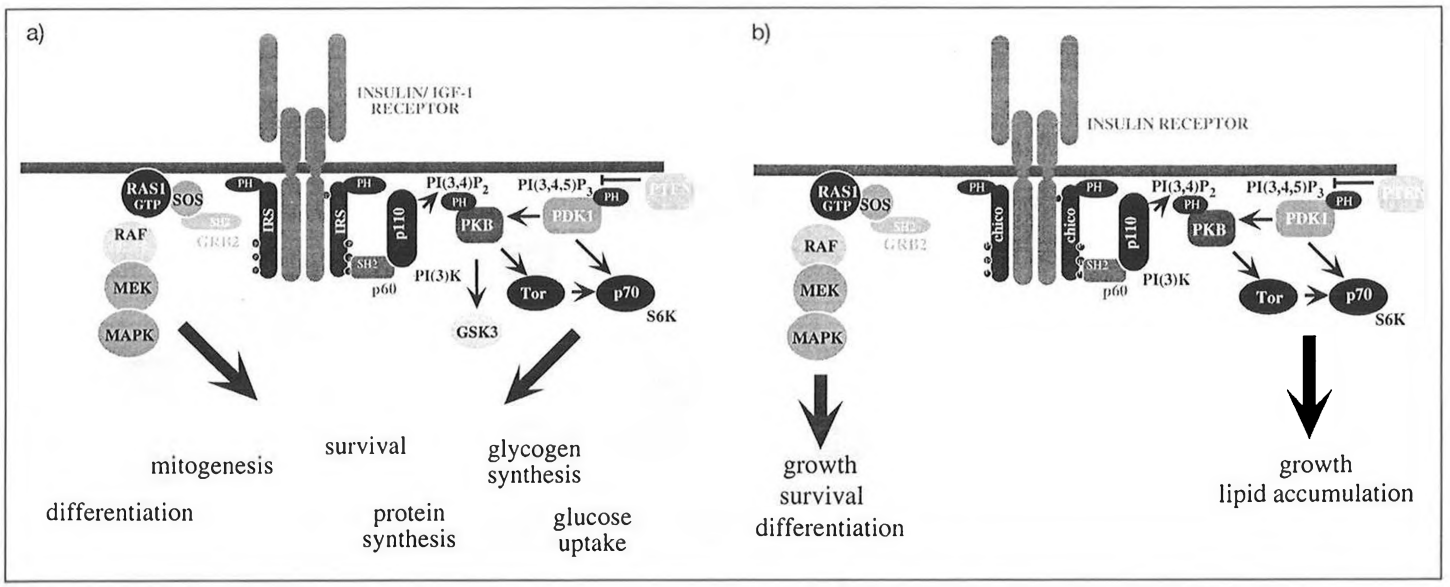

Fig. 2. Comparison of insulin signal transduction pathways in vertebrates and *Drosophila*
a) Insulin/IGF signaling pathway in vertebrates
b) Insulin signaling pathway in *Drosophila*

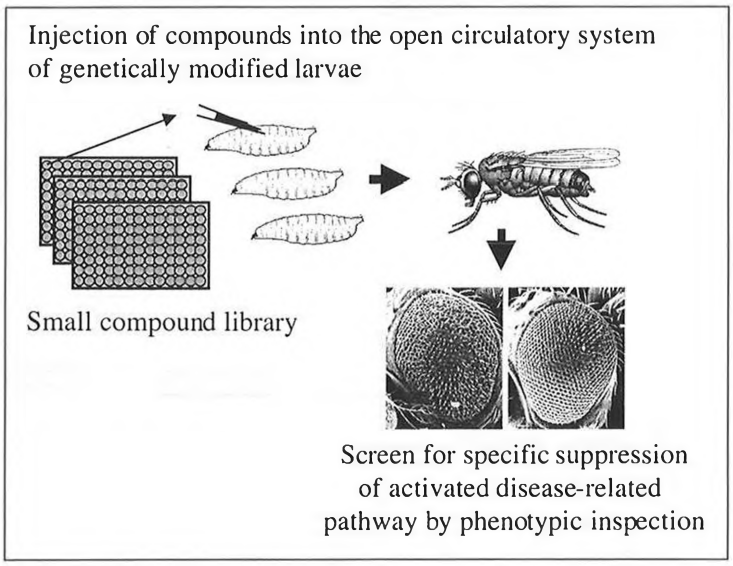

Fig. 3. InvoScreen™

In vivo Small Compound Screening (InvoScreen™)

To date, the identification of new small compound therapeutics relies mostly on high-throughput screens (HTS) of compound libraries using cell-free systems. Such screens are limited to specific candidate targets (*i.e.* receptors, kinases) and do not provide an inherent test for the specificity, therapeutic relevance and toxicity of the compound.

TGC has developed a proprietary technology for the *in vivo* screening of small compounds in genetically modified *Drosophila* strains that serve as model systems for human diseases such as cancer and NIDDM. Thus, compounds are injected into the open circulatory system of genetically modified *Drosophila* larvae which are subsequently inspected for the reversion of phenotypes generated by the activation of disease-related pathways (Fig. 3).

Concluding Remarks

TGC's expertise in developmental biology and morphogenetic modulation, combined with its proprietary technologies, uniquely positions TGC in the quest for disease targets, innovative drugs and pioneering therapeutic approaches, and creates new opportunities for partnerships with pharmaceutical companies.

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Upstream Solutions

Upstream Solutions GmbH
UpSol™ – Scientific Software Development for Chemists

Christian Affolter*, Andreas Gloor, and Ernö Pretsch

Abstract: Upstream Solutions develops scientific software with emphasis on structure elucidation for chemists and engineers and provides services to research and development facilities. The company was founded in 1997 as a spin-off company from ETH Zürich, employs six Ph.D. scientists and has its development center in Zürich, Switzerland. Upstream Solutions' products and services are sold worldwide.

Keywords: Partition coefficients · Spectra prediction · Structure elucidation

1. Introduction

Upstream Solutions develops scientific software with emphasis on structure elucidation for chemists and engineers and provides services to research and development facilities. The company was founded in 1997 as a spin-off from ETH Zürich, employs six Ph.D. scientists and has its development center in Zürich, Switzerland.

2. Goal and Philosophy

Upstream Solutions provides scientists with software tools that generate information from chemical data. Besides stand-alone programs, tools are available that can be integrated in standard software packages that chemists are accustomed to work with. The latest research results from leading scientists and from our own investigations are implemented. Since the ease of communication with the user is a central objective, the user interfaces support graphical input and output and the programs are capable of reading structural and spectral information in standard formats. All products run on PCs with current operating systems.

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3. UpSol™ Programs and Services

3.1. *The Structure Generator UpSol™ Assemble 2.0*

The structure generator, UpSol™ Assemble 2.0 is capable of calculating all chemical structures which comply with a user-defined set of constraints. Its main use is the quality control and the increase of productivity of the structure elucidation process. Based on the molecular formula, substructures that must be present or absent, as well as global constraints such as the molecular symmetry, the program calculates all possible isomers. In addition to the graphical user interface and the structure assembling core, modules for post-processing of the output are available. Spectroscopic data as well as physical properties can be used to automatically rank the results by comparing measured and estimated data.

3.2. *Estimating n-Octanol/Water Partition Coefficients: UpSol™ TLogP*

The program UpSol™ TLogP estimates logarithmic octanol/water partition coefficients (log K_{ow}) of uncharged organic compounds. The calculations use a database of experimental values and are based on a sophisticated encoding of chemical structures as uniform-length vectors. If structurally similar references are found for a target, their data are automatically selected for the prediction (local modeling). Otherwise, a global prediction model is applied that is generated from all available data. The calculations thus provide one of the following results:

a) the experimental log K_{ow} value is presented if the molecule is found in the database;
b) a local model is used to calculate log K_{ow} with high reliability if the molecule closely resembles others in the database;
c) the global model is used to calculate log K_{ow} providing a less accurate estimation if there are no structurally related references available.

A database with about 3000 entries is part of TlogP. The program supports automatic model building so that the models can be recalculated by adding user data or new models can be created that are based on proprietary databases. For the estimations, the structure input can be

generated with a graphical user interface or read from a file (a single MOLFILE of an entry or an SD file of a series of entries).

3.3. *UpSol™ PredictNMR*

Prediction of ^{1}H NMR and ^{13}C NMR chemical shift values are based on linear models applying about 3000 and 4000 parameters, respectively, and use several extrapolation strategies. In the case of ^{1}H NMR, shifts of about 90% of all CH_x groups can be predicted with a mean deviation of 0.2–0.3 ppm if non-polar solvents are used. In the case of ^{13}C NMR, over 95% of the shifts can be predicted with a mean deviation of 3.8 ppm. The graphical structure input can be generated with an enclosed drawing program or PredictNMR can be interfaced to ISIS/DRAW™. The output consists of the molecular structure with the predicted shifts and a detailed protocol of the calculation.

3.4. *Check of Consistency*

Spectrum prediction is often used for checking the consistency of a structure with the corresponding spectrum. The consistency check programs of UpSol™ combine the estimation and comparison steps. Files of structures and corresponding spectra can be used as input and tables that can be further processed with a spreadsheet programs can be generated as output. The combination of the estimation and comparison increases the productivity, and in some cases also the quality of the results. Parameters of the check modules can be set by the user to minimize the number of either the false positive or the false negative results.

The consistency check programs can be used for directly processing spectrometer outputs. The increased productivity is especially important in view of high-throughput analysis as required *e.g.*, in connection with combinatorial chemistry. Another application of these programs is the quality control of spectroscopic in-house databases. Especially with the advent of data-mining tools that automatically generate information from data collections the reliability of the data is of paramount importance. Upstream Solutions' spectroscopic database quality control tools for IR, ^{1}H and ^{13}C NMR as well as MS are capable of scanning large databases and reliably detecting erroneous records.

UpSol™ IRCheck

UpSol™ IRCheck is, in essence, a sophisticated database search with interpolation capabilities for regions not populated with sufficient data. It selects relevant reference spectra from the database and compares them with the target. The key step is the structure coding in uniform-length vectors that has been optimized for this application. The current program holds a reference database of some 11 000 entries and, under a given decision threshold, it is capable of recognizing 71.7 % true pairs as true with only 0.07% of wrong positive answers. The program includes all model building modules so that it is also able to build new models from a given database in a fully automatic mode of operation.

UpSol™ CheckNMR

The NMR consistency checks combine three procedures in that they a) automatically extract chemical shift, intensity, and simple multiplicity information from the experimental ^{1}H NMR and ^{13}C NMR spectra, b) predict ^{1}H NMR and ^{13}C NMR shifts and multiplicities from the proposed structures, and c) compare the data obtained from the spectra and the structure. Parameters set by the user can be adjusted to obtain a minimum of either false positive or false negative results.

3.5. *Further Activities*

In addition to developing standard software products, Upstream Solutions provides individual services in software development, customizing and integration as well as consulting for customers all over the world. Focusing on customized software solutions will be a key success factor in the future.

Upstream Solutions distributes its products internationally through various channels. Products are marketed directly, through online-shops, as well as through software dealers and partners worldwide. There are relationships with a number of leading software vendors and developers operating in chemical and scientific computing, which have integrated UpSol™ structure elucidation modules into their software packages. ChemNMR™ of CambridgeSoft's ChemOffice and several modules of SpecInfo™ (Chemical Concepts) are well-known examples. Customers are segmented in industries and universities using site licenses, OEMs sub-licensing the programs and modules for use in their environments, single users supplied by wholesalers and distributors, and industries using the individual services in software development. Customers can therefore be found among the most important chemical and pharmaceutical industries worldwide, universities, government research laboratories, leading scientific software companies as well as small business units with spectroscopic applications.

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WENGER CHEMTECH
There is Nothing more Powerful than Illusion

Roland M. Wenger*

Abstract: Illusion becomes reality with Wenger Chemtech's new generation of cyclosporin derivatives. A lot can happen in a two-year timespan. Challenges faced, solutions found, deadlines met. Wenger and his team have spent the past two years finding new procedures, solving problems, exceeding customer expectations.

Keywords: Antiviral cyclosporins · Combinatorial chemistry · Cyclosporin A · Cyclosporin derivatives · Solid-phase synthesis.

Wenger Chemtech for advice in organic chemistry started its activities in January 1997. At the beginning this firm was created with the goal of preparing Cyclosporin A metabolites on a large scale in collaboration with the University of Basel. This work did not find financial support and was then carried out at Novartis.

The field of activity of Wenger Chemtech changed to the preparation of cyclosporin derivatives with the aim of finding drug candidates with antiviral activity but no immunosuppressive activity for licensing. This research was started in collaboration with Professor M. Mutter at the University of Lausanne [1].

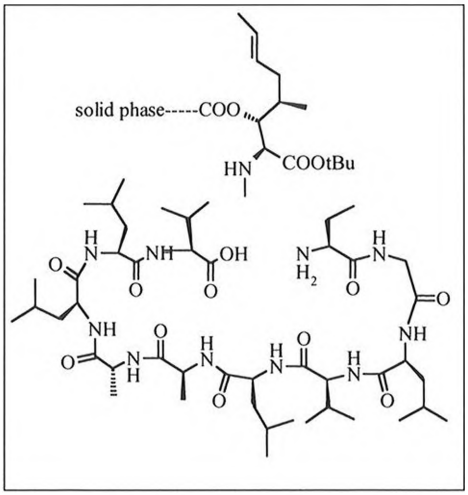

Figure: Synthesis of 11-peptide on a solid phase. Decapeptide is added stepwise

In 1998 with the financial help of the Novartis Venture Fund and the collaboration of Professor B. Giese, a second research activity was started at the Institute for Organic Chemistry, University of Basel. A Peptide Research Group [2] was formed with two Ph.D. students. The research goal of this group is the development of synthetic techniques for the combinatorial synthesis in the solid phase of partially N-methylated peptides. The long-term goal is the combinatorial synthesis of cyclopeptides and cyclosporins in the solid phase (Figure). In the case of success, all the synthetic substances will be tested in a general screening at Novartis Pharma.

This consulting firm has more than 20 years experience in cyclosporin chemistry and can produce, on request, a large variety of cyclopeptides.

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XERAGON
OLIGORIBONUCLEOTIDES

Xeragon AG
Specialists for RNA Synthesis

Patrick A. Weiss[a]* and Stefan Pitsch[b]

Abstract: In contrast to DNA-related research, RNA-related research is limited by the availability of synthetic sequences. Recent improvements in chemical synthesis allow Xeragon AG to offer custom RNA sequences – up to 100mers – in high quantity and quality at an affordable price.

Keywords: Oligoribonucleotides · Oligonucleotide synthesis · Protecting groups · Phosphoramidites

In all life-forms, nucleic acids are responsible for the storage and transfer of genetic information. Deoxyribonucleic acid (DNA) is permanently localized in the nucleus of each cell and contains the information required for the bio-synthesis of proteins which ultimatively constitute the phenotype of each individual. Ribonucleic acid (RNA) is involved in the transfer of genetic information, but also in the assembly of peptides, since it is a major constituent of the ribosomes and carrier of the amino acids.

DNA and RNA are both linear macromolecules, each consisting of four structurally related nucleotide building blocks (Fig. 1). In a chemical sense, DNA is a quite stable molecule, and therefore easy to prepare and to handle. In contrast, RNA is much more labile and decomposes under weakly basic conditions [1].

The chemical synthesis of nucleic acids has been automated and is carried out

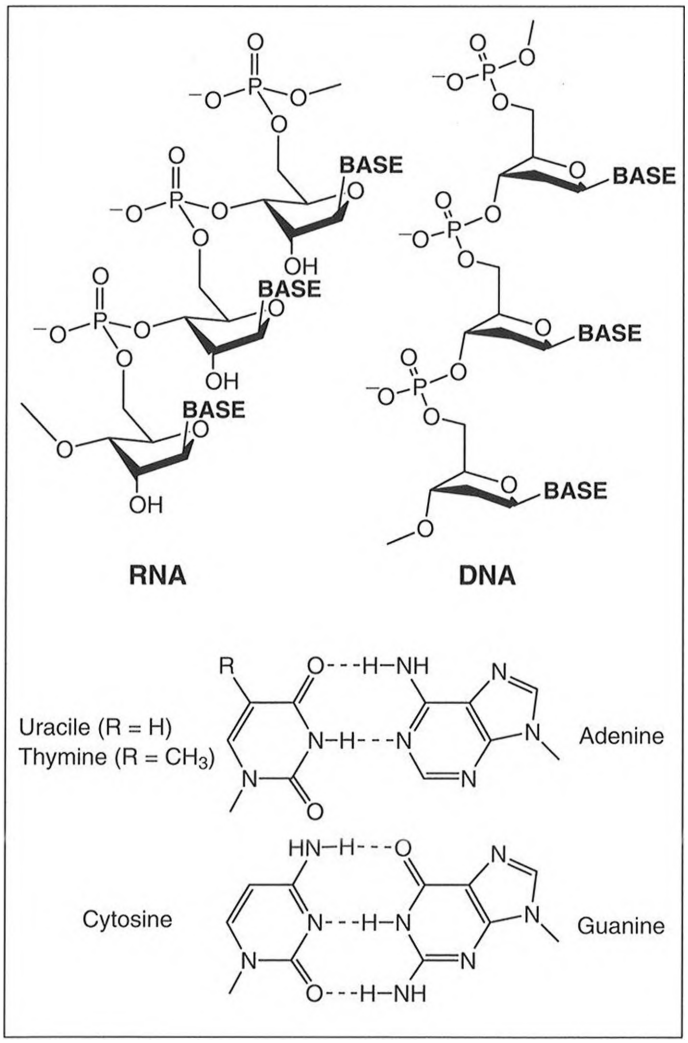

Fig. 1. Structure of RNA- and DNA-type nucleic acids (top) and structure of the nucleobases (bottom).

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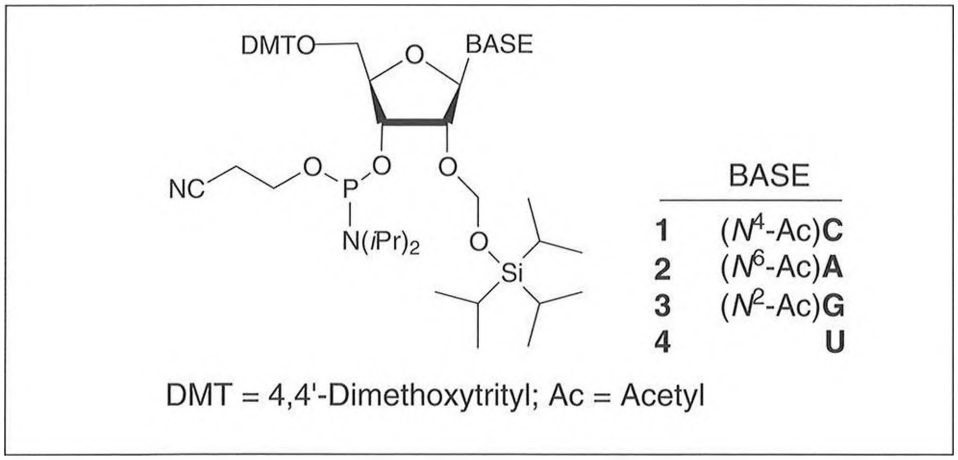

Fig. 2. tom-protected phosphoramidite building blocks used for the efficient assembly of RNA sequences.

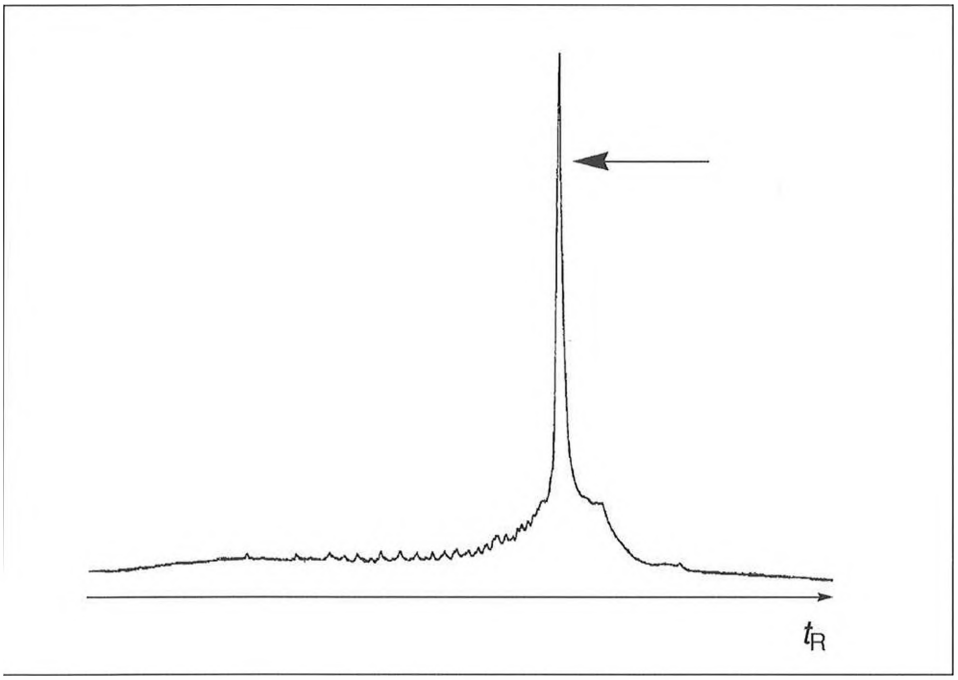

Fig. 3. Ion-exchange HPLC (Dionex GenPak) of a crude 64mer RNA sequence prepared from tom-phosphoramidites under DNA coupling conditions. After isolation, the main product (as indicated by the arrow) was obtained in a purity of >95%.

on a solid phase by stepwise addition of appropriately activated nucleotide building blocks, until the desired sequence has been obtained. Finally, all protecting groups, required during the assembly procedure, are removed and the product is cleaved from the solid support. Length and uniformity of the product are limited by the coupling and deprotection efficiencies.

For biological and biophysical research related to nucleic acid interactions, the accessability of synthetic derivatives is crucial, since they can be prepared in large quantities and can be labeled with almost any desired reporter group. Natural and modified nucleic acids also find use as tools for selective recognition and/or selective modification of nucleic acid targets and are therefore interesting candidates in medical diagnostics and therapy. Due to fundamental methodological advances in the past twenty years, the chemical synthesis of DNA can be carried out routinely and DNA sequences are commercially available. In contrast, chemically synthesized RNA sequences are restricted to relatively short sequences.

Compared to DNA, each nucleotide unit of RNA contains a 2'-OH group, which has to be protected during the assembly. Unfortunately, these supplementary protecting groups sterically interfere with the coupling process and require an additional deprotection step. From the large number of 2'-*O* protecting groups investigated so far, the *t*BDMS group has found the widest application. However, several factors, including the relatively low coupling yields obtained with such building blocks, were not optimal and limited the length of the chemically synthesized RNAs to about 40 units [2].

In this context, we recently developed the novel 2'-*O*-[(triisopropylsilyl)oxy]-methyl (tom) protected RNA building blocks (Fig. 2) [3][4]. By combining the advantages of the *t*BDMS protecting group with a sterically non-demanding linker, our tom group allows the synthesis of RNA sequences with excellent coupling yields (under DNA-coupling conditions) and reliable deprotection [5].

Fig. 3 shows a HPLC trace (obtained under preparative conditions) of a crude 64mer RNA sequence. Under standard DNA conditions (6 equivalents tom-phosphoramidites/2 min coupling time), the average coupling efficiency was 99.3%. The full-length sequence was isolated in an overall yield of 25% (purity >95%, as estimated by gel electrophoresis).

Based on the scope of our tom protecting group for the efficient chemical synthesis of RNAs, a patent [4] was filed and the company *Xeragon AG* was founded in late 1997. Xeragon is primarily dedicated to the synthesis of RNA and congeners, but also offers non-routine DNA synthesis and a custom nucleoside synthesis service. Since early 1999, our tom-protected phosphoramidites are commercially available through Glen Research (Sterling, USA) [6].

Received: February 10, 2000

[1] Additionally, the ubiquitous presence of ribonucleases (enzymes which cleave RNA) requires sterile conditions for the handling of RNA.

[2] N. Usman, K.K. Ogilvie, M.-Y. Jiang, R.J. Cedergren, *J. Am. Chem. Soc.* **1987**, *109*, 7845; K.K. Ogilvie, N. Usman, K. Nicoghosian, R.J. Cedergren, *Proc. Natl. Acad. Sci.* **1988**, *85*, 5764; S.L. Beaucage, M.H. Caruthers, in 'Bioorganic Chemistry: Nucleic Acids', Ed. S.M. Hecht, Oxford Univ. Press, Oxford, **1996**, p. 36.

[3] X. Wu, S. Pitsch, *Nucl. Acids Res.* **1998**, *19*, 4315; S. Pitsch, P.A. Weiss, X. Wu, D. Ackermann, T. Honegger, *Helv. Chim. Acta* **1999**, *82*, 1753.

[4] S. Pitsch, P.A. Weiss, L. Jenny, United States Patent No. 5,986,084 (16.11.1999).

[5] Typical individual coupling yields are <98% for *t*BDMS-protected and >99% for tom-protected phosphoramidites, respectively. With such coupling yields, the synthesis of a 50mer results in an overall yield of <35% and >65%, respectively.

[6] Further information on *www.glenres.com*.

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zeptosens
Bioanalytical Solutions

Zeptosens AG
The Most Sensitive Biochip, or How to Find the Dot of an i in an Area the Size of Switzerland

Markus Ehrat* and Gerhard M. Kresbach

Abstract: With the Zepto™ product line, Zeptosens has introduced a revolutionary new fluorescence-based detection technology embedded in a comprehensive bioanalytical concept. This will set new standards in microarray-based generation of information in life sciences.
Zeptosens, a high-tech start-up company in the field of microarrays, will provide high-quality customer-oriented 'solutions' for nucleic acid and protein applications that cover the complete range of aspects from sample preparation, assay development, assay and system validation, high-quality/high-performance data generation to data analysis. Zeptosens has brought the planar waveguide detection technology (PWG) used for the readout of its proprietary low to mid density chips to a level where the results of classical chip imaging approaches can be outperformed at least 100-fold in terms of sensitivity.
The first readers and chips based on the Zepto™ approach will be launched on the market within one year.

Keywords: Bioanalytics · DNA chip · Gene expression · Genomics · Microarray · Planar waveguide · Protein chip · Proteomics

If you ever thought that you are becoming overwhelmed by the flow of information from the daily news, the amount of information is still modest compared to the information that can be provided by today's miniaturized and highly integrated analytical chip systems. Bioarrays may contain as many as 60 to 100 thousand different biological elements on little more than 1 cm^2. Such chips will be used to unravel the relationship of newly discovered genes to metabolic pathways in cells or to monitor the reaction of organisms upon exposure to a potential drug. In such a case an organism might react with subtle changes in the scale of 1 to 10 molecules per cell. Alterations of genes in chromosomes – be it by heritage, by accidental or deliberate mutation or *via* gene transfer – occur at a one event per cell level. Being able to detect such states or changes in a relatively low number of cells – say several hundreds – is crucial for pharmaceutical and agricultural companies in their search for new targets, the early information of toxicological behavior. The Zeptosens team has developed a technology and applications for use in this field which will be commercially available within a year.

About Zeptosens

Zeptosens AG, a start-up company in the field of bioarrays, has entered the segment of highest sensitivity/mid density biochips for nucleic acid and protein assays by introducing and marketing its 'Zepto™' approach. 'Zepto' is derived from 'Zeptomol' (10^{-21} mol, equivalent to about 600 molecules). This clearly states the company's goal to establish reliable and quantitative detection at the level of a few hundred molecules. To visualize this ambitious task: assuming the area of Switzerland to be one mole, one Zeptomol corresponds to 41 μm^2, an area smaller than the dot of the letter i.

Zeptosens' mission is to develop and market high sensitivity/high performance comprehensive analytical solutions. This clearly indicates that Zeptosens will provide customers with comprehensive 'solutions' which cover a wide range of analytical steps from sample preparation, high-quality data measurement to data analysis software. The current Zeptosens

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core technology is based on planar waveguide sensors, which have been brought to technical feasibility within the last eight years while the founder team was still at Ciba-Geigy AG and later at Novartis Pharma AG. In collaboration with external companies and research centers, the planar waveguide technology will be developed to commercial products by Zeptosens within one year.

Zeptosens AG started its operations in March 1999 and has since grown to eleven associates and employees. The scientific team members have their background in physics, chemistry, molecular biology, and biology and are all well experienced in modern bioanalytical technologies and methods.

Zeptosens has already established a broad patent portfolio. It has, among others, acquired the exclusive worldwide rights to the proprietary high-sensitivity planar waveguide technology from Novartis Pharma AG for all applications (including applications in genomics) except for the diagnosis of human and veterinary health.

Zeptosens has formed an alliance with Qiagen N.V. in Venlo, the Netherlands, the worldwide leading company in the area of nucleic acid purification and sample handling, for the joint development and commercialization of biochips for nucleic acid detection in areas including functional genomics, toxicology and pharmacogenomics. Thus the established sales and marketing resources from Qiagen will provide optimal support to the benefit of the customers.

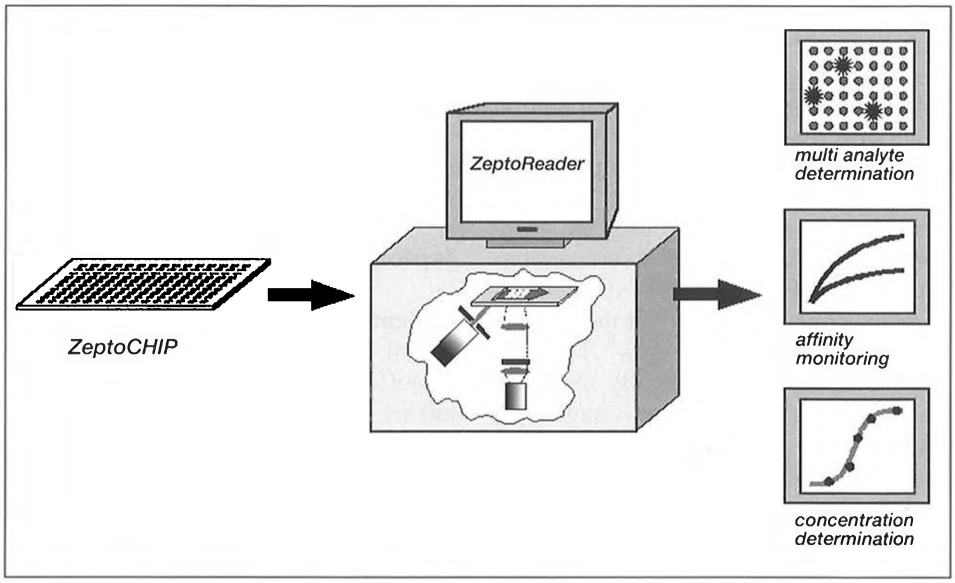

Fig. 1: Principal setup of the ZeptoREADER. From an instrumental point of view the ZeptoREADER can be compared to a CD-player system set-up to read individual compact discs: the ZeptoREADER as a sensing platform takes on the role of the CD-player, the individual ZeptoCHIPs carrying specific recognition elements, tailored for different applications, that of the CDs carrying music from different composers.

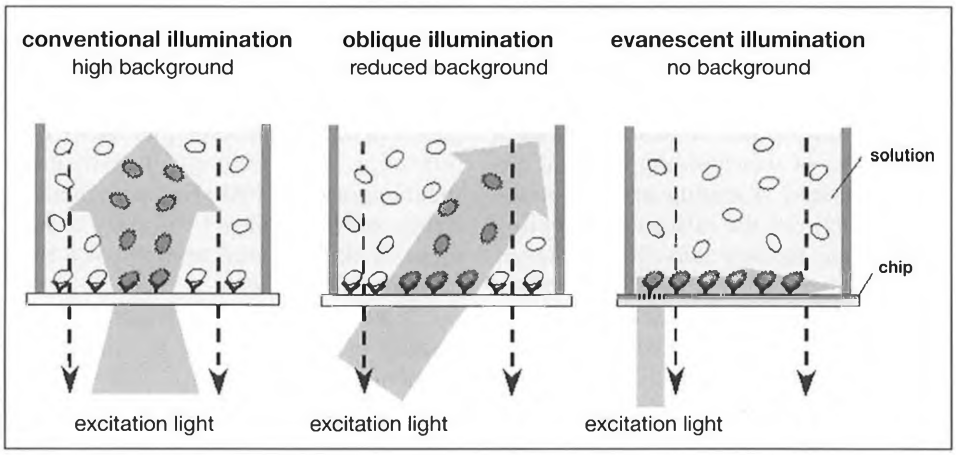

Fig. 2. Conventional microarray scanners are based on bulk illumination of a sample (left picture). Fluorescence excitation is not restricted to the surface but can extend to the whole volume occupied by the sample. As a consequence fluorescence emission can be induced on the surface as well as in the bulk solution resulting in an adverse reduction of the signal to noise value. This disadvantage can only be partly reduced by using an inclined path of the excitation light (middle picture). The surface-confined fluorescence excitation and detection scheme of ZeptoREADER (right picture) provides a fundamental solution of the background problem by a complete separation of the excitation light spot from the detection area and the restriction of the optical interaction to the evanescent field penetration depth, *i.e.* a few hundred nanometers from the waveguide surface.

Zeptosens Technology Platform

Zeptosens' **ZeptoTAS**, a dedicated **T**otal **A**ssay **S**ystem, consists of the ZeptoREADER and the ZeptoCHIPs both based on Zeptosens' proprietary planar waveguide technology (Fig. 1). The ZeptoTAS represents the workbench that allows a wide variety of array-based processes to be performed and detected at sensitivities that are up to 100-fold better than those of currently available reader systems.

Samples are processed automatically or semi-automatically in a parallel or fast sequential fashion using matching reagent kits, protocols and assay architectures. Utilizing biomolecular interaction reactions, measurements are performed with high sensitivity and selectivity on proprietary disposable optical waveguide chips – the ZeptoCHIPs – which have the capability to determine simultaneously up to 1000 analytes. Signal readout is performed on a ZeptoREADER specifically designed for the automated high-capacity measurement of the waveguide chips. For subsequent image analysis, a dedicated software package will be available.

The ZeptoTAS will allow highest sensitivity multi-analyte determination, affinity monitoring, parallel determination of concentrations of different analytes even in the presence of high background matrices (Fig. 2).

The ZeptoREADER

This optical readout device consists of multiple laser light sources for the excitation of fluorescent molecules bound at the surface of the ZeptoCHIPs and an electronic CCD camera for the spatially resolved detection of the fluorescence on the ZeptoCHIPs. The specific design is based on the planar waveguide approach: Laser light of a specified wavelength is coupled into a waveguiding layer deposited onto an optically transparent support

where it can propagate a certain distance without significant attenuation. The evanescent field generated along the propagation pathway has a short penetration depth (less than the wavelength of visible light) into the aqueous sample layer above the waveguiding layer. The evanescent field can thus be used to selectively excite fluorescence of surface-confined molecules. Molecules situated beyond the penetration depth of the evanescent field remain in the 'dark'. They are not excited and thus optically invisible. The resulting fluorescence images are visualized by a high-performance CCD camera and analyzed using image analysis software. Zeptosens has brought this technology to a level where the results of classical chip imaging approaches can be outperformed in terms of sensitivity at least 100-fold (Fig. 3).

The ZeptoCHIP family

To take full advantage of the ZeptoREADER perfectly matching ZeptoCHIPs have been developed. They consist of optically transparent planar support substrates (glass or plastic) on which a thin layer of waveguiding material has been deposited. A grating structure in the substrate allows the efficient incoupling of light into the thin waveguiding layer. Specific chemical treatment and activation (*e.g.* by silanization) of this surface is required for the controlled immobilization of a large number of biological recognition elements in selected small spots (approx. 100 to 300 μm) without losing their biological binding affinities. Furthermore unspecific binding of molecules onto the surface has to be minimized for optimal selectivity of the chip surface.

Specific binding of fluorescently labeled ligands to the immobilized recognition elements can be detected and quantified with high accuracy. Fluidic structures allow the controlled and efficient use of minute sample volumes.

ZeptoGENE and ZeptoMARK

ZeptoGENE and ZeptoMARK are the first of a series of specifically sensitized ZeptoCHIPs for the life sciences market and are designed to perform parallel protein based assays and nucleic acid hybridizations.

ZeptoGENE chips utilize the potential of the high selectivity inherent to nucleic acid / nucleic acid interaction or recognition. Depending on the specific application, arrays with 100 to 1000 different oligonucleotides (for gene expression or mutation analysis) or a similar number of cDNAs (for gene expression monitoring) are immobilized on the preconditioned surface. The chips are produced either in a generic format or according to customer specifications. For applications in drug metabolism the monitoring of genes of low abundance can be of high relevance. In toxicology investigations the monitoring of P450 first path metabolizing enzymes allows an early assessment of the potential toxicity of a drug compound to be made.

ZeptoMARK chips will carry proteins instead of nucleic acids as recognition elements on the surface and will be able to monitor *e.g.* an array of disease-specific biological markers such as hormones, growth factors or Cytokines simultaneously with specific drugs of interest. The key advantage is the potential to significantly reduce drug development costs by simultaneously monitoring a set of relevant drug responsive markers in the very early phase of the drug development process.

The ability to selectively measure the ligands bound to receptors immobilized on the chip surface without the requirement to eliminate unbound ligands by washing steps will allow ligand / receptor interaction studies at very low volumes to be expediated.

Furthermore ZeptoMARK chips will be of value in nutrition analysis. The determination of food contaminations, the identification of genetically modified organisms or the quality control of raw materials for food processing require extremely high detection sensitivities which can be provided by Zeptosens' unique analytical technology.

Conclusions

The Zepto™ product line will set new standards in the automation of chip processing and reading. With the ZeptoTAS approach, Zeptosens will introduce a highly versatile and powerful new platform for all bioanalytical tasks relying on fluorescence labeling. The ZeptoREADER will outperform current fluorescence detection systems in terms of sensitivity by one to three orders of magnitude. The ZeptoCHIPs will offer a unique selective and sensitive base for highly parallel determination of assays utilizing molecular recognition schemes.

Within one year Zeptosens will launch their first products of the ZeptoTAS product line.

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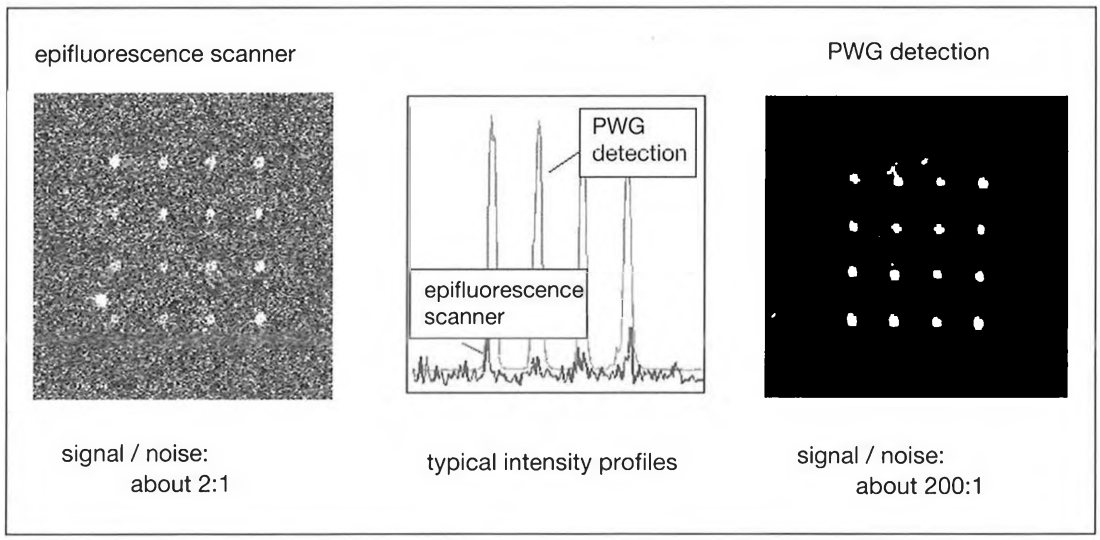

Fig. 3. Comparison of detection limits of different reader technologies. Sample: oligonucleotides labeled with Cy5 fluorescence dye hybridized to complementary oligonucleotides immobilized on a chip surface. Left: scanned by a conventional epifluorescence reader; right: scanned using a ZeptoREADER in the PWG mode; center: comparison of the signal to noise profiles of both detection modes.

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ADvantage Consulting

ADvantage Consulting
From Strategy to Action in the Fine Chemicals Industry: Opportunities and Threats for New Entrants

Walter Graf*

Abstract: Outsourcing manufacturing activities in the life-science industry has created new and attractive business perspectives in the fine chemicals industry. Many new entrants start to tussle for a piece of the pie – but what is the entrance fee for such activities? Described are the prerequisites and the key success factors to be a successful player in the exclusive custom manufacture business.

Keywords: Consulting · Fine chemicals · Key success factors · Outsourcing · Resources

The current trend in the life-sciences industry to outsource manufacturing activities has attracted many chemical companies to divert from their traditional chemical businesses and to enter into the fine chemicals manufacturing/exclusive synthesis business.

The attractiveness of fine chemicals manufacture is primarily derived from the higher margins that presumably can be obtained from sophisticated, advanced intermediates and bulk actives. For many new entrants the opportunity to get away from saturated chemical commodities market segments, which confront them with heavy price pressure, to higher growth rate markets is also a driving force for their strategic realignment. Sometimes such a move becomes a matter of survival.

However, with better attractiveness comes a whole new set of risks that need to be managed with new skills and capabilities in order for the strategic realignment to succeed. What are these new risks, and how can they be successfully managed to achieve expected returns in a timely manner?

The answer is quite simple: Resources, resources, and resources.

Human resources: highly qualified people in marketing, R&D and manufacturing.

Technical resources: an up-to-date, modern process and equipment technology base are prerequisites for success.

Finally, to get these resources you need substantial *financial resources*.

The following guidelines may be used to make an approximate estimate of the resources needed by new entrants who currently do not have the necessary marketing, R&D and multipurpose manufacturing capabilities:

- *Investment in hardware* – triple the annual turnover you envisage in your strategy.
- *Research & Development* – annually and *per capita*, about 300000 CHF of new business in terms of potential annual sales can be generated from R&D projects after you have reached critical mass. Long-term business growth is directly linked to investment in R&D resources which averages 12% or more of net sales in the initial phase and decreases then gradually to about 6%.
- *Human resources in R&D* – 30% with university degrees or equivalent, 30% with lab technician training or equivalent, and 40% are operators in pilot plants and workshops, and support staff. The total analytical work force needed is roughly equivalent to the laboratory staff in R&D and is ever increasing.
- *Manufacturing* – about 800 000 CHF value added can be generated *per capita* of manufacturing personnel.

All these measures can vary depending on the specific circumstances and degree of resources already available.

This heavy up-front load of financial resources required, which is very often underestimated, calls for significant changes in the existing business and operational structure in order for a new entrant to be successful. The main points to be considered in redesigning the corporation and its processes are as follows:

- The overall basis is an adequate business strategy, from which the marketing and technology strategies, based on core competencies, are derived.

This then calls for:

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- Implementation of a custom process (Marketing Organization) to manage project acquisition and execution with the focus on customer satisfaction.
- Implementation of an efficient Process Research and Development Organization which is able to design the most economic reaction sequence and the manufacturing processes for the large-scale manufacture of the target molecule.
- Implementation of an adequate Quality Assurance and Quality Control (QA/QC) Organization to meet customers' and regulatory authorities' requirements.
- Implementation of a project management system to shorten time to market by managing the interfaces between Marketing, R&D and Manufacturing efficiently.
- Implementation of portfolio and pipeline management instruments to allow for on-time project status information and consistency checks with the business plans.
- Implementation of a product and process technology management system to assure a timely renewal of the technology base to gain competitive advantage.
- (Re)design of manufacturing equipment, plants and infrastructure to meet the demanding task of frequent product change and equipment validation.

The threats to new entrants are many. Generally, improper implementation or lack of one of the above mentioned actions in redesigning the corporation and its processes leads to deferred realization of the strategy. But one of the most frequently committed errors in strategy realization is to invest first in assets then in people and marketing. Underestimating the time needed to be a key player in this very attractive but also very demanding and risky business segment of the chemical industry is an other shortcoming seen in many business plans.

Dr. Walter Graf, President of the **AD**vantage Consulting Company, advises chemical companies on how to successfully plan, implement, and manage a transition into the fine chemicals/exclusive synthesis business. Dr. Graf obtained his Ph.D. in organic chemistry at ETH Zürich, and then served as a lecturer and research group leader at ETH Zürich for nine years. From 1980–1989, he was Head of Chemical Operations at FLUKA Chemie AG, and from 1989–1999 he was Head of Research & Development and Technology at LONZA AG.

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Dr. B.R. Glutz, Consultant in Safety, Environmental Protection and Risk Management

The Timing of Independence: Early Challenge *vs.* Late Success

Bernhard R. Glutz*

Abstract: The author of this article is a chemical engineer who ventured into independence after a rather long period of employment in the chemical industry. He analyses opportunities and risks, challenges and limitations of choosing entrepreneurial self-determination at a given point in a professional life-cycle. While a decision at a later stage may be somewhat exceptional, it is preferable to build up the necessary professional experience and a solid base of professional contacts during a few years after graduation before taking the carefully planned step.

Keywords: Contacts · Entrepreneur · Experience · Self-determination · Timing

From Individual to Employee

Human beings are born as individuals, are educated as individuals in family and school and, after individual university training, graduate as individuals. The young Ph.D. graduate faces the 'chemical world' as a collective world of industry and of industrial employees. This is essentially also the focus of the academic education of chemical engineers, which is obviously defined by the needs of the industrial world. Consequently it is rather rare to find young chemical engineers

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who decide in favour of professional independence after graduation.

Basics of the Entrepreneur

A list of conditional factors to become an independent entrepreneur in the field of chemistry includes the following elements:

- professional skill
- professional experience
- ability to sell
- professional contacts
- excellence in a professional field or sector

When analysing these elements it becomes rather clear why a typical young Ph.D. graduate in chemistry or chemical engineering might not easily choose professional independence in his or her early professional cycle. While skills are certainly at a maximum, the experience is rather slight, and the contacts and a salesperson's skills are not yet sufficiently developed. The education may, however, have provided excellence in a special professional field, which makes the young engineer at the same time more attractive for a future employer.

It can be concluded, that in a typical case, a few years of employment would be very beneficial for improving and developing professional experience, for the enrichment of professional contacts, and for the build-up of basic economic skills for the future entrepreneur.

Advantages of a Career in Employment

It is possible if not common that the young chemical engineer, having found employment with a good employer who provides him or her with an interesting and motivating job, may feel less and less the need to become an independent entrepreneur. Modern employers can create professional environments for their employees; these may be very close to the ideal environment of an independent entrepreneur. While in earlier years, stability was an almost unconditional factor of the employment, today **flexibility** and the possibility of continuous professional **development** at the workplace are the factors that make employment attractive for both the employer and the employee.

Selecting the Right Moment

The chemical engineer who has not given up the idea of becoming an independent entrepreneur and who has committed himself to building up the conditions for successfully starting his own business should carefully choose the right moment to do so. This choice may be driven by internal or external factors. In the ideal situation the point may very smoothly combine the termination of the employment with the launch of the enterprise. In other situations the point may be defined by the employer. Mergers, acquisitions and related company changes at a given date may or may not create a good moment for departing into independence. In the worst case these changes may even force the entrepreneur to select a date earlier or later than the optimum. This, however, represents a professional risk to which the entrepreneur will be exposed sooner or later in his or her independent professional career.

The Sensitive Period after Take-off

Many introductory handbooks exist for the launch into independence. They recommend the use of a checklist, of a business plan and of other helpful tools. There are a few important points to check before and after take-off.

- Will my contacts continue cooperating with me after I declare my independence?
- Will my contacts of the first weeks keep up cooperation in future?
- Did I allow for a few months for cash flow to start?
- Did I review the list of my contacts for my new situation?
- What is my response in the case of work overflow or of gaps?
- How do I replace my earlier sources of professional experience?

It is recommended to establish a preview of the enterprise two to three years after the start. Such preview will clearly define the weak points of a (too) optimistic starting position of the new business.

The New Swiss Chemical Society (NSCS): Source of Contacts, Information, and Experience for the Entrepreneur

For the young chemical engineer graduate, the New Swiss Chemical Society NSCS presents itself as a society of industrial dimensions and industrial interests. The benefit of becoming a member while employed may not clearly show at a first glance. However the future entrepreneur will find that the NSCS is a society of chemists, not only of industry employees, but mainly also of individuals and entrepreneurs who create and maintain their professional contacts through the channels and sections of the society. In the past and present period of mergers and acquisitions in the chemical world, the Society did not simply observe the ongoing changes but proved to be a stable but flexible institution for the interests of the Swiss chemists and chemical engineers. A future entrepreneur should not fail to join and make full use of the many opportunities of Society membership.

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Heinzer Eco-Management

Environmental Management Systems, Consulting & Audits

Heinzer Eco-Management
Environmental Management Systems – a Company Profile

Franz Heinzer*

Abstract: Heinzer Eco-Management was founded in 1995. The core business is a consulting and auditing activity in the field of environmental management systems according to the ISO 14001 standard. Practical environmental know-how and broad management experience of the founder and director, Dr. Franz Heinzer, result in tailor-made, professional consulting services for the construction of lean and efficient integrated environmental and safety management systems. A complementary part of the business represents the activity of Dr. Franz Heinzer as a licensed freelance ISO 14001 lead auditor on behalf of SGS-ICS Zürich – dealing predominantly with complex and international mandates.
The final objective of both activities is to help companies to shape their environmental or integrated management system (comprising quality, health and environment) into an effective management tool. A tool assuring good management practice is one of the basic conditions for long-term economic success of a company.

Keywords: Audits · Consulting · Environmental Management System · ISO 14001 · TQM System

The Foundation and Start-up Phase

Heinzer Eco-Management was founded by Dr. Franz Heinzer in 1995, one year before the official publication of the environmental management standard ISO 14001. The activity as a member of the board of directors of Collano Ebnöther, a company striving for ecological management since the end of the 1980s influenced Dr. Franz Heinzer's decision to combine this acquired broad practical know-how of environmental management with his profound management experience (see Table) and to become active in the new consulting and auditing market created by the young ISO 14001 standard.

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The Core Competencies and the Business Plan

The original business plan and company strategy of Heinzer Eco-Management can be summarised as follows:

- To offer tailor-made, professional consulting services in the field of environmental management systems according the ISO 14001 standard.
- To combine these consulting services with profound management know-how based upon the long-standing practical experience of the founder to develop the management system into an efficient management tool for the client.
- To manage and lead all company projects as a general rule personally by Dr. Franz Heinzer.
  As a consequence, a top working quality and a close personal link with the client is guaranteed. In case of large projects or in need of special know-how Heinzer Eco-Management co-operates through a well established network with partner consulting firms.
- To exploit the excellent language skills of Dr. Franz Heinzer through international mandates.

The Core Activities Today and Their Development From 1995 to 2000

The core activities of Heinzer Eco-Management today can be described as follows:

- Consulting to create ISO 14001 environmental management systems; combination with existing quality management systems and/or safety management systems into lean, process-oriented, integrated management or total quality management systems (TQM Systems). The clients represent medium-sized companies (or single production sites of larger corporate organisations).

Table. Dr. Franz Heinzer, Curriculum vitae and personal profile

Training	
1967–1971	ETH Zürich, 1971 Dipl. Natw. ETH
1972–1977	ETH Zürich, Ph. D. thesis in organic chemistry with Prof. Dr. A. Eschenmoser, 1977 Dr. sc.nat. ETH
1977–1978	Woods Hole Oceanographic Institute, Woods Hole, Mass. USA: Postdoctorate with Dr. R.B. Gagosian in marine chemistry
Professional Experience	
Since 1995	Heinzer Eco-Management, Zürich, Director
1990–1995	Collano Ebnöther Inc., Sempach-Station, Switzerland, Adhesives production: Technical Director and member of the board of directors, Member of the board responsible for Environment and Quality
1989–1990	MBT Environmental Technology Inc., Zürich, Switzerland: Associate Director, Head of the department 'Environmental Management Consulting'
1982–1989	F.J. Burrus SA, Boncourt, Switzerland; Tobacco company:
	Head of Research and Development; Responsible for diversification activities
1978–1982	Ciba-Geigy Inc., Basel Switzerland, Research Chemist, Central Research Laboratories

- Strategic support and coaching of upper management concerning environmental issues.
- Training of management representatives in the area of integrated management systems, training of internal auditors.
- Certification of ISO 14001 environmental management systems as a licensed lead auditor on behalf of SGS-ICS International Certification Services, Zürich.

Since the start-up five years ago the business activities have developed as follows:

Consulting Activities:

Since 1995 five full consulting mandates to create an ISO 14001 environmental management system have been successfully completed – such projects usually last a period of more than one year. Clients representing the chemical, food, perfumery and technology sectors. In addition, ongoing environmental training and coaching activities for the upper management of a chemical company as well as for an international technology group complete the field of consulting activity.

Auditing Activities:

A freelance activity as an ISO 14001 auditor for SGS-ICS in Zurich was taken up as early as 1995; since 1997 Dr. Franz Heinzer has acted as a licensed environmental lead auditor. The activity as auditor for SGS-ICS developed from a few audits to an important activity. Due to language skills and profound experience, the auditing mandates today represent primarily complex and international mandates. The following list shows the ISO 14001 audits performed so far on behalf of SGS-ICS:

1995: 2 Audits; all Switzerland
1996: 4 Audits; all Switzerland
1997: 8 Audits; 4 Switzerland, 3 South Korea, 1 Hungary
1998: 11 Audits; 7 Switzerland, 1 Hungary, 2 Morocco, 1 Portugal
1999: 17 Audits; 4 Switzerland, 2 South Africa, 1 Zimbabwe, 2 Greece, 1 Morocco, 3 Czech Republic, 1 United Arab Emirates, 2 France, 1 Spain

The combination of consulting and auditing activity has proven to be very fruitful for Heinzer Eco-Management: both activities are mutually influenced in a positive way by each other.

Strategy and Objectives of Today and for the Future

The main objective of Heinzer Eco-Management is to encourage companies through consulting and through audits to use their environmental and combined management system as an efficient management tool. The ISO 14001 certification step should never represent the final objective of the creation of an EMS System – it rather marks the beginning of a new era of the company: Along with the continual improvement of the *environmental performance* – required by the ISO 14001 standard – the general management system and the *economic performance* of the company should be improved at the same time. A company with an environmental management system well integrated into the general management activities will be more flexible and ready to react more efficiently to new situations. It has a tool at its disposition assuring good management practice which is a basis for long-term economic success [1]. Therefore we consider such an environmental or even better a total quality management system – which is continuously improved – as being an integral part of an intelligent modern company, essentially it can be described in one word as an element of 'business excellence' [2][3].

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IMACO

Innovative Products for a Healthy Company Future: Novel Approaches to Innovation Management are Required

Adolphus P.G.M. van Loon*

Abstract: In the future the most successful companies will be those that manage to combine optimal and continuous improvement of their Shareholder Value with establishing an extremely effective system of developing innovative products with exceptional market potential. Shareholder Value Optimisation approaches as used today typically neglect the particular needs of innovation development management and thus drastically reduce the innovative potential of the company. We offer access to knowledge and skills in optimising Innovation Management and help you to prepare your company for a better future. We help you to make your Shareholder Value Optimisation SUSTAINABLE.

Keywords: Corporate culture · Entrepreneurship · Innovation management · Return-on-Investment · Sustainable Shareholder Value Optimisation

Innovation Management is the Achilles Tendon of Many Large Companies.

The development pipelines of many large organisations do not contain enough innovative products to secure the healthy financial future of the company. The Return-on-Investment (ROI) in innovation development is too low, too many programs end up in the company drawer, never to be seen again, too many creative employees become demotivated or even leave the organisation. Typically, the larger the organisation, the bigger the problem. The productivity in those parts of the company that start and control the innovation process needs drastic improvement, the entire pipeline 'from idea to commercial product' can and should be significantly speeded-up. Innovative approaches to innovation management are required. Any novel approach, however, must result in creating TRUE win–win situations for everybody involved, the company's employees, its managers and shareholders. Only under such conditions can an organisation expect exceptional growth for the future. Many of the currently applied management tools are unfortunately inappropriate to reach this goal: they either do not create such win–win situations, or do not truly improve the entire development chain (Fig. 1). Critical for success is to break the vicious circle of top-down reorganisations that results in ever-increasing demotivation and decreasing productivity. The final goal is to drastically increase the efficiency of 'Turning Ideas into Commercial Products' and, thus, to make 'Shareholder Value Creation Sustainable' and simultaneously contribute to further optimisation of the company's short-term shareholder value.

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Product Pipelines do not Contain a Sufficient Number of Innovative Products

The healthy financial future of many companies is critically dependent on the development of a continuous stream of innovative products, each of which has exceptional market potential. Large companies now rely increasingly on other, usually smaller and relatively young companies for obtaining access to innovative products. This development offers much more flexibility than the traditional system in which the company only relied on company-internal development of products and offers increased developmental potential to any large company. Simultaneously, however, large compa-

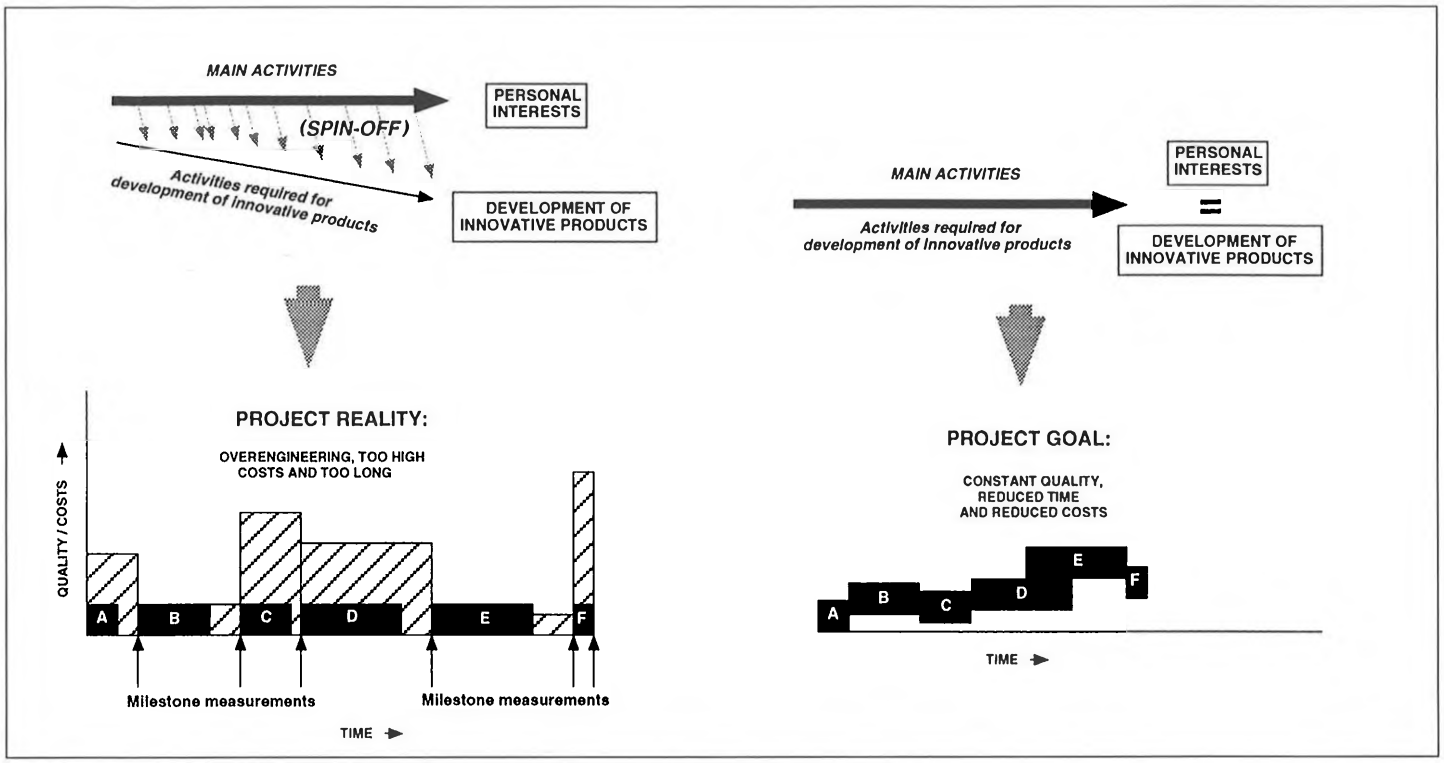

Fig. 1. Project management by milestone measurement does not allow optimisation of the entire product development pipeline. Particularly in innovative areas, the result is a very unbalanced pipeline of individual activities (A-F), many of which use much more time, resources and money (hatched areas) than required (black boxes). The ideal situation (right panel) can only be approached if all key individuals (A-F) have a true personal interest in optimising the entire pipeline.

nies still commit a considerable part of their earnings to support their company-internal research and developmental pipelines. The output of their own internal development of innovative products, the ROI, is usually much less than that of smaller organisations. Many large companies are unable to truly optimise the output of their own developmental pipelines. The need for a drastically increased productivity in Research and Development (R&D) has been recognised, but the success rate is poor and usually only realised 'on paper'. More and more management systems are being implemented to guide, control and measure productivity, usually however without the required increase of ROI. The strong focus on shareholder value creation resulted in spectacular growth of the company's short-term profit and financial health, but also drastically changed the working conditions for internal departments, such as R&D, that concentrate on development of innovative products. Mergers and acquisitions, with the resulting 'synergy' effects that allow immediate cost reductions, indeed improve the short-term financial health of the company. However, they do not solve the basic structural problems responsible for the decreasing productivity and profitability. In contrast these developments even lead to a deterioration

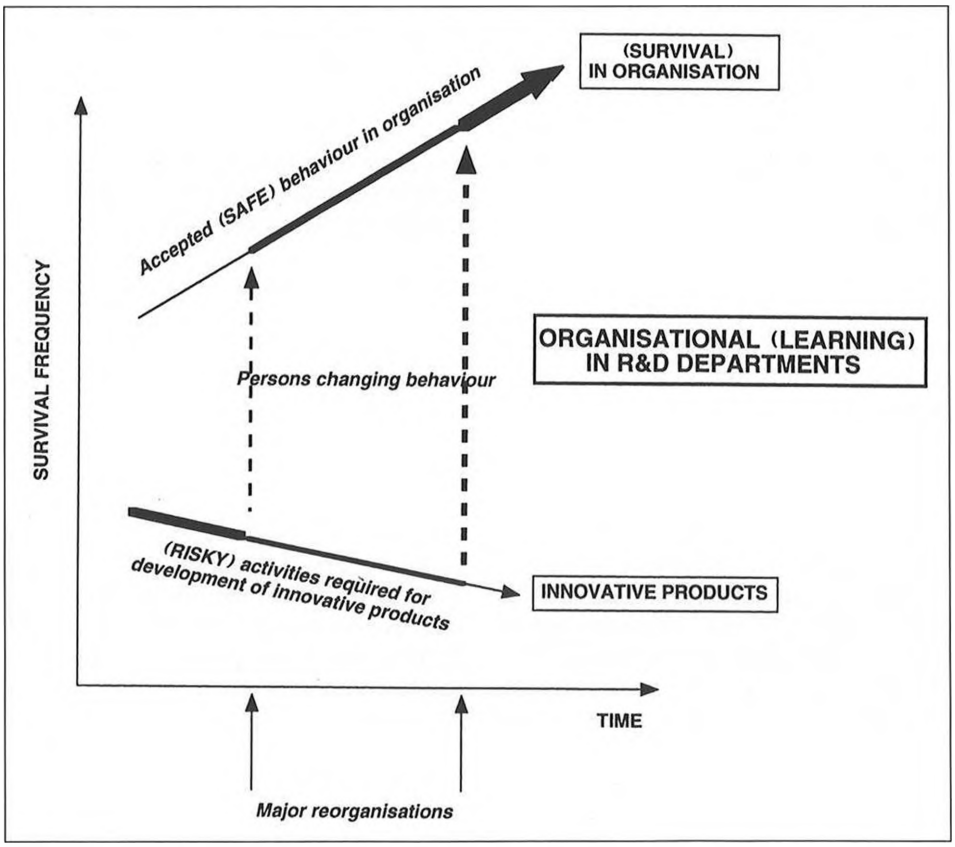

Fig. 2. Development of innovative products requires in many cases actions and behaviour which are not always appreciated in large organisations. In times of increasing pressure, a growing group of individuals is no longer prepared to go the risky path towards optimal development of innovative products but rather concentrates on activities which are much better accepted by key persons in the organisation. Consequently, the efforts towards development of innovative products decrease and the number of potential 'blockbuster' products in the pipeline decreases.

in the situation, because the company's employees are made aware that their negative value as spenders of money is more important in the short-term than their positive value as *e.g.* creators of innovative products for the future. An ever increasing number of employees has lost their believe that they can control their own professional future by their own work and thus lack the above-average commitment to their company and to their work that is required for exceptional performance. Departments such as R&D, whose task is to develop the innovative ideas and start the innovation process of turning ideas into commercial products, suffer heavily. As a justification for the money spent, they cannot offer more today than the promise of future commercial success. The changing company climate decreased the productivity of the developmental pipelines of many multinationals. The frequency of top-down reorganisations of R&D departments is much higher than the time required to develop an idea into an innovative product. Consequently an ever-increasing number of employees concentrate their efforts more on surviving the next reorganisation than on aggressively developing innovative products (Fig. 2). The number of products with exceptional market potential in developmental pipelines thus decreases constantly. Companies, however, rely in their planning more and more on the introduction of potential blockbuster products which are still under development, even for their immediate future.

Dedication and Creativity of Individuals in the Past Resulted in Development of Innovative Products

Traditionally true innovations, in science as well as in development of revolutionary products, were the result of a system in which it was possible to go outside of paths already used by others. 'Academic freedom' and 'stubborn persistence' of individuals were required. Revolutionary developments were typically the result of a combination of factors, all of which had to come together at the same time. Firstly, a group of top-class persons determined the proper setting for generating innovative ideas. These persons were highly motivated, their main goals being to realise their novel ideas and to move the frontiers in their area of interest. This group had a generally defined area of interest, but needed sufficient freedom to find the most rewarding direction in their field. Importantly, individuals in such an environment were allowed to try out their 'crazy ideas'. Their environment offered them the critical feedback, the technical facilities to test their ideas, supported them and gave them sufficient intellectual freedom. The direction was known, but not what the result of the work would exactly be. The time and efforts required to reach that undefined and unclear goal could not be planned but only continuously be optimised, to get there before the competition. Not even the persons directly performing the work could tell what would exactly be the result and when. Prior to the existence of any invention, very few individuals ever believed that they were possible. Inventions as such could not be planned, however, the environment in which they can flourish could be optimised. Real inventions always depended on very few individuals who function on the edge of the system they were in or even outside that system. Many if not all of today's blockbuster products which generate most of the earnings of successful companies were born in such environments and would not have been present without that setting. This system allowed results, but was inefficient because the products were only a side product of work with other goals.

Process Improvements Require Different Skills and Tools than Innovation Development

The development of novel ideas and inventions into products requires further process improvements and effective collaboration of individuals from different disciplines. Process improvements and especially optimisation of production processes require a different set of skills and different settings. These activities can usually be planned and optimised by using a very rational approach to the work to be performed. The further away these activities are from the start of the project, the better planning is possible and the higher the predicted and realised rates of success. Their rate of success is to a large extent dependent on the technical possibilities within the environment and the technical skills of individual collaborators. Given sufficient technical possibilities and technical skills, progress can be obtained 'by brute force'. Efforts to optimise process development and production improvements have generated a set of very useful tools, from project management tools, milestones measurement systems *etc.* These activities also profited greatly from the use of such management tools and systems.

Development of Innovative Products and Extensive Project Planning do not Match Well

The use of management tools and systems also became very popular to try to optimise and control the earlier 'research' and 'developmental' stages, to plan and control the creation of inventions which are the basis for all truly innovative, blockbuster products. Despite the fact that the track record of applying these approaches in these fields rapidly turned out to be very poor, their use became more and more popular with time (Fig. 1). The illusion of control is still powerful. Many persons inside and outside of R&D organisations and many top managers, however, realise that today's blockbuster products typically resulted from activities that did not fit well in such systems. These developments typically resulted from the dedicated activities of one or a few project champions, who pushed their program despite the resistance of the official organisation and of many of their colleagues. In fact, hardly any of the major innovative products that generate most of the revenues in high-tech industries today, resulted from careful project planning, nor did a considerable fraction of the carefully planned programs result in major products. In times in which R&D departments still had sufficient 'scientific freedom', application of many project management tools was an annoyance but not a real stumbling block. Shareholder Value Optimisation, however, drastically changed the environment. The costs became the major company issue. The better costs can be justified by a proven (high) financial return, the higher the chances of support by the organisation are. The more innovative a potential product is, the more problematic is the prediction of its future financial contribution. Development of products similar to those already on the market or improvement of existing production processes are relatively easy to plan and justify financially. Net Present Value calculations (NPVs) for such programs are reliable, easily accepted by many persons in the organisation and thus remain relatively unchallenged during the entire development time of the 'me-too' product. Consequently these programs have a high chance to be supported and keep a con-

stant development speed (Fig. 3, top panel). NPVs of truly innovative programs which can open-up totally new markets or allow unexpected improvements in existing markets typically cannot be planned easily by comparison with existing products. The NPV calculations for such programs depend heavily on predictions of individual persons and, thus, tend to change drastically with time. Since the NPVs control the commitment of the company to pursue the program, these developments are usually much less efficient, in the best case resulting in a considerable loss of time only (Fig. 3, bottom panel). In the last decade, a shift in the activities in large industries away from developing novel innovative products to improving the performance of existing products and developing me-too products was seen, despite their generally much lower financial potential (Fig. 3, top panel). As a result the pipelines of many companies now are in danger of drying-up. They do not contain sufficient potential blockbuster products to support the healthy growth of the company in the future and the products in development have increased chances of failure. More and more companies rely on revenues to be generated in the near future by new products which are still in their developmental pipeline. This is a logical result of their failure to optimise their Innovation Development in the past. Many of the expected blockbuster products already firmly planned in as money-generating products have not yet reached the end of the developmental pipeline and can thus still fail and some will.

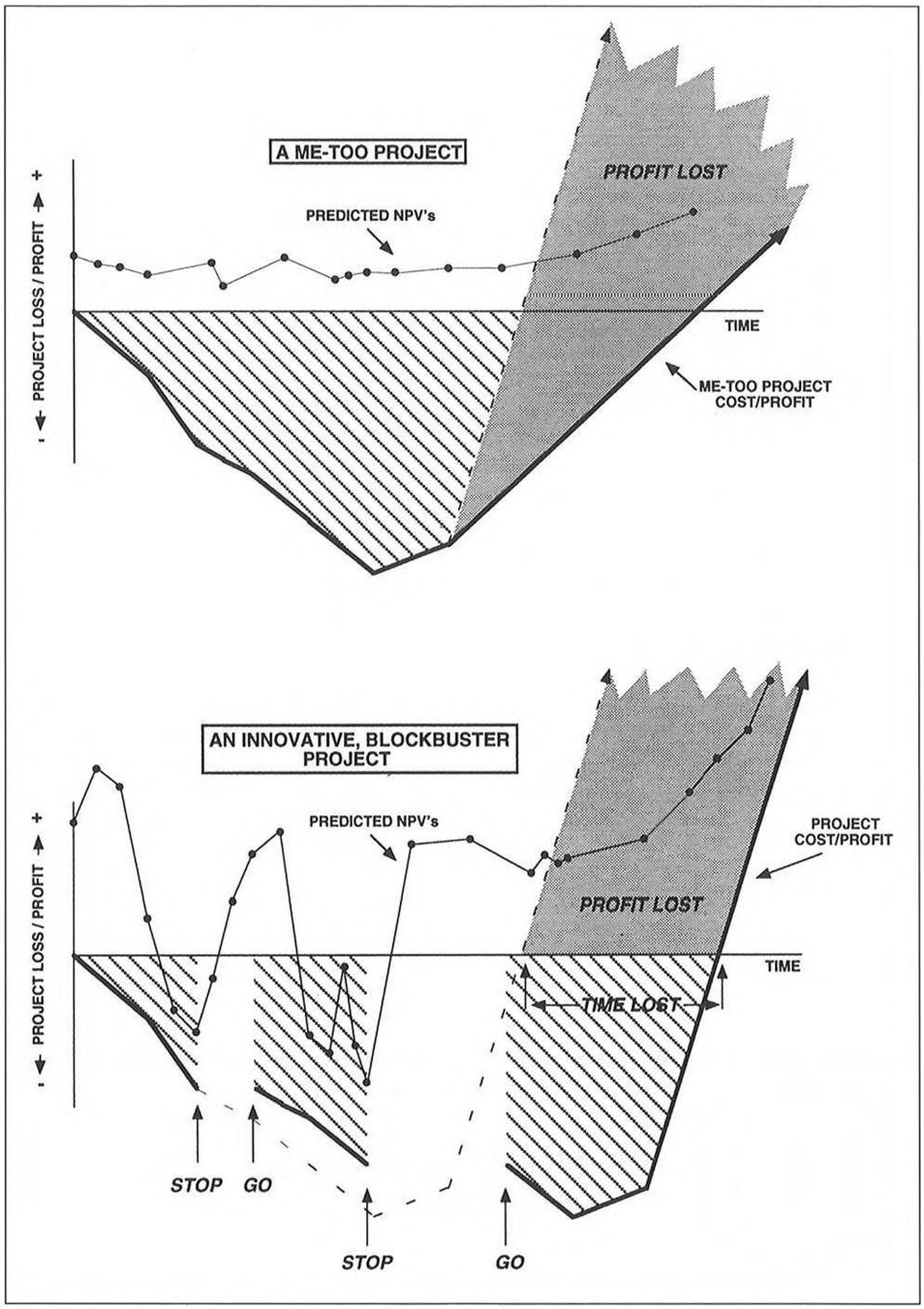

Fig. 3. The investments for product development (hatched areas) are justified by Net Present Value (NPV) calculations (dots), performed with a certain frequency during the development of the program. These NPVs result from market size predictions and predicted product profits and an estimation of the risk of the project, which then determines the required cost-of-capital. The grey areas indicate (top panel) the loss of profit resulting from investing the same amount of money in a me-too project rather than in an innovative product, assuming both would have been successfully completed without interruption and (bottom panel) the profit lost because of interruption of the project due to predictions of a negative NPV for the project. In many cases, in reality, the project would not have been revived after termination and would thus have resulted in 'sunk costs'.

A Different Approach to Innovation Management is Necessary

The drastically changed company environment requires a completely different approach for optimising the development of innovative products for the future. The times in which innovations resulted from the activities of individuals in an environment of 'academic freedom' and as a spin-off of other activities are over. Critical issues for improvement are:

1. Obtain increased commitment of individual employees to exceptional performance in their main area of expertise. Establish a direct link between the work of individual employees and their personal reward. Give all individual collaborators the possibility to control their own future by concentrating on his/her main task. Intrinsic motivation should replace external control. Companies that want to be successful in the future need to help their employees to think and act as entrepreneurs, they need to offer their entrepreneurial employees the possibility to develop their project as if it was their own small company.
2. The goals and working environment of different parts of the company are different. Consequently, locally different optimisation approaches are required. Working environments need to be changed whenever the needs of the project change. The company culture should, however, be the same in different parts of the company and promote optimal creation of financial value.

3. Communication and collaboration between parts of the company is typically difficult because each discipline uses a different specialist language. Particularly R&D departments have a severe problem with their credibility in large parts of the company. Their language is extremely difficult to understand for outsiders because of the high degree of specialisation. In addition, many of their projects of the past did not reach the envisioned commercial goals formulated in the beginning, in many cases for reasons outside of their control. The culture of R&D departments is and should be very individualistic and, in contrast to *e.g.* financial specialists, they have severe problems to convince others short-term by hard facts. A unified set of entrepreneurial skills and a single entrepreneurial language for the entire company are required.
4. Valuation predictions (NPVs) for truly innovative products need to be drastically improved, to optimise the development of potential blockbuster products. The Return-on-Investment (ROI) in innovation development should be drastically increased. The organisational setting for a project should 'automatically' change in case this is required for optimisation of the program.
5. Many potentially profitable programs are prematurely terminated and end up in the company drawer, while technically unsuccessful programs usually cannot be terminated in time. Consequently much of the investment in developing innovative products ends up as sunk costs.

The Company

IMACO is, as a virtual organisation, offering you access to its network of contacts and partners with very different backgrounds and proven track records in diverse fields such as science, finance, consulting, management training and entrepreneurship. This setup allows top experts to be involved in each part of the implementation process and combine the skills required.

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DR. PETER M. MÜLLER
CONSULTING

Dr. Peter M. Müller Consulting
Consulting Based on Enthusiasm, Experience, Change, and Stability

Peter M. Müller*

Abstract: Consultancies in the chemical industry are rarely initiated on the grounds of carefully planned decisions. They grow out of longer careers in different branches of this industry, and their main value is often much closer linked to the unbiased view of independent observation than upon the consultant's direct technical experience.

Keywords: Chemical industry · Consulting · Cosmetics · Pharmaceuticals · Registration · Validation

Introduction

It is remarkable that a journal like *Chimia* dedicates one of its issues exclusively to start-ups and spin-offs, and it is logical that the journal expects the contributors to present the history and the profile of the respective business. After all, there has to be a 'fil rouge' – and the present article attempts to meet the expectation. But there is an additional goal which may be particularly important in the case of a tiny consulting business: the goal to identify the true value companies may get when working with consultants.

Phases

It may be helpful to think in phases, like youth or age, when analyzing the lives of human beings, and it certainly helps to think in phases, like growth or consolidation, when analyzing companies. In addition, one has to consider the two types of phases when attempting to understand the situation of individuals working in companies – and the respective understanding may be crucial in optimizing their chance of success. But the identification of the mentioned phases is often difficult for those who are too closely involved, and the perception of top managers usually differs from that of their staff. This defines the working basis for consultants who might have a less biased view when dealing with individuals and who might refer to a fresh and extended series of standards when discussing the situation and the life cycle of companies... and all this is probably more important than the technical experience a consultant brings.

Enthusiasm and Experience

Enthusiasm is in many cases linked to success, and it may once in a while lead to failure. But it is indispensable in learning – and learning is the only approach to gaining the experience consultants are supposed to have. Thus, experience is not only correlated with age; it also depends on the level of enthusiasm, *i.e.* on the level of an ingredient found especially in start-ups, spin-offs, and good consultants – and the combination results in an almost frightening learning rate.

Change and Stability

Our brain and our sensory systems are designed to perceive change and to suppress steady signals – and the same holds for our social and scientific awareness. This is an almost trivial statement, but some large companies have learned the message so well that they overshoot and constantly change their procedures. The result is lack of comparability, loss of standards, disorientation... and a need for consultants who maintain an individually digestible pace of change and a stable set of values.

Phases and Fate: Profile of the Company

Dr. Peter M. Müller Consulting is a one-man-show, supported by a wife and secretary. It has its roots in the enthusiasm generated in the Ph.D. thesis time in Prof. A. Eschenmoser's chemistry group at ETH and the post-doctoral fellowship with Prof. G. Büchi at MIT, and it owes the bulk of its experience to two main phases in industry, *i.e.* pharmaceutical research with Roche and fragrances, flavors and cosmetics research with Givaudan (-Roure), and to a shorter phase of added experience with diagnostics (Pentapharm).

The status of an independent consultancy was assumed in 1997 as a result of fate rather than of a carefully planned decision, and the courage to learn something new, *i.e.* quality assurance, validation, and risk management aspects after chemistry, toxicology, pharmacology, sensory science, and general management, was the key for the further positive development. Today, the main mandate has resulted in a status which might almost be called a marriage (with AMCIS AG in Bubendorf, a dynamic producer of active pharmaceutical ingredients, which unfortunately is just a bit too old to be called a start-up). But there remains the contractual right and some time to further pursue the goals as elaborated above and to also pursue the ones originally defined in the commercial registration file of the Canton Basel Landschaft: Consulting in the context of pharmaceuticals, cosmetics, chemicals, proof of activity, product safety, validation, and registration.

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Die Ausbildung in analytischer Chemie an der Hochschule für Technik Wallis

Romolo Cicciarelli*, Urban Frey, Jean-Luc Luisier, Umberto Piantini und Carlo Täschler

The Training in Analytical Chemistry at the Engineering School of Valais

Abstract: The restructuring of the engineering schools into well-defined competence centres has led to a reorganisation of chemistry training in western Switzerland: chemical engineering and computational chemistry at Fribourg, and analytical chemistry at Sion, in both cases within a general chemical training framework. Each school will carry out increased amounts of applied research, technology transfer, and continuing education, often in collaboration with industries and foreign institutes, which will strongly influence teaching practice.

Today, analytical chemists are confronted with a multitude of different problems to be solved. Teaching analytical chemistry thus pursues two main objectives: transmitting scientific knowledge and know-how. These objectives cover not only the classical wet methods and separation techniques and spectroscopic methods, but also surface analysis, electrochemical and coupled methods, which are indispensable for solving particular problems. Students should leave school with their own critical vision of analytical chemistry. This means that they should be able to correctly 'analyse' analytical results and judge them in an appropriate context. In this sense, sampling and sample preparation deserve a very careful treatment.

In order to reinforce this orientation at the Engineering School of Valais, two new professors with extensive industry experience have been appointed.

Keywords: Analytical chemistry · Education · Engineering school · Training

Die Neuausrichtung der Ingenieurschulen

Nach einer Periode des 'Alle machen alles' hat der Bund in seiner Fachhochschul-Strategie beschlossen, die diversen Aktivitäten der verschiedenen Schulen neu zu gliedern und gegebenenfalls zu konzentrieren. Es ist in der Tat nicht zu leugnen, dass durch diese Konzentration und die Bildung von Kompetenzzentren in klar umrissenen Gebieten eine deutlich zielgerichtetere Ausbildung gewährleistet wird. Nicht zuletzt auch durch den Einsatz von industrieerfahrenen Dozenten im Unterricht dürfte die Qualität der Ausbildung gesteigert und den künftigen Anforderungen des Marktes in erhöhtem Masse entsprochen werden.

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Was die Fachhochschule Westschweiz (HES-SO) angeht, wurden die Ausbildungsgänge im Fach Chemie wie folgt neu gegliedert: chemische Verfahrenstechnik und Computerchemie wird an der Ingenieurschule Freiburg, analytische Chemie wird an der Hochschule für Technik Wallis (HTW) in Sitten angesiedelt. Mit dieser Aufteilung soll vor allem den Vorlieben und Fähigkeiten der angehenden Studenten Rechnung getragen werden, wobei gleichzeitig die Mobilität und Flexibilität der Studierenden gefördert wird, was den jungen Absolventen den Einstieg in das ökonomische Netzwerk des Berufslebens erleichtern dürfte. Allerdings darf unseres Erachtens trotz der Ausrichtung auf relativ eng begrenzte Ausbildungsschwerpunkte eine allgemeine Fachausbildung nicht zu kurz kommen.

Über die reine Ausbildung hinaus werden die zukünftigen Fachhochschulen – um dieser Bezeichnung auch gerecht zu werden – vermehrt Aktivitäten in den Bereichen angewandte Forschung & Entwicklung (aF&E), Technologietransfer und Weiterbildung vorweisen müssen. Auch die Aufrechterhaltung internationaler Beziehungen zu Hochschulen im Ausland wird ein wesentlicher Bestandteil der zukünftigen Strategie an unseren Schulen sein. All diese Aktivitäten dürften einen tiefgreifenden Einfluss auf die Qualität der Ausbildung bewirken, indem sie einerseits die Dozenten mit der industriellen Realität konfrontieren und es andererseits den Studenten ermöglicht wird, praxisbezogene Projekte zu bearbeiten, mit denen sie sich auch im späteren Berufsleben konfrontiert sehen werden.

Es ist uns ein grosses Vergnügen, mit diesem Artikel die neue Struktur und die chemisch-analytische Ausrichtung der Abteilung Chemie an der HTW vorzustellen. Als analytischen Chemikern ist es uns natürlich eine ganz besondere Freude, eine Wissenschaft vorstellen zu dürfen, welcher wir uns mit grosser Hingabe verschrieben haben, auch wenn dies für uns, die wir uns oft in der Welt des Mikrosko-

pischen und der Moleküle verlieren, eine grosse Herausforderung darstellt.

Wie lässt sich die Tätigkeit des analytischen Chemikers definieren?

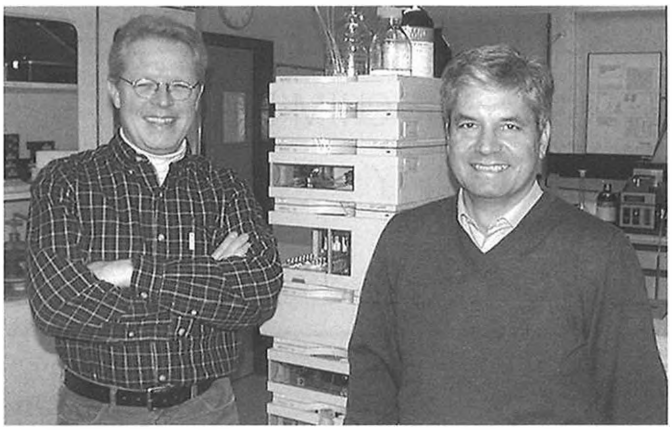
Es scheint nicht übertrieben, wenn man behauptet, dass die Arbeit des analytischen Chemikers darin besteht, die verschiedensten Fragestellungen aus den verschiedensten Arbeitsgebieten anzugehen: von der Medizin zur Umwelt, von der Geologie zur Elektronik, von der Metallurgie zur Lebensmittelwissenschaft. Je nach Fragestellung oder Einzelprobe muss der Analytiker in der Lage sein, Probleme zu lösen, welche höchste Anforderungen an die Genauigkeit der Resultate stellt, denken wir z.B. an das heikle Problem der Bestimmung des Plutoniumgehaltes. In anderen Fällen kann die Problemlösungsstrategie völlig anders geartet sein: Wie bestimmt man z.B. mit genügender Präzision und Richtigkeit Umwelteinträge in arktischem Eis? Welche Vorkehrungen müssen getroffen werden, um allfällige Kontaminationen während Probenahme und -transport zu verhindern? Die Notwendigkeit, die exakte chemische Zusammensetzung eines Untersuchungsobjektes in allen Details zu kennen, wie dies z.B. bei kriminalistischen Untersuchungen oder beim Nachweis der Echtheit eines Kunstgegenstandes der Fall ist, zeigt eine weitere Facette in der Vielfalt der chemischen Analytik. Dies sind nur einige wenige Fragestellungen, die illustrieren mögen, welcher Art die Fähigkeiten und das Know-How eines Analytikers sein sollten. Unzählige weitere Beispiele dieser Art könnten an dieser Stelle noch aufgeführt werden, und viele betreffen wichtige Bereiche menschlicher Tätigkeit.

Als verantwortliche Dozenten für die Ausbildung in chemischer Analytik an einer Fachhochschule sehen wir uns daher mit der folgenden Grundfrage konfrontiert:

Welches ist die bestmögliche Ausbildung für einen zukünftigen Chemiker analytischer Richtung an einer Fachhochschule?

Unser Ausbildungsprogramm beruht im wesentlichen auf zwei Säulen: Vermittlung von Fachwissen und Vermittlung von Know-How. Dabei wollen wir eine eingehende Ausbildung im Bereich grundlegender Methoden und Technologien anbieten, wie sie im modernen analytischen Labor anzutreffen sind.

Zunächst beschäftigen wir uns mit klassischen Methoden wie Gravimetrie und Volumetrie. Weiter mit der Anwendung von Trennmethoden wie Dünnschicht- Flüssig- und Gaschromatographie und schliesslich mit spektroskopischen Methoden wie Kernmagnetresonanz, Spektrophotometrie, Infrarotspektroskopie und Massenspektrometrie.



Carlo Täschler (links) und Romolo Cicciarelli (rechts)

Ebenso wichtig scheint uns aber auch die Vermittlung von Kenntnissen über analytische Methoden welche zwar weniger häufig angewendet werden, die sich jedoch manchmal für die Lösung bestimmter Problemstellungen nicht nur als nützlich, sondern als notwendig erweisen. Wir denken hier insbesondere an verschiedene elektrochemische Methoden sowie an speziellere Methoden der Oberflächenanalyse aber auch an gekoppelte Methoden wie z.B. die Mikroskopie mit FTIR-Analyse.

Über die reine Wissensvermittlung im engeren Bereich der Methoden und der Messverfahren hinaus wird es heute immer wichtiger, den Studenten auch einen 'kritischen Blick' auf ihr eigenes Fach mit auf den Weg zu geben.

Was verstehen wir darunter?

Eine der wichtigsten Eigenschaften des erfahrenen Analytikers ist es, ein einmal gewonnenes Messresultat zu 'analysieren', d.h. es in einen Sinnzusammenhang mit der ursprünglichen oder einer übergeordneten Fragestellung zu stellen. Dies umso mehr, wenn es sich bei der geforderten Arbeit um etwas für das betreffende Labor Ungewöhnliches oder ausserhalb der Routine gelegenes handelt. Fragen zu den Eigenheiten der angewendeten Analysemethoden, aber auch zum untersuchten Objekt müssen beantwortet werden bevor man sich mit einem möglicherweise ungeeigneten Vorgehen auf den falschen (Lösungs-)Weg macht. Eine weitere Tatsache, deren sich ein gut ausgebildeter Analytiker bewusst sein muss ist jene, dass die Anschaffung eines noch so kostspieligen und ausgefeilten Analyseinstrumentes niemals bedeutet, dass damit die Fragestellung schon gelöst sei. Grosse Aufmerksamkeit muss auch dem Problem der Probenahme und der Probenvorbereitung beigemessen werden. Nur allzu oft können fehlerhafte Analysenresultate auf einen Mangel an Sorgfalt in dieser überaus wichtigen Phase einer chemischen Analyse zurückgeführt werden. Auch die raffiniertesten Apparate messen in der Regel lediglich eine Konzentration in einer Lösung, wobei diese in entscheidender Weise von der Qualität der vorangegangenen Behandlung abhängt welche damit zur entscheidenden Phase im analytischen Verfahren wird. Es scheint uns daher ausserordentlich wichtig, einen grossen Teil der Ausbildung den Methoden der Probenahme und -behandlung zu widmen. Vorlesungen über Qualitätsmanagementssysteme wie cGMP; GLP und Akkreditierung sowie die Arbeiten in einem akkreditierten Labor vervollständigen die Kenntnisse der Studenten zu diesem Thema.

Zum Aufbau der Studienrichtung analytische Chemie an der HTW wurde der Lehrkörper durch zwei neue Dozenten mit grosser Industrieerfahrung verstärkt:

Romolo Cicciarelli

Nach einer Ausbildung an der Ecole d'ingénieurs de Genève (EIG) in Maschinenbau Studium der Chemie an der Universität Genf. Zahlreiche Tätigkeiten in der Industrie, u.a. Leitung des chemisch-analytischen Labors in der Abteilung Schweisstechnik der Ateliers de Sécheron und Leitung eines der zentralen Labors der LONZA AG in Visp

Carlo Täschler

Ausbildung zum dipl. Chemiker und Abschluss mit Doktorat an der Universität Zürich mit Schwerpunkt Kernresonanz. Diverse Tätigkeiten in der Industrie, u.a. fünf Jahre Leitung des zentralen Analysenlabors der Firma Bestfoods Europe (Muttergesellschaft der KNORR Nährmittel AG)

Eingegangen am 3. März 2000

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- ***Werner-Preis***
  An schweizerische oder in der Schweiz tätige Nachwuchswissenschafter für ausgezeichnete Forschungsarbeiten (CHF 10 000 + Medaille); jährlich
- ***Sandmeyer-Preis***
  Für hervorragende Arbeiten auf einem Gebiet der industriellen oder angewandten Chemie an ein Arbeitsteam (CHF 20 000) oder einen Einzelnen (CHF 10 000); jährlich
- ***Dr. Max-Lüthi-Preis***
  Für ausgezeichnete Diplomarbeiten, die an Chemiabteilungen von Fachhochschulen der Schweiz ausgeführt worden sind (CHF 1000 + Medaille); jährlich

Mitglieder

- 2200 ordentliche Mitglieder und 7 Kollektivmitgliedgesellschaften

CHIMIA 2000, 54, No. 4

9. Generalversammlung der NSCG vom 27. März 2000, ETH-Zentrum, Zürich

Begrüssung durch den Präsidenten

Sehr geehrte Damen und Herren,

werte Kolleginnen und Kollegen,

ich begrüsse alle Mitglieder der *Neuen Schweizerischen Chemischen Gesellschaft* zur 9. ordentlichen Generalversammlung und heisse Sie in Zürich willkommen. Ich begrüsse auch die Vertreter von Gesellschaften, die bei uns Kollektivmitglied sind.

Gemäss Jahresbericht 1999 zählten wir Ende des Jahres 2189 *Mitglieder*, was dem Stand von Ende 1998 entspricht. Darin enthalten sind 65 Delegierte von Kollektivmitgliedsgesellschaften. Mitgliederwerbung ist immer noch ein wichtiges Anliegen, weshalb ich Sie auffordere, Kolleginnen, Kollegen und Freunde zum Beitritt zu bewegen.

In Anbetracht dessen, dass die *Schweizerische Gesellschaft für Chemische Industrie (SGCI)* ihre Mitgliedschaft gekündigt hat und uns auch nicht mehr finanziell unterstützt, ist es mir wichtig, dass Sie wissen, welche Unternehmen uns finanziell helfen. Für das Frühlingssymposium dieses Jahres, das Eschenmoser-Symposium, sind dies Novartis, Roche, Ares-Serono, Firmenich, Ciba SC, Givaudan-Roure, Lonza und Siegfried. Ich danke diesen Firmen auch an dieser Stelle ganz herzlich für die Unterstützung

Wir bemühen uns gegenwärtig, mit den wichtigsten Chemiefirmen der Schweiz eine direkte Verbindung aufzubauen. Dabei interessiert es uns zu wissen, wer für die Forschung oder die Produktion verantwortlich ist, um mit diesen Personen Kontakte knüpfen zu können. In der Politik der Chemie gibt es noch viele Themen, die Industrie, Universität und Fachhochschulen interessieren, und da kann unsere Gesellschaft Verbindungen schaffen. Wir haben zum Beispiel mit Sorge festgestellt, dass laut einer Statistik des Bundesamtes für Statistik von 1998/1999 die Zahl der Chemiestudierenden um 20% gesunken ist. Die der Chemieingenieure ist allerdings gestiegen. Insgesamt zählen wir aber doch einen Schwund von 14%. Wir bemühen uns, die 'Internationale Chemieolympiade' im Jahr 2004 in der Schweiz durchzuführen. Dies braucht viel Organisation und Planung. Wir hoffen, durch diese Olympiade bei der Bevölkerung die Chemie in ein gutes Licht zu stellen. Vielleicht kann diese Aktion auch die Begeisterung für Chemie wieder etwas anfachen. Der 'International Chemistry Celebration Day', von dem ich Ihnen letztes Jahr berichtet habe, wurde während der ILMAC in Basel, aber auch in anderen Städten, mit grossem Erfolg durchgeführt. Besonderen Dank für den Erfolg gebührt Herrn Dr. *G. Naville* für die Organisation und den Herren Prof. *A. von Zelewsky* und Prof. *F. Emmenegger* aus Fribourg und Dr. *R. Kaiser* von Givaudan-Roure für die Demonstrationsvorlesungen.

Unsere Gesellschaft ist heute acht Jahre alt. Wie ich Ihnen schon letztes Jahr mitgeteilt habe, wurden gewisse Korrekturen in der Struktur vorgenommen. Ein Ressort wurde aufgelöst. Bei näherer Durchsicht stellt sich nun heraus, dass die Statuten allgemein auf die heutige Aktualität durchgesehen werden sollten. Wir haben deshalb eine kleine Arbeitsgruppe geschaffen, welche die Statuten überarbeiten soll. Wir planen, Ihnen an der nächsten Generalversammlung im Frühling 2001 revidierte Statuten zur Begutachtung vorlegen zu können.

H.L. Senti, Präsident der NSCG

Protokoll der 9. Generalversammlung

Geschäftlicher Teil

1. Der Präsident Dr. *H.L. Senti* eröffnet um 14.30 Uhr die Versammlung. Er begrüsst die zahlreich erschienenen Mitglieder und heisst sie in Zürich willkommen. In die Begrüssung schliesst er auch die Vertreter von Gesellschaften ein, die bei der NSCG Kollektivmitglied sind. Dann informiert er kurz über den Mitgliederbestand, die Aufnahme direkter Kontakte mit den wichtigsten Chemiefirmen der Schweiz, die Bemühungen der NSCG, junge Leute für Chemie zu begeistern, sowie über vorgesehene Strukturanpassungen in der Gesellschaft. Er dankt allen Firmen, die das Frühlingssymposium dieses Jahr finanziell unterstützt haben.
2. Als Stimmenzähler amtieren Frau Dr. *U. Bünzli-Trepp* und Prof. *R. Neier*.
3. Das Protokoll der 8. Generalversammlung vom 23. März 1999 wurde in der CHIMIA publiziert (*Chimia* **1999**, *53*, 246). Es gibt keine Bemerkungen und das Protokoll wird genehmigt.
4. Der Jahresbericht 1999 ist in der CHIMIA publiziert (*Chimia* **2000**, *54*, 70). Der Bericht wird einstimmig genehmigt.
5. Finanzen

5.1. Dr. *R. Scartazzini* kommentiert die mit der Einladung zur Generalversammlung verschickte Bilanz per 31. Dezember 1999 sowie die Gewinn- und Verlustrechnung. Das Gesamtvermögen betrug zum Jahresende CHF 3 809 742.–. Die Jahresrechnung ergibt einen Verlust von CHF 50 980.–.

5.2. Der Bericht der Revisoren Prof. *H. Heimgartner* und Prof. *J. Wirz* vom 22. März 2000 wird verlesen und die Jahresrechnung 1999 einstimmig genehmigt.

5.3. Der Entlastung des Vorstandes wird ohne Gegenstimme entsprochen.

6. Die Mitgliederbeiträge bleiben unverändert:

Ordentliche Mitglieder	CHF	120.–
Studentinnen/Studenten	CHF	35.–
Pensionierte Mitglieder	CHF	60.–
Firmenmitglieder	CHF	600.–

7. Wahlen

7.1. Zur Wahl in den Vorstand schlägt der Vorstand *Heinz Schmid*, Sulzer Chemtech AG, Winterthur, als Delegierter des SVC vor. Für eine Wiederwahl stellen sich die folgenden Vorstandsmitglieder zur Verfügung: Prof. *C. Ganter*, Prof. *R. Neier* und Dr. *R. Scartazzini*.
Von der Generalversammlung werden keine weiteren Vorschläge gemacht. Alle Herren werden einstimmig gewählt.

8. Unter *Varia* werden keine Wortmeldungen verlangt.
Damit schliesst der Präsident den geschäftlichen Teil der Generalversammlung und geht zur Verleihung der Preise der Gesellschaft über.

Preisverleihung

Der *Sandmeyer-Preis* (CHF 10 000.–) für hervorragende Arbeiten auf dem Gebiet der industriellen oder angewandten Chemie ging dieses Jahr an Prof. *Hubert Mimoun*, Firmenich S.A., Genf, in Anerkennung seiner Arbeiten über die industrielle Entwicklung einer neuen Technologie zur Reduktion von Carbonylverbindungen mit Polymethylhydrosiloxan.

Die für herausragende Diplomarbeiten an Chemieabteilungen schweizerischer Fachhochschulen verliehene Dr. *Max-Lüthi-Auszeichnung* (CHF 1000.– und Medaille) ging an *Pascal Beer*, Hochschule für Technik und Architektur Burgdorf, sowie an *Thomas Roth*, Ecole d'ingénieurs et d'architects de Fribourg.

Dr. H.L. Senti
Präsident

Dr. R. Darms
Geschäftsführer

Sandmeyer-Preis 2000 der NSCG

Foto: R. Häfliger

Hubert Mimoun

Der Sandmeyer-Preis 2000 wird Prof. *Hubert Mimoun*, Firmenich S.A., Genf, verliehen.

Hubert Mimoun was born in Tunisia in 1943 and entered the University of Strasbourg, obtaining the Licence ès Sciences in 1963. After a degree in chemical engineering at the Ecole Nationale Supérieure des Pétroles et Moteurs in Rueil Malmaison, he obtained a Doctorat d'Etat ès Sciences at University Paris VI in 1969. Following that, he was a postdoctoral associate at Biochemisches Institut in Giessen in 1970 under the supervision of Prof. V. Ullrich. He was appointed Senior Research Engineer at Institut Français du Pétrole, where he remained from 1971 to 1989. From 1990 to now, he works as a Senior R&D leader at Firmenich S.A., a major flavor & fragrances company located in Geneva. He has taught industrial chemistry as invited professor at the University of Lausanne since 1991.

Prof. Mimoun is a world famous specialist in catalytic oxidations and has discovered many reactions such as transition metal-catalyzed epoxidation and ketonization of olefins, hydroxylation of hydrocarbons by molecular oxygen, hydrogen peroxide and alkyl hydroperoxides. He conceptualized the mechanisms of heterolytic oxygen transfer reactions – called cyclic and pseudocyclic peroxymetalation – and homolytic ones, allowing a heuristic interpretation of most catalytic oxidation reactions. He discovered a new safe and economical industrial technology for the reduction of aldehydes, ketones, esters, triglycerides and epoxides by poly(methylhydrosiloxane) in the presence of homogeneous zinc catalysts, which is operated in multipurpose reactors up to the multi-ton scale.

Dr. Max-Lüthi-Auszeichnung 2000

Der Preis wird verliehen an *Pascal Beer*, Hochschule für Technik und Architektur Burgdorf, sowie an *Thomas Roth*, Ecole d'ingénieurs et d'architects de Fribourg.

Pascal Beer hatte in seiner mit annähernder Maximalnote abgeschlossenen Diplomarbeit im Bereich Analytik und Prozesskontrolle das Thema mit dem Titel 'Zerstörungsfreie Analyse von Magnesium und Titan in Papier mittels Röntgenfluoreszenz' zu bearbeiten. Herr Beer hat seine Diplomarbeit beim Industrie-Auftraggeber unter Praxisbedingungen selbständig durchgeführt. In dieser sehr anspruchsvollen Aufgabe ging es um die Abklärung der generellen Tauglichkeit des Messverfahrens zur Beurteilung des Behandlungserfolges der Papierentsäuerung nach dem Batelle-Verfahren. Die Papierentsäuerung spielt u.a. auch für die Rettung der 'sterbenden Bücher' in Bibliotheken eine grosse Rolle. Herr Beer hat in kurzer Zeit ein beachtliches Wissen in der komplexen Materie der Röntgenfluoreszenz erarbeitet. Neben der effizienten Arbeitsgestaltung und sorgfältiger Planung bewies er auch die nötige Flexibilität zum Improvisieren. Dadurch war es ihm möglich, die im Verlaufe der Arbeit zunehmend komplexer werdenden Probleme zu erkennen und sie auf fachlich beachtlichem Niveau zu lösen. Herr Beer hat mit seiner Arbeit einen namhaften Beitrag zum Aufbau der Analytik für die Prozesskontrolle der Papierentsäuerung geleistet.

Thomas Roth a achevé la note maximale au sein de son travail de diplôme avec le sujet en thème 'Investigation de la stabilité thermique du Bis-(methylbenzylidène)-sorbitol et mesure du coefficient de diffuse de son produit d'hydrolyse dans le polypropylène'. Le problème a été posé par 'Bundesamt für Gesundheit'. Bis-(methylbenzylidène)-sorbitol est utilisé en additif pour l'augmentation de la transparence optique des films en polypropylène. Ceux-ci sont de leur parts utilisé en tant qu'emballage pour les produits alimentaires. Comme les procédés de finition se déroulent à des températures de plus de 250 °C, la stabilité thermique de tous les composants matériaux est extrêmement important. Egalement d'importance est la vitesse de migration d'éventuels produits de décomposition. Monsieur Roth a donné des réponses concluantes aux questions posées dans ce sujet par des expériences intelligentes et des contemplations critiques. Pour cela il a mis en place et combiné différentes méthodes d'analyse moderne (comme TG-MS, Solid Phase Injection-GC, IR-spectrometrie). Pour déterminer le coefficient de diffusion, Monsieur Roth a utilisé un programme Labview qu'il a établi lui même. En produit annexe a son travail de diplôme, Monsieur Roth a développé un programme lequel autorise l'estimation de la concentration de molécules migrantes.

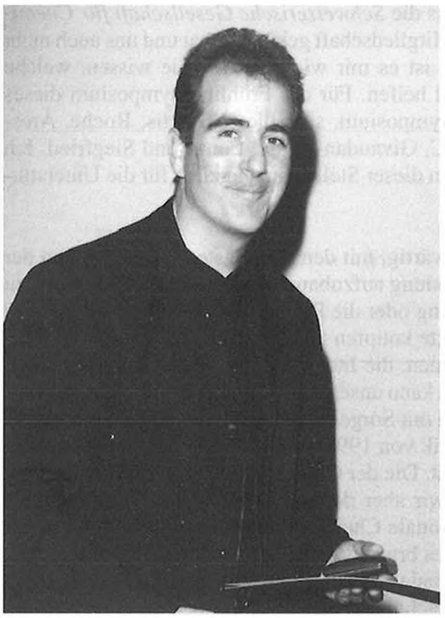

Foto: R. Häfliger

Pascal Beer

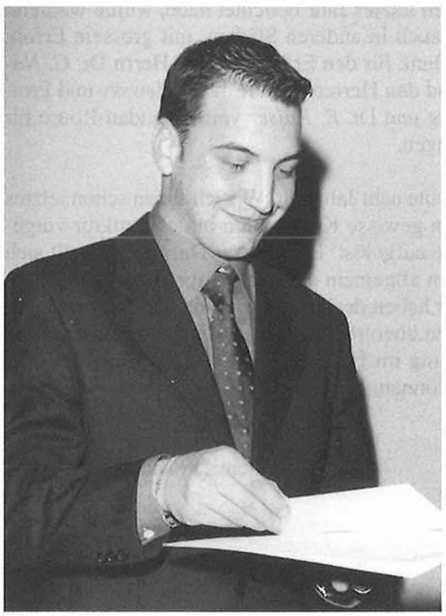

Foto: R. Häfliger

Thomas Roth

Events 2000 and Preview 2001

Events 2000

January to September 2000

Continuous Education – Courses in Quality Control and Quality Assurance

Organized by: NCSC, Division of Analytical Chemistry, FLB, SCV, SLV

Information:
Secretary of Division of Analytical Chemistry NSCS, Fachhochschule Burgdorf, Abteilung Chemie, Pestalozzistrasse 20, CH–3400 Burgdorf
Tel.: +41 79 645 26 24, Fax: +4134 426 43 91
E-Mail: Ausbildung-SACh@hotmail.com
http://www.sach.ch

May 4, 2000
Basel

Mini-Symposium: Chemical Mechanisms of Toxicity, Basic Knowledge for Designing Safer Chemicals

Organized by:
NSCS, Division of Medicinal Chemistry

Information:
E-Mail: medichem@netsurfer.ch
http://www.nscs.ch/smc/ or *http://www.efmc.ch/*

May 5, 2000
Siegfried AG, 4800 Zofingen

General Assembly of the Division of Industrial Chemistry and Plant Tour

Organized by:
Division of Industrial Chemistry of NSCS

Contact address/information:
Dr. H.R. Dettwiler, Lonza Group AG, CH–3930 Visp
Tel.: +41 27 948 56 39, Fax: +41 27 948 61 80
E-Mail: hans-rudolf.dettwiler@lonza.ch

May 14–18, 2000
Convention Center Basel

PBA 2000, 11th International Symposium on Pharmaceutical and Biomedical Analysis

Organizing committee: Renate Eberle, Basel; Eric. R. Francotte, Basel; Michel Marti, Basel; Jacky Vonderescher, Basel

Information:
PBA 2000, Convention Center Basel, P.O.Box, Messeplatz 21, CH–4021 Basel
Tel.: +41 61 686 28 28, Fax: +41 61 686 21 85
E-Mail: congress@messebasel.ch
http://www.congress.ch/pba

Sept. 27/28, 2000
Fachhochschule Fribourg

5th Freiburger Seminar 2000 'Chemical Production in Multi-Purpose Plants'

Organized by: NSCS, Division of Industrial Chemistry

Contact address/information:
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Tel.: +41 27 948 56 39, Fax: +41 27 948 61 80
E-Mail: hans-rudolf.dettwiler@lonza.ch

Sept. 26–28, 2000
Universität Zürich-Irchel

Applica 2000

Organized by: NSCS Division of Analytical Chemistry, and SLV

Information:
Dr. A. Wehrli, Dörrmattring 30, CH-5070 Frick
Tel. and Fax: +41 62 871 19 21
Tel.: +41 79 645 26 24

Oct. 8–13, 2000
Leysin

Fourth Swiss Course of Medicinal Chemistry

Organized by: NSCS, Division of Medicinal Chemistry

Information:
http://www.pharma.ethz.ch/leysin/ and
http://www.nscs.ch/smc/

Organization:
Prof. Dr. Gerd Folkers
Professor for Pharmaceutical Chemistry, ETH Zürich
Winterthurerstrasse 190
CH–8057 Zürich/Switzerland
Tel.: +41 1 635 6060, Fax: +41 1 635 6884
E-Mail: folkers@pharma.ethz.ch
and
Prof. Dr. Beat Ernst
Professor of Molecular Pharmacy
University of Basel
CH–4051 Basel
Tel.: +41 61 261 79 41, Fax: +41 61 261 79 07
E-Mail: ernstb@ubaclu.unibas.ch

Oct. 12, 2000
UNIL/EPF, Lausanne

Fall Meeting 2000 of the New Swiss Chemical Society, NSCS

Organized by: NSCS Division of Chemical Research

Information:
Prof. A.E. Merbach, Institut de Chimie Minérale, Université de Lausanne, BCH-Dorigny, CH–1015 Lausanne
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E-Mail: andre.merbach@icma.unil.ch
and/or
Prof. D. Stahl, Département de Chimie, EPFL-Ecublens, CH–1015 Lausanne
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E-Mail: daniel.stahl@epfl.ch

Preview 2001

March 29/30, 2001
Université de Neuchâtel

Spring Meeting 2001 – 'SWISS Chemistry'

Organized by: NSCS and Universities of Neuchâtel and Fribourg

Information:
Prof. Dr. R. Neier, Institute of Chemistry, Université de Neuchâtel, Avenue de Bellevaux 51, CH–2000 Neuchâtel
Tel.: +41 32 718 24 28, Fax: +41 32 718 25 11
E-Mail: reinhard.neier@ich.unine.ch

SACh Section of Analytical Chemistry

NOCH 3 VERANSTALTUNGEN VOR DEN SOMMERFERIEN

Aktualisieren Sie Ihr Wissen in:

HPLC- Troubleshootingkurs *1.2.4*
Probleme, Prävention und Fehlersuche in der HPLC

Ziel:
Sie sind über die Ursachen von Störungen und deren Erkennung informiert und können anhand von Diagnoserichtlinien Ihre HPLC-Anlage Schritt für Schritt untersuchen und mögliche Fehler orten.

Referent:
J. C. Hildenbrand, Novartis Services AG, Basel

Ort/Termin:
Berner Fachhochschule, Burgdorf / 8.–9. Mai 2000

QS-Spezialisierungsseminar *4.1.4*
Validieren von Analysenverfahren

Ziel:
Sie haben die Fähigkeit, den Validierungsumfang von Analysenverfahren sachgerecht dem konkreten Einzelfall anzupassen.

Leitung:
Dr. B. Wampfler, EMPA, St. Gallen

Ort/Termin:
Fachhochschule Aargau, Brugg/Windisch / 8. Mai 2000

QS-Spezialisierungsseminar *4.1.5*
Qualitätssicherung, eine Führungsaufgabe

Ziel:
Sie kennen die Massnahmen, welche ergriffen werden müssen und den Aufwand, welcher erforderlich ist, um die gewünschte oder versprochene Produkt-Qualität wirtschaftlich sicherzustellen.

Leitung:
Dr. P. Radvilla, ehem. EMPA, St. Gallen
Dr. B. Schreiber, Novartis Pharmanalytica SA, Locarno

Ort/Termin:
Fachhochschule Aargau, Brugg/Windisch / 19. Juni 2000

Kosten/Anmeldung/Informationsmaterial

- **Kosten der Kurse:**

Nichtmitglieder:	CHF 450.–/1 Tag		CHF 810.–/2 Tage	
Mitglieder:	CHF 400.–/1 Tag		CHF 720.–/2 Tage	
Ich bin Mitglied von	FLB ❑	NSCG ❑	SCV ❑	SLV ❑

- **Anmeldung für:**

Veranstaltung	Nr. 1.2.4 ❑	Nr. 4.1.4 ❑	Nr. 4.1.5 ❑

- **Mehr Informationen**
  Senden sie mir unentgeltlich die
  SACh-Weiterbildungsbroschüre 2000/2001 ❑

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Zusenden oder übermitteln an:
Fax: 034 426 43 91
E-Mail: Ausbildung_SACh@hotmail.com (www.sach.ch)

Sekretariat SACh
Fachhochschule Burgdorf
Abteilung Chemie
Pestalozzistrasse 20
CH–3400 Burgdorf

New Members

Bataillard, Pierre, Dr., F – 68170 Rixheim

Blanc, Alain, 5000 Aarau

Cati, Sakir, 2000 Neuchâtel

Dietemann, Patrick, 8057 Zürich

Duclos, Séverine, 3007 Bern

Faurite, Jean-Philippe, 2000 Neuchâtel

Gasser, Gilles, 2034 Peseux

Iskander, George M., Prof., AUS – Sydney, NSW 2761

Kinzy, Willy R., Dr., 4002 Basel

Maisse-Francois, Aline, 2000 Neuchâtel

Pacifico, Jessica, 2208 Les Hauts-Geneveys

Schmid, Heinz, 8353 Elgg

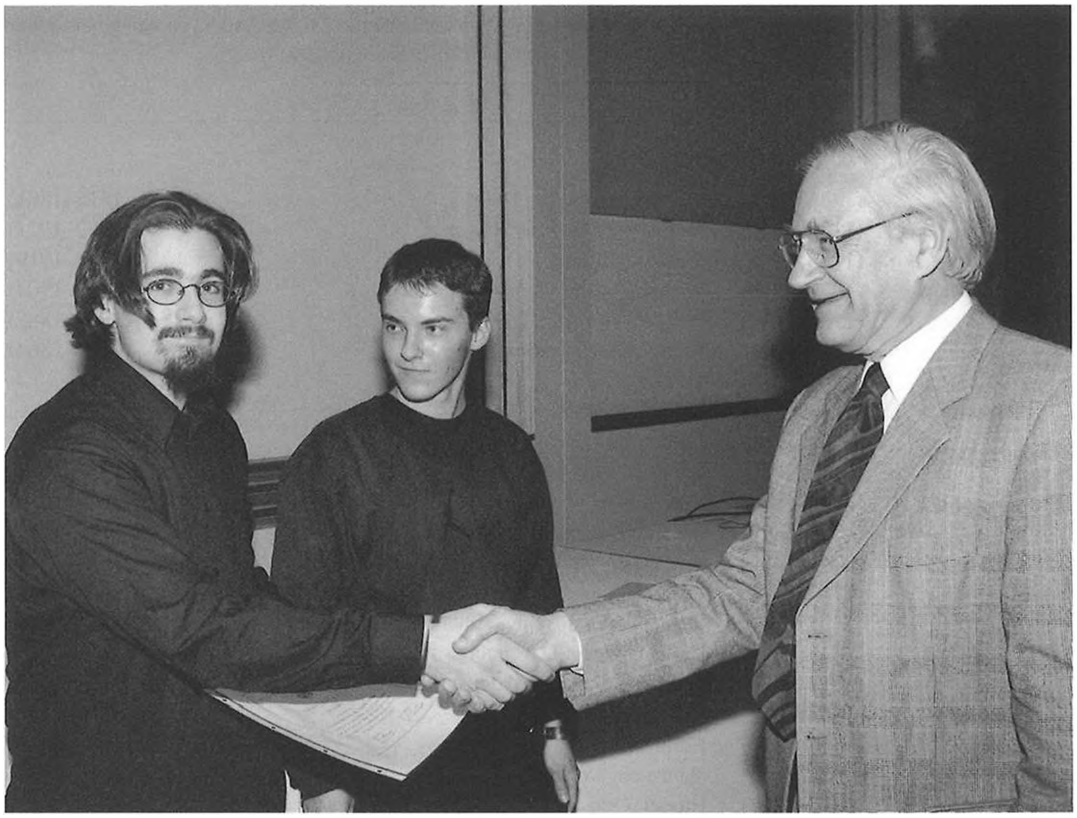
Sekanina, Klara, 8037 Zürich

Vallat, Olivier, 2000 Neuchâtel

CHIMIA 2000, 54, No. 4

Nationaler Chemie-Wettbewerb 1999

Keywords: Chemistry competition · Chemistry olympiad · Weight and value of chemistry teaching



v.l.n.r. Jean Garnier, Daniel Torricelli, Prof. Richard R. Ernst

In der CHIMIA (*Chimia* **2000**, *54* (1–2), 72) haben wir im Beitrag des VSN zum Jahresbericht der NSCG davon kurz berichtet: vom Nationalen Chemie-Wettbewerb für Gymnasiastinnen und Gymnasiasten unter dem neuen Signet CXH (χ griechisch CHI für Chemie, CH für die Schweiz, für Chemie und für Kohlenwasserstoffe!). Aus 21 Schulen schrieben 147 Schülerinnen und Schüler die einstündige Prüfung in ihren Schulen, mit 8 multiple-choice-Fragen (1 Punkt pro Frage) und 8 Fragen für Antworten mit Text, Rechnungen und Formeln (3 Punkte pro Frage). Fünf Kollegen haben je für bestimmte Aufgaben alle 147 Teilnehmer-Antworten korrigiert (für die Antworten waren deshalb 5 Blätter pro Teilnehmer vorgesehen), so dass eine korrekte Bewertung gewährleistet war. Die Rangliste ergab 33 Teilnehmer(innen) aus 10 Kantonen mit mehr als der Hälfte der möglichen Punkte und dies mit einer sehr erfreulichen Verteilung: Einerseits 15 Romands und 18 Deutschschweizer, andreseits 12 Schülerinnen und 21 Schüler. Sogar der erste Rang wurde *ex aequo* von einem Lausannois und einem Zürcher geteilt (Bild). Diese 33 Besten wurden an die Schlussfeier vom 24. November 1999 im Chemie-Hörsaal der Universität Fribourg eingeladen, an der Nobelpreisträger Prof. R. Ernst ihnen eine Urkunde (Bild) überreichte. Alle 33 wurden einzeln zusammen mit dem Nobelpreisträger fotografiert und erhielten nachher die Foto zur Erinnerung. Alle 147 Wettbewerbsteilnehmer(innen) erhielten sehr gelungene T-shirts, die von der Riechstoff-Firma Givaudan-Roure gesponsort wurden und weiss auf dunkelgrün vorne das CXH Signet und hinten die Strukturformel des Geruchs-Moleküls Citronellol ($C_{10}H_{19}OH$) tragen.

Der Nationale Chemie-Wettbewerb 1999 wurde vom VSN (Verein Schweizerischer Naturwissenschafts-Lehrerinnen und -Lehrer) organisiert, unter dem Patronat der NSCG (Neue Schweizerische Chemische Gesellschaft) und mit finanzieller Unterstützung der Firma Novartis.

Durchführung, Resultat und Abschluss dieses ersten Nationalen Chemie-Wettbewerbes waren sehr erfreulich, ein zweiter Nationaler Chemie-Wettbewerb ist für Herbst 2000 geplant.

Wozu überhaupt ein Nationaler Chemie-Wettbewerb?

Einerseits: durch das neue Maturitäts-Anerkennungs-Reglement, das 1995 durch die Erziehungsdirektoren-Konferenz erlassen wurde, und das leider zu einer ungeheuren Belastung der Gymnasien führte und eine Herabnivellierung der schweizerischen gymnasialen Bildung mit sich bringt, werden die naturwissensschaftlichen Fächer im Gymnasium ganz allgemein und auch die Chemie in ihrer Bedeutung im gymnasialen Unterricht herabgesetzt. Das Schweizer Maturitäts-Zeugnis enthält in Zukunft für die 'Fächergruppe Naturwissenschaften' Biologie/Chemie/Physik eine einzige (Durchschnitts-)Note, die gleiches Gewicht hat wie die Note für jede einzelne Sprache. Der Vollständigkeit halber sei allerdings erwähnt, dass es neben andern Wahlfächern das Schwerpunktsfach Biologie/Chemie mit einer eigenen Note gibt. Das Fach Chemie braucht eine Förderung auch ausserhalb des Unterrichts, um im Rahmen der gymnasialen Allgemeinbildung seine Bedeutung zu bewahren. Durch Öffentlichkeitsarbeit, auf die in Zukunft besonders geachtet werden soll, wird diese Förderung durch den Chemie-Wettbewerb nach aussen getragen.

Andrerseits nimmt die Schweiz seit vielen Jahren mit beachtlichem Erfolg regelmässig mit einer Vierer-Delegation an der Internationalen Chemie-Olympiade teil (siehe *Chimia* **2000**, *53*, 451–455). Der Nationale Chemie-Wettbewerb kann auch als Kandidaten-Basis für die Selektion und Vorbereitung der Schweizer Teilnehmer(innen) an Chemie-Olympiaden dienen.

Korrespondenz: Dr. Gustave Naville
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CH–8126 Zumikon
Tel.: +41 1 918 00 58
Fax: +41 1 918 22 70

NOUVELLE SOCIETE SUISSE DE CHIMIE NSSC
SOCIETE SUISSE DES PROFESSEURS DE SCIENCES NATURELLES SSPSN

CXH

CERTIFICAT

JEAN GARNIER

a participé au

Concours National de Chimie 1999

et a obtenu le 1er rang ex-aequo sur 147 participants.
Prof. Dr. R. Ernst, prix Nobel de chimie, lui a remis ce document en reconnaissance de ses mérites.

à Fribourg 24 novembre 1999.

pour la NSSC — pour la SSPSN

Prof. Dr. R. Neier — Prof. Dr. W. Bachmann

NEUE SCHWEIZERISCHE CHEMISCHE GESELLSCHAFT NSCG
VEREIN SCHWEIZERISCHER NATURWISSENSCHAFTS-LEHRERINNEN UND -LEHRER V S N

CXH

URKUNDE

Wir gratulieren

DANIEL TORRICELLI

Er hat am

Nationalen Chemie-Wettbewerb 1999

teilgenommen und hat mit seiner Leistung im Wettbewerb den 1. Rang ex-aequo von 147 Teilnehmenden erreicht.
Nobelpreisträger Prof. Dr. R. Ernst hat ihm diese Urkunde, in Anerkennung seiner Leistung, an der Schlussfeier in Fribourg 24. November 1999 überreicht

für die NSCG — für den VSN

Prof. Dr. R. Neier — Prof. Dr. W. Bachmann

Die Urkunden für die Preisträger

FECS Liste '100 Distinguished European Chemists'

Die Federation of European Chemical Societies (FECS) hatte im Jahre 1999 beschlossen, zum Millenium eine Liste bekannter europäischer Chemiker zu erstellen, welche die Chemie wesentlich geprägt und Wissenschaft, Industrie und Gesellschaft weltweit beeinflusst haben. Diese Liste sollte den Zeitraum vom 18. bis 20. Jahrhundert umfassen, wobei jedoch noch lebende Chemiker nicht berücksichtigt werden sollten. Dazu wurden alle Mitgliedsgesellschaften eingeladen, Vorschläge ein zureichen.

Von der grossen Zahl eingegangener Vorschläge traf die FECS Working Party on History aufgrund festgelegter Kriterien eine Auswahl und übergab diese dem FECS Executive Committee zur endgültigen Entscheidung. Diese Entscheidung kam nicht ohne Kontroverse zustande, da viele bekannte Chemiker nicht berücksichtigt werden konnten. Auch von den Schweizer Vorschlägen blieben einige auf der Strecke. Dieser Aspekt ist bei der erstellten Liste zu berücksichtigen. Die Namen sind nachfolgend aufgeführt, wobei die Darstellung in alphabetischer Reihenfolge erfolgt.

FECS List of 100 Distinguished European Chemists

18th Century

Bergman, Tobern Olof	(1735–1784)
Berthollet, Claude Louis	(1748–1822)
Black, Joseph	(1728–1799)
Cavendish, Henry	(1731–1810)
Gadolin, Johan	(1760–1852)
Kirwan, Richard	(1735–1812)
Klaproth, Martin Heinrich	(1743–1817)
Lavoisier, Antoine Laurent	(1743–1794)
Lomonosov, Mikhail Vasilievich	(1711–1765)
Priestley, Joseph	(1733–1804)
Richter, Jeremias Benjamin	(1762–1807)
Ruprecht, Antal	(1748–1818)
Scheele, Carl Wilhelm	(1742–1786)
Vauquelin, Louis Nicolas	(1763–1829)

19th Century

Arrhenius, Svante August	(1859–1927)
Auer, Karl	(1858–1929)
Avogadro, Amedeo	(1776–1856)
Baeyer, Johan Friedrich Wilhelm Adolf	(1835–1917)
Berthelot, Pierre Eugène Marcelin	(1827–1907)
Berzelius, Jöns Jakob	(1779–1848)
Bunsen, Robert Wilhelm Eberhard	(1811–1899)
Butlerov, Alexander Mikhailovich	(1828–1886)
Cannizzaro, Stanislao	(1826–1910)
Claisen, Ludwig	(1851–1930)
Dalton, John	(1766–1844)
Davy, Humphry	(1778–1829)
de Marignac, Jean Charles Galissard	(1817–1894)
Dumas, Jean Baptiste André	(1800–1884)
Faraday, Michael	(1791–1867)
Fischer, Emil	(1852–1919)
Frankland, Edward	(1825–1899)
Fresenius, Carl Remigius	(1818–1897)
Gay-Lussac, Joseph Louis	(1778–1850)
Graham, Thomas	(1805–1869)
Hofmann, August Wilhelm	(1818–1892)
Kekulé, Friedrich August	(1829–1896)
Kolbe, Adolph Wilhelm Hermann	(1818–1884)
Laurent, Auguste	(1807–1853)
Le Chatelier, Henri Louis	(1850–1936)
Liebig, Justus	(1803–1873)
Mendeléev, Dmitri Ivanovich	(1834–1907)
Meyer, Julius Lothar	(1830–1895)
Moissan, Ferdinand Frédéric Henri	(1852–1907)
Ostwald, Friedrich Wilhelm	(1853–1932)
Pasteur, Louis	(1822–1895)
Perkin, William Henry (sr.)	(1838–1907)
Proust, Joseph Louis	(1754–1826)
Ramsay, William	(1852–1916)
Solvay, Ernest	(1838–1922)
Stas, Jean Servais	(1813–1891)
Ste-Claire Deville, Henri Etienne	(1818–1881)
Van't Hoff, Jacobus Henricus	(1852–1911)
Werner, Alfred	(1866–1919)
Williamson, Alexander William	(1824–1904)
Wöhler, Friedrich	(1800–1882)
Wurtz, Charles Adolphe	(1817–1884)

20th Century

Aston, Francis William	(1877–1945)
Barton, Derek Harold Richard	(1918–1998)
Bosch, Karl	(1874–1940)
Brönsted, Johannes Nicolaus	(1879–1947)
Butenandt, Adolf Friedrich Johann	(1903–1995)
Curie, Marie	(1867–1934)
Debye, Peter Joseph Wilhelm	(1884–1966)
Diels, Otto Paul Hermann	(1876–1954)
Grignard, François Auguste Victor	(1871–1935)
Haber, Fritz	(1868–1934)
Hahn, Otto	(1879–1968)
Hantzsch, Arthur Rudolf	(1857–1935)
Hassel, Odd	(1897–1981)
Haworth, Walter Norman	(1883–1950)
Hevesy, Gÿorgy Charles	(1885–1966)
Heyrovsky, Jaroslav	(1890–1967)
Hinshelwood, Cyril Norman	(1897–1967)
Hodgkin, Dorothy Mary	(1910–1994)
Ingold, Christopher Kelk	(1893–1970)
Karrer, Paul	(1889–1971)
Kendrew, John Cowdery	(1917–1997)
Natta, Giulio	(1903–1979)
Noddack, Ida Eva	(1896–1978)
Nernst, Walther Hermann	(1864–1941)
Pregl, Fritz	(1869–1930)
Prelog, Vladimir	(1906-1998)
Reppe, Walter Julius	(1892–1969)
Robinson, Robert	(1886–1975)
Rutherford, Ernest	(1871–1937)
Ruzicka, Leopold Stephen	(1887–1976)
Sabatier, Paul	(1854–1941)
Semenov, Nikolay Nikolaevich	(1896–1986)
Soddy, Frederick	(1877–1956)
Sörensen, Soren Peter Lauritz	(1868–1939)
Staudinger, Hermann	(1881–1965)
Stock, Alfred	(1876–1946)
Svedberg, Theodor H.E.	(1884–1971)
Todd, Alexander Robertus	(1907–1997)
Tswet, Michail Semënovic	(1872–1919)
Wilkinson, Geoffrey	(1921–1998)
Willstätter, Richard Martin	(1872–1942)
Wittig, Georg Friedrich Karl	(1897–1987)
Ziegler, Karl	(1898–1973)
Zsigmondy, Richard Adolf	(1865–1929)

INFORMATION

Congresses · Conferences · Workshops

2000 Lausanne Workshop on Glycomimetics

supported by the European COST-Chemistry program
and the University of Lausanne

When: Friday 12th May, 2000, 9.00–18.00
Where: Science Faculty of the University Lausanne-Dorigny, Switzerland

Invited lectures by:
- Prof. Richard R. Schmidt, University of Konstanz (Germany)
- Prof. Andrea Vasella, ETHZ, Zürich
- Prof. Beat Ernst, University of Basel
- Prof. Jacques Van Boom, University of Leiden (Netherlands)
- Dr. Jesus Jimenez-Barbero, CSIC Madrid (Spain)
- Dr. Rudolph Duthaler, Novartis Pharma, Basel

Keynote lectures by Prof. V. Jäger (Stuttgart), Prof. I. Robina (Seville), and oral presentations of selected papers. Poster session open to all participants.

Information and correspondence: Prof. Pierre Vogel
Institut de chimie organique de l'Université de Lausanne
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Fax: +41 21 692 39 55
E-Mail: pierre.vogel@ico.unil.ch

5th Symposium/Workshop on Pharmacy and Thermal Analysis PhandTA 5

eurostar-science (European Society for Applied Physical Chemistry)

19.–21. September 2000
Pharmazentrum der Universität Basel, Schweiz

Kontakt: Dr. Erwin Marti
Tel.: 061 686 61 68
Fax: 061 686 62 33
E-Mail: eurostar-science@solvias.com
http://www.eurostar-science.org

Computational Chemistry: Entering a New Century

A One-Day Symposium
in honour of the 60th birthday of Prof. Jacques Weber

Friday, June 9, 2000, 8.45–18.15

University of Geneva, Sciences II, Auditoire J.Ch. De Marignac
30, Quai E. Ansermet, 1211 Geneva (Switzerland)

The speakers
- Alessandro Bencini, University of Florence, Italy
- Maurice Bourquin, President (Recteur), University of Geneva, Switzerland
- Jürgen Brickmann, University of Darmstadt, Germany
- Roberto Car, Princeton University, USA
- John W.D. Connolly, Center for Computational Science, University of Kentucky, USA
- André Merbach, University of Lausanne, Switzerland
- Francois Gilardoni, University of California at Berkely, USA
- Dennis R. Salahub, Director Steacie Institute for Molecular Sciences, Ottawa, Canada
- Nadia Magnenat Thalmann, Director Miralab, Computer Science Department, University of Geneva, Switzerland
- Roland Wenger, President of Section Chemical Research of the New Swiss Chemical Society, Basel, Switzerland

Lectures

Novartis Chemistry Lectureship 1999/2000

jeweils Mittwoch, 10.30 Uhr
Auditorium Horburg, K-430.3.20
Mühlheimerstrasse, Basel

May 3, 2000 — Prof. *S. Kobayashi*
University of Tokyo, Japan
'New Dimensions of Catalysis in Synthetic Organic Chemistry'

Basler Chemische Gesellschaft

Donnerstag, 17.30 Uhr
Institut für Organische Chemie, Kleiner Hörsaal

18. Mai 2000 — Prof. *D.A. Evans*
Harvard University, Cambridge, USA
'The Development of Chiral Metal Complexes for Asymmetric Synthesis'

Institut für Physikalische Chemie der Universität Basel

Mittwoch, 16.30 Uhr
Kleiner Hörsaal (2. Stock)
Klingelbergstrasse 80

10. Mai 2000 — Prof. *P. Ehrenfreund*
Leiden Observatory, University of Leiden, NL
'Ices and Organics in Space: A Voyage from Dark Clouds to the Early Earth'

17. Mai 2000 — Prof. *I.W.M. Smith*
Department of Chemistry, University of Birmingham, UK
'Molecules in Space – The Chemical Laboratory at the End of the Universe'

24. Mai 2000 — Prof. *L.M. Tolbert*
Georgia Institute of Technology, USA
Title will be announced later

Berner Chemische Gesellschaft

jeweils Mittwoch, 16.30 Uhr
Hörsaal EG 16
Departement für Chemie und Biochemie
Freiestrasse 3, Bern
(Kaffee um 16.10 Uhr vor dem Hörsaal)

17. Mai 2000 — Prof. *Walter Keller*
Abteilung Zellbiologie, Biozentrum, Universität Basel
'3'-end Processing/Polyadenylation of mRNA Precursors (pre-mRNAs) and Editing of pre-mRNAs and Transfer RNAs'

Freiburger Chemische Gesellschaft (FCG)

Dienstag, 17.15 Uhr
Grosser Hörsaal der Chemie-Institute der Universität (Pérolles)

9. Mai 2000 — Prof. *L.M. Tolbert*
School of Chemistry and Biochemistry, Georgia Institute of Technology, Atlanta
'Is There Such a Thing as a Molecular Wire?'

23. Mai 2000 — Prof. *F. Vögtle*
Kekule-Institut für Organische Chemie und Biochemie, Universität Bonn
'Catenane, Rotaxane, Brezelane – Templatsynthesen und topologische Chiralität'

Département de Chimie Organique, Université de Genève

Auditoire A-100, Sciences II,
30, quai Ernest Ansermet, Genève

Jeudi
11 mai 2000
16h30 — Prof. *N.A. Porter*
Dept. of Chemistry, Vanderbilt University, Tennessee, USA
Titre à communiquer

Vendredi
12 mai 2000
16h30 — Prof. *E. Nakamura*
Dept. of Chemistry, The University of Tokyo, Japan
'New Possibilities in the Carbometalation of Olefins'

Vendredi
19 mai 2000
16h30 — Prof. *E. Vedejs*
Dept. of Chemistry, University of Michigan, USA
'Phosphorus-based Chiral Acylating Agents'

Société Chimique de Genève

Lundi, 17.30 h
Amphitéatre A 150, UNI Sciences II
30, Quai E. Ansermet

8 mai 2000 — Prof. *J. Hulliger*
Departement für Chemie und Biochemie, Universität Bern
'Supramolecular Chemistry in the Solid State'
prov. Titel

Institut de Chimie, Université de Neuchâtel

Avenue de Bellevaux 51, Neuchâtel

Mardi
9 mai 2000
16h30
Salle B24 — Prof. *E. Nakamura*
Université de Tokyo (Japon)
'Interface of Chemistry and Biology through the Exploration of New Functional Molecules'

Mercredi
17 mai 2000
10h30
Petit Auditoire — Prof. *H. Berke*
Université de Zurich
'Hydridicity of Transition Metal Hydrides and its Implications for Reactivity'

Jeudi
18 mai 2000
16h30
Salle E 14 — Prof. *E. Vedejs*
University of Michigan (Ann Arbor USA)
'Kinetic Resolution Using Phosphorus Catalysts'

Mercredi
24 mai 2000
10h30
Petit Auditoire — Prof. *R. Winpenny*
Université d'Edimbourg (UK)
'High Nuclearity Cages: Molecule Magnets and Models for Metal Surfaces'

Mercredi
31 mai 2000
10h30
Petit Auditoire — Prof. *W.K. Jozwiak*
Université Technique de Lodz (Pologne)
'The Behavior of Ru/Fe_2O_3 Catalysts and Fe_2O_3 Supports in Temperature Programmed Reduction and Temperature Programmed Oxidation Conditions'

Organisch-chemisches Institut der Universität Zürich

Dienstag, 17.15 Uhr
Hörsaal 91
Winterthurerstrasse 190
Zürich-Irchel

2. Mai 2000 — Prof. Dr. *Jean-Luc Reymond*
Department für Chemie und Biochemie der Universität Bern
'Design and Screening for Catalytic Antibodies'

9. Mai 2000 — Prof. Dr. *Alois Fürstner*
MPI für Kohlenforschung, Mülheim/Ruhr
'Neue Beiträge zur Methathese von Alkenen und Alkinen'

16. Mai 2000 — Prof. Dr. *Werner Hug*
Institut de chimie physique, Université de Fribourg
'Raman Optische Aktivität'

23. Mai 2000 — Prof. Dr. *Stefan Seeger*
Physikalisch-chemisches Institut, Universität Zürich
'Biochemische Analytik im Laserfokus: Einzelmolekküldetektion und molekulare Kraftsensorik an ultradünnen Grenzschichten'

30. Mai 2000 — Prof. Dr. *Carlo Floriani*
Institut de Chimie Minérale et Analytique, Université de Lausanne
'Stepwise Reduction of Dinitrogen to Nitride: a Perspective View of an Artificial Nitrogenase'

Chemische Gesellschaft Zürich

Mittwoch, 17.15 Uhr
Hörsaal 19
Universität Zürich-Irchel
Winterthurerstrasse 190
Auskünfte: Prof. J.A. Robinson
Tel.: 01 635 42 42; robinson@oci.unizh.ch

17. Mai 2000 — Prof. Dr. *M. Mutter*
Institut de Chimie Organique (ICO), Université de Lausanne, Lausanne-Dorigny
'Peptide Engineering und Protein Design: Kann man Peptide und Proteine neu erfinden?'

Laboratorium für Organische Chemie der ETH-Zürich

Montag, 16.30 Uhr
Hörsaal CHN A 31
Universitätsstrasse 16, 8092 Zürich

15. Mai 2000 — Prof. *V.J. Hruby*
The University of Arizona, USA
'Topographical Considerations in the Design and Synthesis of Ligands for Biological Information Transduction: Chemistry and the Mind-Body Problem'

22. Mai 2000 — Dr. *A. Studer*
ETH Zürich
'Anwendungen von Silizium in stereoselektiven Radikalreaktionen und neue Konzepte zur zinnfreien Radikalchemie'

29. Mai 2000 — Prof. *D.A. Cane*
Brown University, USA
'Polyketide Synthases: Specificity and Tolerance in Erythromycin Biosynthesis'

Laboratorium für Technische Chemie der ETH Zürich

Sicherheit und Umweltschutz in der Chemie

Montag, 10.15 Uhr
Seminarraum CAB D43
Universitätstrasse 6, 8092 Zürich

8. Mai 2000 — Dr. *Kai-Uwe Goss*
EAWAG
'Lineare Freie Energie-Beziehungen zur Vorhersage des Verteilungsverhaltens organischer Chemikalien'

15. Mai 2000 — *Almut Beck*
Gruppe Sicherheit und Umweltschutz in der Chemie, Laboratorium für Technische Chemie, ETH Zürich
'Möglichkeiten und Grenzen der Ökobilanz bei chemikalienintensiven Prozessen: das Beispiel Textilveredelung'

22. Mai 2000 — Dr. *Claus Rau*
Schering AG, Berlin
'Verfolgung von Sicherheits- und Umweltschutzzielen in der Verfahrensentwicklung bei Schering'

29. Mai 2000 — Dr. *Herbert Hugel*
Zentrale Forschung, Bayer AG, Leverkusen
'Neue Wege zu Basischemikalien'

Der Termin und das Programm der Präsentation der Diplomarbeiten wird zu einem späteren Zeitpunkt auf unserer Web-page unter *http://ltcmail.ethz.ch/hungerb/news.html* bekanntgegeben.

Biochemische Institute beider Zürcher Hochschulen

Donnerstag, 17.00 Uhr
UNI: Winterthurerstrasse 190, Zürich-Irchel, Hörsaal G-85
ETH: Universitätstrasse 16, ETH Zentrum, Seminarraum N 23

4. Mai 2000 — Prof. *M. Aebi*
UNI BC — Mikrobiologisches Institut, ETH Zürich
'Where Carbohydrates, Lipids, and Proteins Meet: N-Linked Protein Glycosylation in the Endoplasmic Reticulum'

11. Mai 2000 — Dr. *G. Schiavo*
ETH BC — Molecular Neuropathobiology Lab. ICRF, London, GB
Titel folgt

18. Mai 2000 — Prof. *C. Bron*
UNI BC — Institut de Biochimie, Université de Lausanne
'Role of Lipid Rafts in GPI-Anchored and Transmembrane Receptor-Mediated Signaling in Lymphocytes'

25. Mai 2000 — Prof. *A. Aguzzi*
UNI Vet.-B — Departement Pathologie, Universität Zürich
'Pathogenesis of Prion Diseases'

Anorganisch-chemisches Institut der Universität Zürich

Seminarraum 34 F 48, UZI
Winterthurerstrasse 190, Zürich-Irchel

5. Mai 2000, Freitag, 17.00 Uhr — Prof. Dr. *Paul Knochel*
Ludwig-Maximilians-Universität, München
'Diastereoselctive C–H Activations; a New Tool for the Performance of Chemo-, Regio-, and Stereo-Selective Reactions'

8. Mai 2000, Montag, 15.00 Uhr — Prof. Dr. *Robert Bergman*
University of California, USA
'Metal and Ligand Activation of Carbon–Hydrogen Bonds in Organic Molecules'

22. Mai 2000, Montag, 15.00 Uhr — Prof. Dr. *Gerhard Erker*
Westfälische Wilhelms-Universität Münster
'Neues aus der Metallocen-Chemie'

26. Mai 2000, Freitag, 17.00 Uhr — Prof. Dr. *Michael Knorr*
Université de Franche-Comté, Faculté des Sciences et des Techniques, Besançon, France
'Alkyne Insertions into the Platinum–Hydride Bond of Heterodinuclear Iron-Platinum Complexes – New Pathways to Heterobimetallic μ-Vinylidene, μ-Isonitrile-, and μ-Carbyne Complexes'

Laboratorium für Physikalische Chemie der ETH Zürich

Dienstag, 17.15 Uhr
Hörsaal CHN E7
Universitätstrasse 22, Zürich

2. Mai 2000 — Prof. *K. Bergmann*
Fachbereich Physik, Universität Kaiserslautern
'Manipulation von Quantenzuständen in Atomen und Molekülen'

9. Mai 2000 — Prof. *H. Grützmacher*
Laboratorium für Anorganische Chemie, ETH Zürich
'Spezielle Phosphane, spezielle Effekte'

16. Mai 2000 — Prof. *I.W.M. Smith*
The School of Chemistry, The University of Birmingham, UK
'Gas-Phase Molecular Processes at Very Low Temperatures: The Interstellar Connection'

23. Mai 2000 — *J.-M. Segura*
Laboratorium für Physikalische Chemie, ETH Zürich
'Scanning Confocal Optical Microscopy of Single Molecules'

30. Mai 2000 — Dr. *K.P. Huber*
National Research Council of Canada, Ottawa, Ontario
'The Application of a Synchroton Radiation Source to High-Res'

Physikalisch-chemisches Institut der Universität Zürich

Donnerstag, 10.15 Uhr
Seminarraum 34-K-01
Winterthurerstrasse 190, 8057 Zürich

4. Mai 2000 Prof. Dr. *M. Aeschlimann*
Laser- und Plasmaphysik, Universität Essen
Thema wird später bekannt gegeben werden

11. Mai 2000 Prof. Dr. *S. Seeger*
Physikalisch-chemisches Institut, Universität Zürich
'Lasergestützte biochemische Analytik an Grenzflächen'

18. Mai 2000 Prof. Dr. *H. Paul*
Physikalisch-chemisches Institut, Universität Zürich
'Elektronenpolarisationen bei spinselektiven Reaktionen paramagnetischer Transienten'

News

Lonza Group Fine Chemicals and Specialties Invests in Custom Manufacturing Business

Basel, March 23, 2000. Lonza Group's Fine Chemicals and Specialties Division invested about CHF 100 million in its custom manufacturing business in 1999.

One half of the total sum was spent for new product introduction, new technology and additional capacity. The other half was in facility upgrades and infrastructure for safety, health and environment (SHE) improvements.

Rebuilding and adaptation of Lonza's Los Angeles plant was one of the major projects that were completed in 1999. The plant is now part of Lonza's global multipurpose, cGMP manufacturing base and is especially well suited for the production of high-volume and liquid fine chemicals.

The start of production trains 11&12 in the Riverside plant (Conshohocken, PA) in November and December 1999 expanded multipurpose capacity by 45 m^3 reactor volume at this site. The investment also included substantial upgrades in several other plant capabilities like development and quality laboratories.

A phosgenation plant working under cGMP was constructed at Lonza's Visp site (Switzerland) and came on stream at the beginning of the year. In the pilot hall, a new Low Temperature reactor (down to –80 °C) was installed to produce a key step of a new pharmaceutical product.

Several improvement measures in the area of SHE were implemented in 1999. These include the installation of two blow-down systems at Riverside and the adaptation of the waste gas disposal system of the Fine Chemicals Complex (FCC) in Visp. This assures that all production units in the FCC are directly connected to the central gas/liquid waste incinerator.

This investment program reinforces Lonza's long-term commitment to the custom synthesis business. The geographical split of capital expenditure – 75% in the USA and 25% in Europe – underpins the importance of being close to customers in the major pharmaceutical market.

CHIMIA-REPORT

Bitte an die Inserenten

Richten Sie Ihre Beiträge für die Rubrik CHIMIA-REPORT nicht an die Redaktion, sondern ausschliesslich an: Kretz AG, Postfach, CH-8706 Feldmeilen Besten Dank!

Bund zeichnet Spin-off Start-up-Unternehmen aus

Das Bundesamt für Berufsbildung und Technologie (BBT) verleiht vier Jungunternehmen das 'KTI Start-up-Label'. Das Zertifikat zeichnet die Unternehmen als 'risikokapitalwürdig' aus und öffnet ihnen Türen zu Kapital und Coaching.

Viermal jährlich wird das Zertifikat an mehrere innovative Jungunternehmerinnen und Jungunternehmer im High-Tech-Bereich verliehen. Die Initiative KTI Start-up wurde 1996 im Rahmen der Aktivitäten der Kommission für Technologie und Innovation (KTI) lanciert. Bisher wurden 31 Labels vergeben. Die dabei ausgezeichneten Jungunternehmen haben inzwischen 250 Arbeitsplätze geschaffen und CHF 30 Mio. Umsatz getätigt. Die Hälfte der Unternehmensgründungen erfolgte vor weniger als zwei Jahren.

Synergieeffekt aus der Kooperation zwischen Hochschulen und Bund

An der ersten Label-Vergabe dieses Jahres am 20. März wurden folgende vier Jungunternehmen ausgezeichnet:

- ESBATech AG, Zürich, Biotechnologie: eine Spin-off-Firma der Universität Zürich; Kontakt: Dr. Dominik Escher, Tel. 01/635 31 59
- TransSense GmbH, Lausanne, Biotechnologie: die Forschung wurde an der ETH Lausanne betrieben; Kontakt: Jean-Pierre Rosat, Tel. 079/220 01 94
- VHF-Technologies SA, Neuchâtel, Solarzellenfolien: ein Spin-off des Institut de Microtechnique der Universität Neuenburg; Kontakt: Dr. Diego Fischer, Tel. 032/718 33 40
- Swiss Luggage SL AG, Bern, High-Tech-Reisegepäck: eine Kooperation mit dem Institut für Konstruktion und Bauwesen der ETH Zürich sowie der Fachhochschule Burgdorf: Kontakt: Ruedi Gygax, Tel. 031/323 37 11

Die Palette der Produkte und Dienstleistungen bisheriger mit dem KTI Start-up-Label zertifizierter Firmen ist vielfältig und reicht von intelligenten optischen Sensoren für Sicherheitstechnik und Robotik über Software zum elektronischen Copyright-Schutz von Dokumenten bis zum Elektrofahrrad 'Flyer Powerbike'.

Bereits zertifizierte Jungunternehmen entwickeln sich durchwegs gut. Zum Beispiel die Firma InMotion mit Sitz in Fribourg; erst 1999 gegründet, zählt das Unternehmen bereits rund 30 Mitarbeiterinnen und Mitarbeiter.

Der Bund als Förderer junger Unternehmen

In der Schweiz existieren rund 200 Initiativen, die für Neuunternehmen oder frisch Selbstständigerwerbende Kapital bereitstellen und weitere Unterstützung anbieten. Eine der Stärken der Initiative KTI Start-up ist, dass sie mit Hochschulen und der Privatindustrie kooperieren. Sie ist das Resultat einer exakten Analyse dessen, was in Sachen Jungunternehmen förderungswürdig ist und dessen, was unter schweizerischen Bedingungen sinnvoll und realisierbar ist.

Als Erfolgsparameter für die Initiative gilt allein der Massstab, wieviele Arbeitsplätze in Zukunftstechnologien durch Jungunternehmen geschaffen werden, die mit dem KTI-Start-up-Label ausgezeichnet wurden. Traditionellerweise entstehen Unternehmen aus der Praxis heraus. Moderne Technologien entstehen vor allem auch an der Schnittstelle Hochschule-Privatindustrie. Da setzt der Netzwerk-Gedanke der Initiative KTI Start-up ein: In der heiklen Phase einer Unternehmensgründung, der sogenannten Seedphase, wo die Projektidee an der Schwelle zum Markt steht. Weitere Informationen zur Initiative KTI Start-up, Labelträgern und Industriellen-Begleitgremium sind unter www.ktistart-up.ch erhältlich.

Hochkarätiges Industriellen-Begleitgremium

Das KTI Start-up-Label wird von einem hochkarätigen, 9-köpfigen Industriellen-Begleitgremium unter dem Präsidium von Dr. François L'Eplattenier, Präsident des Novartis Venture Fund und Präsident der Kommission des Vororts für Wissenschaft und Forschung vergeben. Weitere Mitglieder sind u.a. Prof. Fritz Fahrni, Universität St. Gallen (Institut für Technologie-Management), Prof. Jane Royston, Lehrstuhl 'entrepreneurship et innovation' an der ETH Lausanne.

Dr. Bruno H. Dalle Carbonare, Mitglied des Triage Teams, gratuliert Adrian Escher der ESBATech AG, ein Biotechnologie Spin-off der Universität Zürich.

(v.l.n.r.) Dr. Pedro Torres, Alexandre Closset und Dr. Diego Fischer. VHF-Technologies SA ist ein Spin-off Unternehmen der Universität Neuenburg (Institut Microtechnologie).

Gütesiegel öffnet Türen

Das KTI Start-up-Label ist in der Jungunternehmer-Szene bekannt und geniesst zusehends an Ansehen. Dies erstaunt nicht – denn für die Jungunternehmerinnen und Jungunternehmer von morgen bedeutet das Label einen Türöffner zu Risikokapital und Coaching. Damit wird die Zeit von der Produktidee bis zur Markteinführung erheblich verkürzt. Dies bedeutet nicht nur für die neuen Unternehmen einen Wettbewerbsvorteil, sondern auch für die Schweizer Volkswirtschaft.

Die Auszeichnung wird exklusiv durch das Bundesamt für Berufsbildung und Technologie vergeben. Ausgezeichnet werden Start-up-Projekte im High-Tech-Bereich. Damit gewinnen Jungunternehmerinnen und Jungunternehmer an Anerkennung und Bekanntheit.

Das Label hat sich in der Venture-Capital-Szene in kurzer Zeit als Gütesiegel etabliert: Viele Institute betrachten das Zertifikat als Ersatz für eigene, aufwendige Abklärungen in Bezug auf die Venture-Capital-Tauglichkeit. Hans Sieber, Direktor des BBT: 'Mittelfristig wollen wir jährlich 20 Labels an Jungunternehmen im High-Tech-Bereich vergeben. Das Label ist zu einem wahren Türöffner für Risikokapitalfinanzierung und Coaching avanciert.'

Die KTI unterstützt Verbundprojekte, in welchen Forschungsstätten und Industrie gemeinsam an innovativen Vorhaben im High-Tech-Bereich zusammenarbeiten. Nach Erhalt des Zertifikats stehen den neuen Unternehmen ein Netzwerk erfahrener Persönlichkeiten aus der Wirtschaft und so genannte 'Business Angels' beratend zur Verfügung. Um den Wert und das Niveau des KTI Start-up-Labels auszudrücken, sind Bedingungen daran geknüpft: Die Produktidee muss neu und einzigartig sein und über realistische Marktchancen verfügen sowie ein überdurchschnittliches Wachstumspotential aufweisen. Die Jungunternehmerinnen und Jungunternehmer müssen über Kompetenzen in Marketing und Leadership verfügen.

Informationen/Ansprechpartner

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Leserdienst Nr. 2

Standort mit Potential – Biotechnologiepark Luckenwalde auf der BIO 2000 in Boston

Bereits zum vierten Mal präsentiert sich der Biotechnologiepark Luckenwalde (BTPL) auf der weltweit wichtigsten Biotechnologie-Branchenmesse in den USA. Wie in den Vorjahren wird sich der BTPL im Rahmen der deutschen Ausstellergemeinschaft mit einem eigenen Stand ('Biotechnologiepark Lukkenwalde' – Stand 227) präsentieren. 'Unser Ziel ist es, das Konzept und Angebot des BTPL auf internationaler Ebene weiter bekannt zu machen', so Christoph Weber, Geschäftsführer des BTPL. 'Selbstverständlich möchten wir auch möglichst viele potentielle Ansiedelungsinteressenten gewinnen und die in den Vorjahren geknüpften Kontakte erneuern und pflegen.' Die in diesem Jahr in Boston stattfindende BIO ist eine einmalige Plattform die über aktuelle Trends und Entwicklungen informiert sowie einen unmittelbaren Vergleich eigener Projekte mit dem internationalen Angebot ermöglicht.

Wichtiges Standbein der Biotech-Region Berlin-Brandenburg

Der 50 Kilometer südlich von Berlin gelegene Biotechnologiepark Luckenwalde ist eine der modernsten Anlagen seiner Art in Deutschland und ein wichtiges Standbein der Biotech-Region Berlin-Brandenburg. So sind allein knapp 20 Prozent der Biotechnologiefirmen der Region hier beheimatet. Der 28 Hektar grosse Park besitzt durch die räumliche Nähe von Arbeiten, Forschen und Wohnen einen campusartigen Charakter.

Die angesiedelten Firmen können von einem professionellen Umfeld mit günstigen Rahmenbedingungen und Konditionen profitieren. So sind rund **50 Prozent der Mieter Start-up-Unternehmen.**

Der überwiegende Teil der inzwischen 38 Mieter im BTPL – Biotechnologiefirmen, Forschungsinstitute, Zulieferer und Dienstleister – ist im Bereich lifescience tätig.

Eldorado für Unternehmensansiedlungen

Der BTPL bietet speziell für die Ansiedlung von ausländischen Unternehmen – vorzugsweise der Biotechnologie – umfassende, individuelle Dienstleistungen und Beratungen. So bestehen neben der optimalen Hauptstadtlage ausserordentlich günstige Konditionen und Förderungen für die Ansiedlung von Firmen. Gemeinsam werden individuelle Problemlösungen für die Gründung und Entwicklung von Unternehmen erarbeitet. Das Management des BTPL berät ebenso in den Bereichen Business Planung, Finanzierung/Fördermittelbeschaffung, Personalmanagement sowie Patente und Lizenzen.

Umfangreiches Angebot

Kernstück des BTPL ist das Branchenorientierte Technologie- und Gründerzentrum (TGZ). Es umfasst zwei Gebäudekomplexe, von denen sich der zweite – das TGZ II – derzeit im Bau befindet. Die Eröffnung des TGZ II ist für Mai dieses Jahres vorgesehen.

Im Zentrum des 'Biotech-Campus' steht allen Mietern und Gästen ein nach modernsten Gesichtspunkten ausgestattetes Kongresszentrum mit Konferenzräumen, Restaurant und Bibliothek zur Verfügung. Hier finden regelmässig wissenschaftliche Symposien und Branchen-Kolloquien statt.

Neben den Mietwohnungen im Norden des BTPL-Geländes gibt es in idyllischer Lage nahe einem See eine kleine Eigenheimsiedlung mit insgesamt 40 Einfamilienhäusern.

Selbstverständlich verfügt der Campus über ein leistungsfähiges Kommunikationssystem, das eine effektive Anbindung an nationale und internationale Datennetze gewährleistet.

Ideale Bedingungen im TGZ

Die im Technologie- und Gründerzentrum (TGZ) anmietbaren Laborräume verfügen über eine komplette Ausstattung für biotechnische Arbeiten auf höchstem technischen Standard. Bezugsfertig ausgerüstet mit Labortischen und Schränken, Sicherheitswerkbank, Abzug, Autoklav, Reinigungsautomat, Gefahrstoffschrank und Reinstwasseranlage eignen sie sich für gentechnische Arbeiten nach Sicherheitsstufe 2. Alle Laborräume verfügen über eine zentrale Medienversorgung, über die nach Bedarf die technischen Gase O_2, CO_2 und N_2 sowie Erdgas, Druckluft, vollentsalztes Wasser, Warm- und Kaltwasser bezogen werden kann. Weiterhin stehen ein Chemiekalienlager, ein +4°C-Kühlraum, ein –80°C-Tiefkühlschrank und diverse Laborgeräte zentral zur Verfügung.

Ein GMP-Technikum ist in Planung. Aufgrund starker Nachfrage ist auch eine Erweiterung des TGZ II in Vorbereitung.

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Leserdienst Nr. 3

Sensor und Elektronik – alles auf einem Chip

Die rasch wachsende, 1998 als Start-up-Unternehmen gegründete Sensirion AG mit Sitz in Zürich, Schweiz, steht vor der Auslieferung ihrer revolutionären neuen Produkte zur Messung von Strömungen, Druckunterschieden, Temperatur und Feuchtigkeit von Luft und Gasen. Sensirion AG entwickelt und vermarktet innovative Sensor-Lösungen auf CMOS-Basis – der Standard Fertigungs-Technologie für integrierte Schaltung – und entsprechender Nachbearbeitung wie zum Beispiel Mikrobearbeitung. Ihr Know-How und ihre Kompetenz verdankt sie den über 200 Mannjahren an Forschung und ihren talentierten und in Entwicklung und Umsetzung von Chip- und Elektro-Design, Software und Sensorverpackung erfahrenen Mitarbeitern.

Zielmärkte für diese einmaligen Sensorensysteme sind OEM-Kunden verschiedenster Industrien. Kostenempfindliche, klein- und grossvolumige Applikationen der Klimaüberwachung, Prozessautomation, medizinischer Testgeräte und Kabinenluftsteuerungen von Automobilen sind nur einige Beispiele der vielseitigen Einsatzmöglichkeiten dieser Systeme. Die einfache Integration eröffnet Systemherstellern vorher nicht auszudenkende neue Applikationsmöglichkeiten und erlaubt schnellerer Produkteeinführungszeiten.

Die Kombination von Sensor und Elektronik auf einem einzelnen Chip führt zu äusserst genauen und kompakten Systemlösungen. Die Temperaturmessung kommt als Standard mit jedem Sensor – exklusiv bei Sensirion Feuchtigkeitssensoren – und je nach Anwendung, mit integrierter Temperaturkompensation. Die Sensoren sind vorkalibriert und verfügen über normierte digitale Ausgangssignale (RS232 oder SPI). Sowohl vom Massenfluss-Sensor ASP1400, welcher fünf Dekaden von Luftströmungen mit einer Maximalauflösung von 3 mm^3 pro Minute umspannt, als auch vom Feuchtigkeits- und Temperatur-Sensor AH31 mit seinem niedrigen Stromverbrauch (<5 mW) und schneller Antwortzeit (5 bis 10 Sek.), können ab sofort Muster angefordert werden. Zudem werden ab April 2000 Demokits mit betriebsbereiter PC-Software und Anschlusskabel verfügbar sein. Um der per Mitte Jahr erwarteten grossen Nachfrage gerecht zu werden, hat Sensirion AG für die Herstellung und Montage der Sensoren strategische Allianzen mit Partnerunternehmen gebildet. Kalibrierung und abschliessende Tests werden jedoch intern nach etablierten Qualitätsstandards durchgeführt.

Obwohl die Firma sich zur Zeit auf die oben erwähnten Produkte konzentriert, ist sie davon überzeugt, dass sich durch ihr angesammeltes Wissen und die entsprechende Gesamtkompetenz neue Tätigkeitsfelder eröffnen werden. Neue Produkte wie auch Lösungen für ganze Sensorsysteme werden schon jetzt diskutiert, die sicher auch Ihre Produkte revolutionieren könnten. Ihr Input kann die Zukunft prägen.

Für zusätzliche Infos über Sensirion AG und ihre Produkte oder für Muster- und Demokits-Bestellungen, wählen sie *www.sensirion.com* oder nehmen Sie mit Sensirion AG direkt unter *info@sensirion.com* Kontakt auf.

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Leserdienst Nr. 4

Erprobtes Praxis Know-how

Wer sein eigenes Unternehmen starten oder eine bestehende Firma systematisch weiterentwickeln und ausbauen will, braucht ein praxiserprobtes und umsetzungsorientiertes betriebswirtschaftliches Know-how. In den IFJ-Workshops steht die kritische Überprüfung der Geschäftsidee, die individuelle Erarbeitung eines massgeschneiderten Businessplans und die schrittweise Realisierung der Teilnehmerprojekte im Vordergrund. Das IFJ-Kursangebot besteht aus Startimpuls, Praxisinteniv-Workshop und Praxis-Intentensiv-Coaching.

Einzigartig am Kursangebot des IFJ ist, dass die Teilnehmerinnen und Teilnehmer nur an ihren eigenen Projekten arbeiten. Die kritische Hinterfragung und die vielen Inputs der Trainer führen zu schnellen und substantiellen Projektfortschritten. Und die enge und persönliche Begleitung durch die erfahrenen IFJ-Spezialisten ermöglicht eine entscheidende Verminderung des Risikos. So zeigt eine Studie an der Fachhochschule für Wirtschaft St. Gallen, dass 96% der IFJ-Absolventen den Schritt in die Selbständigkeit wieder wagen würden.

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  Internet http://www.ifj.ch

Leserdienst Nr. 5

Neue Spezialisierung Prozessinformatik an der Hochschule Wädenswil

Die Industrie braucht zunehmend Informatikingenieure und -ingenieurinnen in den verschiedensten Unternehmensbereichen. Die Hochschule Wädenswil bietet als erste Hochschule ab Herbst 2000 eine neue Spezialisierung Prozessinformatik an.

Die Prozessinformatik ist eine Spezialisierung, welche die Fachhochschul-Absolventen und -Absolventinnen befähigt als Informatiker/innen mit der erweiterten Ausbildung unmittelbar in den spezifischen, unterstützenden Prozessen der Produktion und Forschung eines Unternehmens tätig zu sein. Die Spezialisierung knüpft an die bestehenden Diplomstudien Biotechnologie und Lebensmitteltechnologie an, setzt aber andere Schwerpunkte im Bereich Informatik, Logistik und Prozessleittechnik.

Die Informatik hat in den letzten Jahren Entwicklungen durchgemacht, die ein hohes Mass an Spezialwissen und gleichzeitig vertiefte Kenntnisse über die Prozesse erfordern. Neue Diplomstudien, welche die technologischen Grundlagen und eine Vertiefung in computertechnischen Fächern anbieten, können die entstandene Lücke schliessen.

Die Informatikspezialisten und -spezialistinnen lösen die komplexen Probleme in den einzelnen Arbeitsfeldern einer Unternehmung. Die Prozessinformatiker/innen sind spezialisiert für Informatikprobleme im Produktionsbereich, ähnlich wie die Wirtschaftsinformatiker/innen auf der Unternehmensleitebene und im Dienstleistungsbereich.

Die zukünftigen Arbeitsplätze der Prozessinformatiker/innen sind in den Branchen Biotechnologie, Lebensmittelindustrie sowie in der chemischen und pharmazeutischen Industrie zu finden. Als Berufsfelder kommen alle Gebiete der Prozesstechnologie mit Bezug zur Informatik in Frage.

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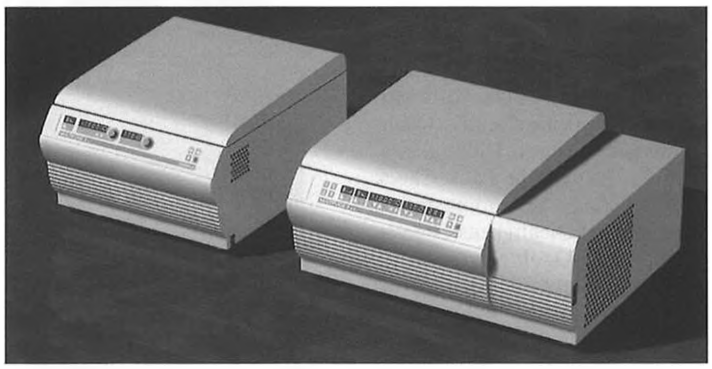
Leserdienst Nr. 6

Neue Zentrifugen-Generation für höchsten Probendurchsatz



Kendro Laboratory Products schickt jetzt eine neue Zentrifugen-Generation an den Start. Ausgerüstet mit einer Vielzahl an Rotoren und Adaptern, sind die leistungsstarken Heraeus Multifugen für den universellen Einsatz konzipiert. Dabei ist die Gefässkapazität besonders hoch, so dass pro Lauf der höchste Probendurchsatz in dieser Gerätegrösse erreicht wird.

Die neue Heraeus Multifugen Reihe erfüllt konsequent die steigenden Anforderungen nach höherem Probendurchsatz in der Biotechnologie, der biologischen Forschung und in der klinischen Routine. Der Ausschwingrotor und der neuartige Windkesselrotor bieten höchste Gefässkapazität bei einem maximalen RZB von 7000 x g. Diese Voraussetzungen ermöglichen einen bis zu viermal höheren Probendurchsatz im Vergleich zu herkömmlichen Zentrifugen dieser Geräteklasse. Ein Gesamtprobenvolumen von 4 x 750 ml oder 4 x 1000 ml kann in nur einem Lauf zentrifugiert werden.

Bei der Entwicklung der Multifugen wurde besonderer Wert auf die optimierte Lösung für die Zentrifugation von Mikrotestplatten gelegt. Der neue Trägereinsatz für einfaches Be- und Entladen bietet eine maximale Kapazität von 16 oder 28 Platten pro Lauf.

Der einzigartige Highplate Rotor ermöglicht die biologisch sichere Zentrifugation von allen gängigen Plattensystemen. Der maximale RZB liegt bei 6000 x g. Dieser Rotortyp kann mit Mikrotest-, Deepwell- oder DNA/RNA-Filterplatten mit einer Beladungshöhe von bis zu acht Zentimetern bestückt werden.

Mit der modularen Gerätebauweise bleiben keine Wünsche offen. Die Multifugen sind als gekühlte und ungekühlte Varianten erhältlich sowie als Tisch-, Stand- und Untertischgeräte. Ein weiteres Plus: Der Anwender hat die Wahl zwischen Geräten mit schneller Drehknopfbedienung oder komfortabler Tastatureingabe.

Heraeus, Multifuge:
eingetragene Warenzeichen

- Kendro Laboratory
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  CH–8054 Zürich
  Telefon 01 454 12 12
  Telefax 01 454 12 99

Leserdienst Nr. 7

Agilent Technologies Combizorb Scavengers zur Reinigung von Reaktionsansätzen chemischer Verbindungen

Agilent Technologies Europe, ein Tochterunternehmen von Hewlett-Packard, gibt die Einführung der Agilent CombiZorb Scavengers bekannt, einer Produktlinie von Adsorbenzien, die auf Kieselgel und makroporösem Polystyrol/Divenylbenzol (PS/DVB) basieren und unerwünschte Reaktionspartner und Nebenprodukte chemischer Reaktionen entfernen.

CombiZorb S (Kieselgel- bzw. Silikatbasis) Scavengers bestehen aus hochreinen (99,995%), porösen, sphärischen Kieselgel-Mikropartikeln mit niedrigem Metallgehalt, die den Anteil kontaminierender Substanzen und Nebenreaktanten vermindern. Diese auf Kieselgel basierenden Scavengers quellen nicht auf und können deshalb in Kartuschen sowie in 96-Well-Plates eingesetzt werden. Sie sind einfach zu handhaben und können sowohl mit polaren (z.B. Methanol) als auch mit unpolaren Lösungsmitteln eingesetzt werden, ohne die Lösungsmittel zwischen Reaktions- und Adsorptionsschritten wechseln zu müssen.

CombiZorb MP (**m**akroporöse)-Scavengers quellen deutlich weniger (+50%) als die Standard-Adsoberharze vom PS/DVB-Geltyp (+500%), weisen eine höhere und gleichmässigere Volumen-Kapazität auf und benötigen kein Vorquellen. Wie auch die auf Kieselgelbasierenden Scavengermaterialien weisen die hochreinen CombiZorb MP-Scavenger eine breite Lösungsmittel-Kompatibilität auf und können ohne Wechsel des Lösungsmittels zwischen Reaktions- und Adsorptionsschritten mit polaren wie unpolaren Lösungsmitteln eingesetzt werden.

Zur Produktlinie der auf Kieselgel basierenden CombiZorb S-Scavengern gehören Kieselgele mit folgenden funktionellen Gruppen: Triamine, Monoamine, Sulfonsäure und tertiäre Amine. Zu den makroporösen Scavengern auf PS/DVB-Basis zählen Harze mit Aldehyd- und Isocyanat-Gruppen. Jedes Adsorberharz ist in Bulkgrössen von 10g und 100g erhältlich. Darüberhinaus ist eine Kombinationspackung aller verfügbarer CombiZorb S- und MPScavenger-Produkte abgepackt in Flaschen von jeweils 5g enthältlich.

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Leserdienst Nr. 8

Nextech Venture – a Venture Capital Partnership for Early Stage Companies

Nextech Venture, L.P. is a venture capital partnership with over CHF 70 million in assets investing in early stage high-technology companies. A. Scheidegger, G. Operto, F. Hofstetter and S. Ciccone bring many years of expertise in technology, management, marketing and finance in and connections with public and private research centers, private industry and high finance.

Nextech Venture seeks investments in talented, decisive and committed people with ideas and innovations, who want to initiate a business venture that provide high-technology based products and services for industries with high market growth. The technical focus is in the areas of biotechnology, new materials and energy systems, as well as information technology. Nextech Venture is primarily interested in companies based in Switzerland and neighboring regions.

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Leserdienst Nr. 9

Erweiterte Grundausstattung, gleicher Preis: Die legendäre Heraeus Baureihe 6000

Die Heraeus Standardgeräte der Baureihe 6000 von Kendro Laboratory Products haben ab sofort eine erweiterte Grundausstattung – und dies zum unverändert niedrigen Preis. Alle Trocken- und Wärmeschränke, Brutschränke und Heissluftsterilisatoren zeichnen sich durch ihre hohe Qualität und Zuverlässigkeit aus. Ein 24-Stunden-Timer und eine serielle Schnittstelle sorgen in Zukunft für noch mehr Anwenderfreundlichkeit.

Kendro Laboratory Products hat auf Grund jahrzehntelanger Erfahrung in Entwicklung und Produktion die Baureihe 6000 immer wieder neu dem Kundenbedarf angepasst und mit innovativem Zubehör aufgewertet. Ausgereifte Technik und solide Verarbeitung machen die Geräte robust und langlebig. Alle Modelle der Baureihe 6000 zeichnen sich durch ihr äusserst stabiles Temperaturverhalten aus und eignen sich somit für alle Anwendungen, die eine genaueste Temperaturkontrolle erfordern.

Jedes Labor findet innerhalb der Baureihe 6000 genau das Gerät, das zu seinem Anwendungsprofil passt.

Denn charakteristisch ist die Typenvielfalt. Hinzu kommt eine umfassende Palette an Optionen – und diese sind nahezu ausnahmslos jederzeit nachrüstbar. Auch kundenspezifische Sonderlösungen können realisiert werden.

Ob Trocken- und Wärmeschrank, Brutschrank oder Heissluftsterilisator: Kendro bietet zu allen Gerätevarianten auch eine Version mit Umluftzirkulation. Dabei haben alle Umluft-Geräte jetzt standardmässig einen Drehzahlsteller zur stufenlosen Regulierung des Lüfters bekommen. Das ermöglicht die Anpassung der Luftgeschwindigkeiten oder der Luftwechselraten an die individuellen Anforderungen des Anwenders.

Alle Geräte der Baureihe 6000 verfügen ab sofort über eine 24-Stunden-Zeitschaltuhr: So kann die Programmierung für jeden Prozess bequem festgelegt werden. Die Temperaturdaten können jetzt via neuer Schnittstelle an den PC übergeben werden. Mit dem Kendro-Dokumentationssystem Heranet (unter Windows) können Daten gespeichert und grafisch dargestellt werden. Damit unterstütz Kendro die Qualitätssicherung im Labor.

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Leserdienst Nr. 10

Strategische und Operative Unternehmensentwicklung

Am 7. September führt Birri MCG AG eine weitere Tagung für Verantwortliche und Interessierte von Managementsystemen durch. Zielsetzung des Anlasses: Den Teilnehmern Perspektiven für die weitere Entwicklung aufzeigen und Ergebnisse ableiten, die in den Unternehmen direkt umsetzbar sind. Mit Referaten wird eine Standortbestimmung vorgenommen, die den Teilnehmern als Ausgangslage für die Sichtbarmachung und Realisierung ihrer zukunftsbezogenen Bedürfnisse dient. Der Anlass wird durch Bruno Birri von Birri MCG betreut und moderiert.

Die Referenten und ihre Themen:

- Dr. Pierre Clausen: Strategische Positionierung in der gegenwärtigen Marktentwicklung
- Dr. Michael Loebbert: Die Persönlichkeit des Unternehmens als Erfolgsfaktor
- Christa M. Schweizer-Toggenburger: Veränderungsprozesse lösen emotionale Reaktionen aus

Die Veranstaltung ist der einzige öffentliche Anlass im Rahmen der Jahresaktivitäten der PRO-S-A-Managementsysteme und steht allen Interessierten offen. Für die teilnehmenden Unternehmen ist der 7. September eine einmalige Gelegenheit, sich mit Belangen des Qualitätsmanagements auseinanderzusetzen und den Nutzen auf einer 'höheren Ebene' zu suchen. Nicht der Nachweis von Normenkonformitäten entscheidet über das Weiterbestehen im Markt, sondern die Fähigkeit, künftige Ereignisse vorwegzunehmen und in der Gegenwart die richtigen Entscheide für die Zukunft zu treffen.

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Leserdienst Nr. 11

Seminar: 'Innovative Sicherheitstechnik' mit Gastreferat der SUVA zum Thema 'Zertifizierung in der Schweiz nach internationalen und europäischen Normen'

Sicherheitssteuerungen und sichere BUS-Systeme finden immer mehr Verwendung in den bis anhin durch konventionelle Technik oder aufwendige Sicherheitssysteme geprägten Anwendungsgebieten.

Nebst dem Bereich der Arbeitssicherheit in Industrieprozessen findet man diese Systeme heute auch bei Förderanlagen, Brennersteuerungen, Drahtseilbahnen, Bahneinrichtungen und dergleichen mehr. Anlässlich der beiden Abend-Seminare vom **11.05.00** an der Fachhochschule Aargau in Windisch und am **31.05.00** im Restoroute Motel de la Guyère (in Französisch) zeigt die Firma Pilz Industrieelektronik GmbH die Möglichkeiten solcher Steuerungssysteme an Hand der Produktefamilie PSS 3000 und des sicheren BUS Systemes SafetyBUS p auf. Ein Anwendungsbeispiel aus dem Bereich einer schweizer Zahnradbahn, vorgetragen durch einen Kunden, zeigt eine der vielseitigen Einsatzmöglichkeiten. Das Gastreferat der SUVA beleuchtet das internationale Normen- und Vorschriftswesen, welches die Grundvoraussetzungen für den Einsatz dieser Systeme darstellt.

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  Internet: www.pilz.com

Leserdienst Nr. 12

Dichtigkeitsprüfer

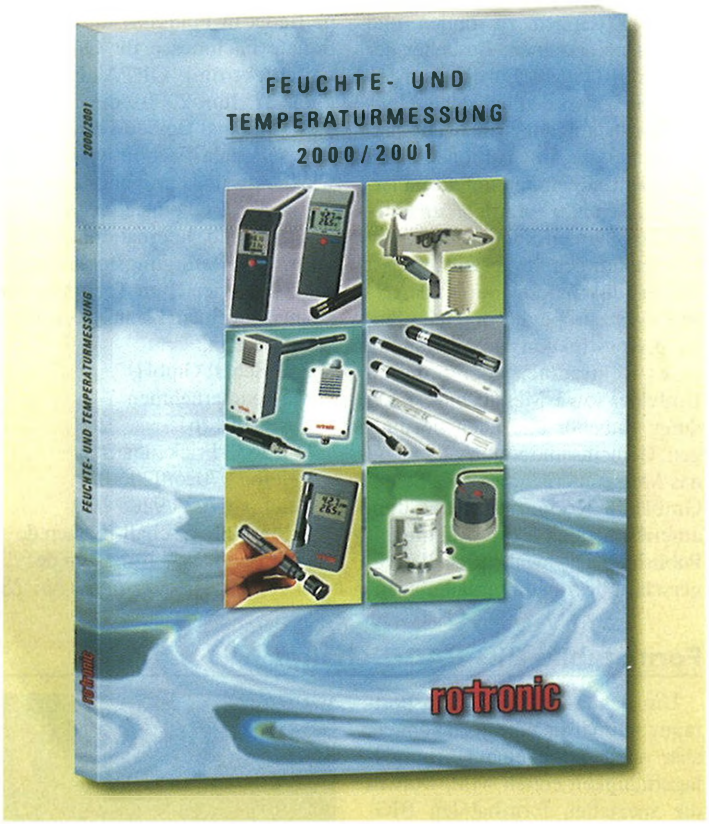
Pack Check der Micro-Leck-detektor für sämtliche Anwendungen mit Schutzatmosphäre

Bei der Verpackung von Lebensmitteln sind undichte Verpackungen eine ständige Gefahr. Die Folgen von undichten Verpackungen sind erhöhte Kosten, Imageprobleme, Kundenverluste etc. Das beste Mittel dagegen ist eine effektive Qualitätssicherung durch Dichtigkeitsprüfung. Dansensor Pack Check funktioniert als zerstörungsfreies, automatisches Dichtigkeitstestgerät, welches mit CO_2 als Spurengas arbeitet. Pack Check detektiert Mikrolecks an elastischen Verpackungen (z.B. Teigwaren, Käse, Wurstwaren etc.) und an harten Verpackungen wie z.B. Trockenmilchdosen. Je nach der Grösse der jeweiligen Verpackung kann Pack Check auch mit Sammelpackungen arbeiten, z.B. Transportkartons. Der Test wird an den Packungen zerstörungsfrei durchgeführt. Die Packung einfach in die Kammer legen und den Deckel schliessen. Dansensor Pack Check nimmt hiernach den Test vollautomatisch vor. Das Testergebnis wird dem Benutzer auf der Anzeige deutlich dargestellt. Ein weiteres Leistungsmerkmal von Dansensor Pack Check ist die Datenspeicherung. Sämtliche Testergebnisse werden für den jeweiligen Pakkungstyp, bzw. die jeweilige Verpackungsmaschine, Maschinenstrasse etc. gespeichert und lassen sich auf einen Drucker oder Computer übertragen. Dansensor Pack Check hat eine komplette Selbstdiagnose. Diese gewährleistet, dass kein Bedienungs- bzw. Systemfehler übersehen wird. Bei Fehlern wird ein Alarm ausgelöst, und eine Fehlermeldung erscheint auf der Anzeige. Sie können sich daher immer auf die korrekte Funktion und Bedienung Ihres Dansensor Pack Checks verlassen.

- LAUPER Instruments
  Länggasse 13
  Postfach
  CH–3280 Murten
  Telefon 026 672 22 40
  Telefax 026 672 22 49
  www.lauper-instruments.ch

Leserdienst Nr. 13

Feuchtemessung – komplett und kompetent



Rotronic AG – der weltbekannte Hersteller von Feuchte- und Temperaturmessgeräten, stellt auf 200 Seiten sein komplettes Messgeräte-Programm vor. Überzeugend durch die Benutzerfreundlichkeit und den hohen Informationsgehalt, dient dieser Katalog in idealer Weise sowohl als Nachschlagewerk für den Applikationsingenieur, wie auch als wertvolle Auswahlhilfe für die Evaluation des passenden Produktes. Technische Daten, Masszeichnungen sowie elektrische Anschlussschemata sind komplett und übersichtlich für jedes Produkt dargestellt. Neu im Katalog sind das umfassende HygroClip Programm, alle Neuigkeiten der Loggerfamilie, sowie ein spezielles Kapitel für den Papierfachmann.

Abgerundet durch Informationen über das eigene SCS Kalibrierlabor, die Kalibriernormalen und das ausführliche Zubehörprogramm zeigt dieser Katalog auch die Stärke der Rotronic in der Serviceleistung nach dem Kauf. Bestellen Sie Ihr Gratisexemplar noch heute.

- Rotronic AG
  Grindelstrasse 6
  CH–8303 Bassersdorf
  Telefon 01 838 11 11
  Telefax 01 836 44 24
  Internet http://www.rotronic.ch

Leserdienst Nr. 14

ChemDraw 6.0 – Mehrseitige Dokumente, E-Commerce und vieles mehr

Cherwell Scientific Ltd freut sich, die Neuerscheinung von ChemDraw in der Version 6.0, entwickelt von der CambridgeSoft Corporation, ankündigen zu können. Die neueste Version von ChemDraw verfügt über eine Vielzahl neuer Funktionen und Erweiterungen vorhandener Funktionen. Dabei wurden auch Anregungen von BenutzerInnen berücksichtigt.

So verfügt ChemDraw in der Version 6.0 über mehrseitige Dokumente, eine Vergrösserungseinstellung, ein verbessertes ChemNMR, das Korrelationen zwischen Atomen und Linienspektren zeigt, die neue Funktion Show Stereochemistry, die Stereochemie automatisch zuweist, grössere Flexibilität der Dateiformate, gestrichelte geometrische Konstrukte und Kontextmenüs für die rechte Maustaste.

Neu ist das Online Menü, das es ermöglicht, eine bereits in ChemDraw gezeichnete Verbindung in der Chemie-Anbieterdatenbank von ChemACX.Com nach Anbietern zu suchen, die diese Verbindung verkaufen. Anwender können dann einen Anbieter auswählen und direkt über ChemACX.Com einen Einkauf tätigen. Langjährige Benutzer von ChemDraw werden zu Beginn ihrer Arbeit mit ChemDraw 6.0 über rote Rechtecke um manche ihrer Strukturen verwundert sein! Diese Rechtecke dienen zur Warnung für den Benutzer, dass auf der Seite eventuell eine fragliche Struktur vorhanden ist: Wenn z.B. eine Struktur mit einer unüblichen Valenz für eines der Atome erzeugt wurde.

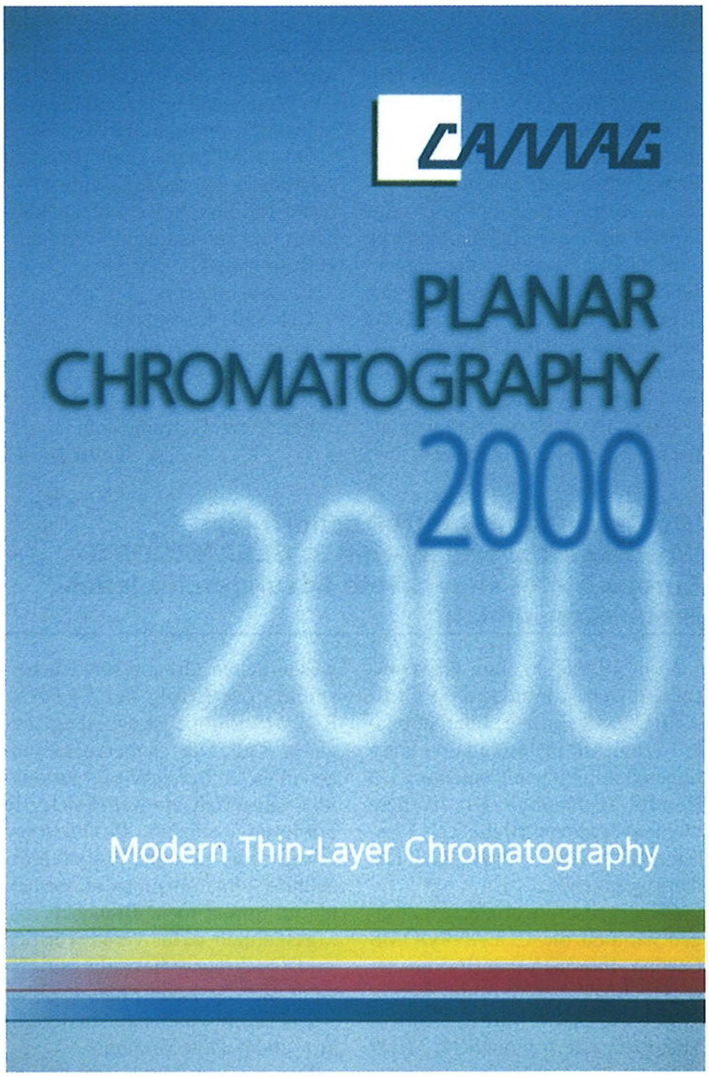
Weitere Verbesserungen betreffen die Geschwindigkeit und die Genauigkeit des Programms und selbst das Installationssystem wurde verbessert.

Diese neueste Entwicklung macht ChemDraw zu dem fortschrittlichsten und leistungsstärksten unter den Strukturzeichenprogrammen.

- Cherwell Scientific Limited
  c/o CHEM Research GmbH
  Hamburger Allee 26–28
  D–60486 Frankfurt
  Germany
  Telefon +49 69 970841-11
  Telefax +49 69 970841-41
  E-Mail: csp.d@cherwell.com
  URL: http://www.cherwell.com

Leserdienst Nr. 15

New CAMAG catalog: Planar Chromatography 2000 – Modern Thin-Layer Chromatography



Planar Chromatography is a modern separation technique which is accepted by regulatory agencies and analysts as an extremely flexible, reliable, and cost-effective method. It is successfully used in pharmaceutical industry, food analysis, natural products/herbals and many other fields of application.

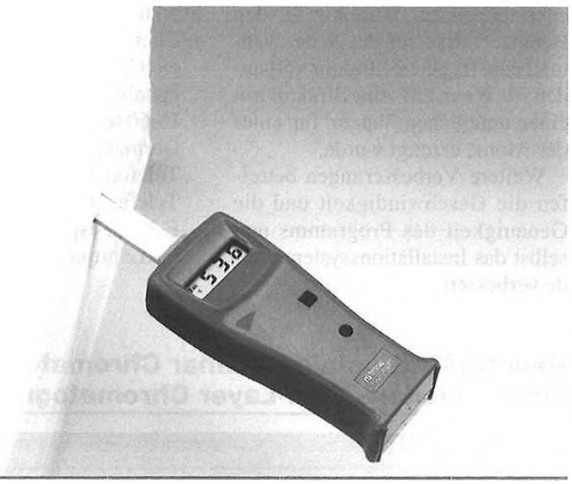
Besides information on CAMAG products and services the catalog includes a brief guide to the operating procedure of Planar Chromatography.

The catalog contents and ancillary information on CAMAG services can also be accessed in the Internet under www.camag.ch

- CAMAG
  Sonnenmattstrasse 11
  CH–4132 Muttenz
  Telefon +41 61 467 34 34
  Telefax +41 61 461 07 02
  E-Mail info@camag.ch

Leserdienst Nr. 16

GTS robustes Handgerät für die Papier- und Druckindustrie



Seit über 20 Jahren wird das Hygrometer Typ GTS von Rotronic erfolgreich in der Druckindustrie und in Lagerräumen für Karton und Papier eingesetzt. Der äusserst robuste Aufbau und das sehr gute Preis-/Leistungsverhältnis, haben es zum Lieblingsprodukt der Papierfachleute gemacht. Aufgrund der hohen Nachfrage wurde das GTS nun modernisiert und ist nun neu mit einer Genauigkeit von ±1,5%rF und ±0.3 K (bei 23°C) erhältlich.

Ebenfalls wurde neu eine automatische Abschaltung integriert. Die Mechanik wurde neu optimiert um den Widerstand beim Einführen des Schwerters zu minimieren.

Das Handgerät kann jederzeit sehr kostengünstig mit Kalibrierzubehör für die relative Feuchte kalibriert und neu einjustiert werden.

- Rotronic AG
  Grindelstrasse 6
  CH–8303 Bassersdorf
  Telefon 01 838 11 11
  Telefax 01 836 44 24
  Internet
  http://www.rotronic.com

Leserdienst Nr. 17

'Contamination Control' schafft klare Wettbewerbsvorteile – die 3. CLEANROOMS Europe bietet angepasste Lösungen für jedes Produktionsumfeld

Vom 28. bis 30. Juni 2000 präsentiert sich in Frankfurt die CLEANROOMS Europe, Internationale Fachmesse für Produktion unter reinen Bedingungen/Contamination Control Technology. Drei weitere themenverwandte High-Tech-Messen ergänzen das hochwertige Informationsangebot.

Bereits nach zwei Veranstaltungen hat sich die CLEANROOMS Europe, Internationale Fachmesse für Produktion unter reinen Bedingungen/Contamination Control Technology, erfolgreich im Markt etabliert. Rund 190 beteiligte Unternehmen und fast 3000 Fachbesucher wurden 1999 registriert. Zur diesjährigen Veranstaltung vom 28. bis 30. Juni 2000 im Messegelände Frankfurt ist eine weitere Steigerung der Aussteller- und Besucherzahlen zu erwarten: 110 Firmen haben bereits gemeldet und das attraktive Angebot der CLEANROOMS Europe sowie der drei themenverwandten Parallel-Messen wird ein noch umfangreicheres Fachpublikum nach Frankfurt locken als in den vergangenen Jahren. Einer der wesentlichen Gründe für den beispielhaften Erfolg der CLEANROOMS Europe ist der stetig steigende Bedarf an 'sauberen' Lösungen in vielen Bereichen der Produktion. Unaufhaltsam weitet sich die Forderung, einzelne Produktionsschritte oder gesamte Produktionsabläufe kontaminationsfrei zu halten, in immer mehr Branchen aus. Massgeblich dafür verantwortlich sind Qualitätsverbesserungsmassnahmen, Materialeinsparungen sowie neue Entwicklungen in der Mikro- und Nanotechnologie.

Die 3. CLEANROOMS Europe in Verbindung mit der CLEANROOMS European Conference und einem praxisorientierten Ausstellerforum bringt Lösungssuchende sowie Anbieter von Lösungen in geeigneter Weise zusammen.
Insbesondere Firmen, die sich erstmals mit Fragen der reineren Produktion konfrontiert sehen, finden hier den Austausch und die fachliche Diskussion mit Beratern, Forschungsinstituten, Herstellern von Reinräumen, Messgeräten und Reinraumzubehör. Die Messe und der Kongress bieten dem Fachpublikum die richtige Plattform, um Informationen auszutauschen, angepasste Lösungen zu finden und Trends zu erkennen. Besucher der CLEANROOMS Europe werden feststellen, dass deutlich reinere Produktionsbedingungen nicht automatisch mit hohen Investitionen in ein komplettes Reinraumumfeld einhergehen. Schon wesentlich einfachere Massnahmen können messbare Erfolge bringen. Insgesamt umfasst die Produktpalette der CLEANROOMS Europe die Bereiche Planung, Konstruktion und Ausstattung eines Reinraumes oder reineren Umfeldes sowie Messtechnik, Kleidung, Zubehör und Dienstleistungen. Gemeinsame Veranstalter sind das Messeunternehmen P.E. Schall GmbH in Kooperation mit dem amerikanischen Verlag Pennwell Publishing. Die fachlich-ideelle Trägerschaft liegt beim Fraunhofer Institut für Produktionstechnik und Automatisierung (IPA), Stuttgart. Parallel zur CLEANROOMS Europe findet in Frankfurt die Internationale Fachmesse für Optik und Optoelektronik OPTATEC (Beginn: 27. Juni 2000), die 3. TechMed/ Medical Device Technology, Internationale Fachmesse für Entwicklungs- und Fertigungstechnologie in der Medizintechnik und die 2. CleanTech, Internationale Fachmesse für Reinigungstechnologie statt. Alle vier High-Tech Messen können mit einem Kombi-Ticket besucht werden.

- P.E. Schall GmbH
  Messeunternehmen
  Postfach 1261
  D–72633 Frickenhausen
  Telefon 07025/9206-0
  Telefax 07025/9206-620
  E-Mail info@schall-messen.de
  http://www.schall-messen.de

Leserdienst Nr. 18

Formstabile BIG-BAG-Behälter

Um den Lager- und Transportraum optimal ausnützen zu können, aber auch damit eine Hochregallagerfähigkeit erzielt wird, wurden die speziellen formstabilen BIG-BAG's entwickelt. Diese sind sowohl als Einweg-, wie auch in verstärkter Version als Mehrweg-Gebinde verwendbar.

Diese BIG-BAG's, grundsätzlich aus beidseitig beschichtetem Polypropylen-Gewebe, können mit Einlauf-Stutzen oder -Schürzen, sowie mit geschlossenem Boden oder mit Auslaufstutzen versehen werden. Fest eingebaute oder bei Mehrweg-Ausführung auswechselbare Innensäcke (Inliner), ermöglichen auch den Einsatz in der Nahrungsmittel- und Chemie-Industrie. Dadurch ist eine einwandfreie Hygiene erreichbar.

BIG-BAG's erzielen im Allgemeinen eine Kosteneinsparung von bis zu 70% durch einfaches Handling, günstigere Verpackungskosten sowie optimaler Ausnutzung von Lager- und Transportraum.

- WISAG
  Oerlikonerstrasse 88
  CH–8057 Zürich
  Telefon 01 311 40 40
  Telefax 01 311 56 36
  E-Mail wisag@swissonline.ch

Leserdienst Nr. 19

Analysentechnik und andere chemische Highlights

Unter dem Motto 'Über Tage – Unter Tage – Alle Tage' steht das 8. Seminar, das SPECTRO A.I., das Kaliforschungs-Institut und die Europa Fachhochschule Fresenius gemeinsam durchführen.

Grund für dieses Motto ist der ungewöhnliche Veranstaltungsort: 460 m unter Tage im Erlebnis Bergwerk Merkers in der Rhön. Im Mittelpunkt des eintägigen Seminars stehen neue Analysetechniken.

Dr. P. Heitland von SPECTRO wird über Applikationen mit dem neuen ICP-Spektrometer SPECTRO CIROS^{CCD} referieren.

M. Schröder von Kali und Salz berichtet über den Einsatz eines ICP Spektrometers, das seit 4 Jahren 28000 Stunden in Betrieb ist und in dieser Zeit 250000 Proben analysierte und 500000 Messwerte lieferte. Ein weiteres Referat befasst sich mit dem Einsatz der polarisier-

ten energiedispersiven RFA in der Additiv- und Schmierstoffindustrie.

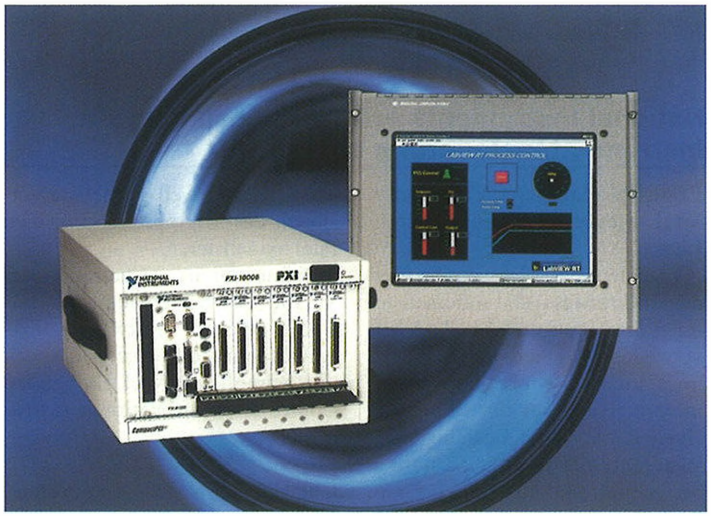
Prof. Dr. Henatsch von der Europa Fachhochschule Fresenius hält eine 'Hommage an die Alkali- und Erdalkali-Elemente, aufgezeigt am Beispiel der Pfeilgiftfroschtoxine', während Prof Dr. Dr. Roesky von der Universität Göttingen chemische Kabinettstücke vorführt und mit geistreichen Zitaten würzt. Eine Besichtigung des Erlebnis Bergwerk Merkers bildet den Abschluss des Seminars. Die Veranstaltung findet statt Montag, dem 8. Mai 2000.

Die Teilnahme ist kostenlos.

- Spectro Analytical Instruments GmbH & Co. KG
  Postfach 1762
  D–47516 Kleve
  Telefon 02821 892-0
  Telefax 02821 2 31 44

Leserdienst Nr. 20

Kombination aus CompactPCI und LabVIEW™ RT zur Echtzeit-Steuerung



Lab VIEW RT von National Instruments beschleunigt Entwicklung und Einsatz von Echtzeit Applikationen

National Instruments stellt nun eine neue auf LabVIEW RT basierende Lösung zur Echtzeit-Steuerung mit CompactPCI vor. LabVIEW ist die einfach zu handhabende graphische Programmierumgebung von National Instruments für die Entwicklung und den Einsatz von Embedded Echtzeit-Applikationen. Mit LabVIEW RT können Systemintegratoren und Regelungstechniker Überwachung und Steuerung von Datenerfassungsapplikationen in Echtzeit durchführen, aber auch diskrete Steuerungsapplikationen mit einem Standard-Windows-PC entwickeln. Durch einen einfachen Mausklick wird die Applikation über das Ethernet-Netzwerk auf einen PXI™/CompactPCI-Rechner geladen, auf dem die Applikation deterministisch und zuverlässig läuft.

Einmal auf den PXI/CompactPCI Controller heruntergeladen, erhalten die LabVIEW RT-Applikationen Zugang zu zahlreichen analogen und digitalen PXI/CompactPCI-Modulen zur Datenerfassung und Signalkonditionierung von National Instruments. Auf der Basis dieser modularen, industriegeeigneten Plattform kann der Anwender auf einfache Art und Weise auf die unterschiedlichsten Echtzeit-Applikationen zugreifen. HMI-, Datenlogger-, Analyse- und Überwachungsapplikationen, die unter LabVIEW RT oder BridgeVIEV™ (LabVIEW für die Industrieautomation) erstellt wurden, können mit der Embedded LabVIEW RT-Applikation über das Ethernet kommunizieren und diese steuern.

'Mit LabVIEW RT können Systemingenieure Echtzeitsysteme für die Mess- und Automatisierungstechnik unter Verwendung von Industriestandard Entwicklungswerkzeugen erstellen. An diese Applikationen können nun PXI Embedded Controller oder Datenerfassungskarten der RT-Serie für PCI and PXI/CompactPCI angekoppelt werden', erläutert Norma Dorst, National Instruments Real-Time and Emmbedded Marketing Manager. 'Und das ist erst der Anfang: National Instruments wird weitere skalierbare Hardwareplattformen für LabVIEW RT entwickeln und andere Technologien, wie Windows CE und Windows NT Embedded (NTE) für integrierte und tragbare Mess- und Automatisierungslösungen unterstützen.'

Der PXI/CompactPCI-Controller für LabVIEW RT verwendet die gleiche National Instruments ComputerTechnologie wie sie heute in PXI/CompactPCI-Systemen eingesetzt wird. Somit können Anwender der derzeitigen PXI/CompactPCI-Systeme ihre bestehenden Windows-basierenden PXI/CompactPCI-PCs auf der Basis von LabVIEW RT in einen Echtzeit Embedded Controller umwandeln und erhalten so zuverlässige, deterministische Systemperformance. Zudem ist ein PXI/CompactPCI Controller mit bereits installiertem LabVIEW Echtzeit-Motor erhältlich.

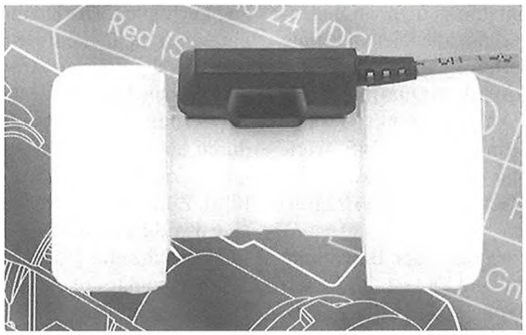
Die Einfachheit des Industrie-Standards in der Echtzeit

Seit etwa 15 Jahren entwickelt National Instruments die einfach zu handhabende, zuverlässige Programmiersprache LabVIEW zur Erstellung von computerbasierten Mess- und Automatisierungslösungen. LabVIEW hat sich als ein grafisches Programmierpaket des Industriestandards etabliert, das von Ingenieuren und Wissenschaftlern weltweit verwendet wird. Mit LabVIEW RT erweitert National Instruments nun die einfache Handhabung der graphischen Programmierung mit LabVIEW, um auch Anwendern ohne tiefergehende Kenntnisse von Echtzeittechniken und nicht standardisierten Computersystemen die Entwicklung von Echtzeitapplikationen zu ermöglichen.

- National Instruments Switzerland
  Sonnenbergstrasse 53
  CH–5408 Ennetbaden,
  Telefon 056 200 51 51
  Telefax 056 200 51 55
  E-Mail ni.switzerland@ni.com,
  oder
  National Instruments Instrumentation Web™ unter www.ni.com/switzerland

Leserdienst Nr. 21

Neuer Turbinen-Durchflusssensor +GF+ SIGNET 2100 – für Anwendungen mit niedrigen Strömungsraten



Georg Fischer hat der Typenreihe von Strömungssensoren den neuen Turbinensensor +GF+ SIGNET 2100 hinzugefügt. Der Typ 2100 wurde spezifisch für Anwendungen mit niedrigen Strömungsraten und kleinen Abmessungen entwickelt. Er bietet genaue Ablesungen in zwei Strömungsbereichen: 0,38 bis 3,8 L/M (0,1 bis 1,0 GPM) und 3,0 bis 37,8 L/M (0,8 bis 10 GPM)

Der Spritzgusskörper aus PVDF und die keramischen Lager gewährleisten eine ausgezeichnete chemische Kompatibilität und eine lange Lebensdauer bei Dosierungs- und Chargenanwendungen. Radialer Ein- und Ausbau, sowie die austauschbare IP65-geschützte Elektronikeinheit ermöglichen einen mühelosen Zusammenbau und Austausch am Montageort.

Das Modell 2100 kann mit Schlauchleitungen von 1/4", 3/8" oder 1/2" Durchmesser oder mit Rohren von DN15 (1/2") Durchmesser eingesetzt werden. Es stehen Verschraubungen in PVDF für Schlauchtüllen, Schweissmuffen und IR/Stumpfschweiss-Stutzen zur Verfügung, sowie in PVC für Klebemuffen und NPT-Gewinde. Der Sensor verfügt über einen Offenen-Kollektor-Frequenzausgang, der mit sämtlichen +GF+ SIGNET Anzeigegeräten mit Offenem-Kollektor-Frequenzeingang kompatibel ist.

Das Modell 2100 ist für transparente und nicht-transparente Flüssigkeiten geeignet, und bietet eine Messgenauigkeit von ±3% vom aktuellen Messwert.

Das Produktangebot von +GF+ SIGNET umfasst ein breites Spektrum an Durchfluss- und Analytik-Sensoren, Transmitter, Anzeigegeräte, Regler und Fittinge, zur Überwachung und Regelung von Prozessen.

- Georg Fischer
  Rohrleitungssysteme
  (Schweiz) AG
  CH–8201 Schaffhausen
  Telefon 052 631 30 26
  Telefax 052 631 28 96
  e-mail:
  info@rohrleitungssysteme.georgfischer.ch
  Internet: http://www.piping.georgfischer.com

Leserdienst Nr. 22

Neuer Grosskapazitäts-Inkubationsschüttler 'Innova 4430' von NBS New Brunswick Scientific

Der neue Innova 4430 Gross-kapazitäts-Inkubationsschüttler von New Brunswick Sclentific lässt sich mit bis zu drei unabhängigen Einheiten stapeln. Der Zeit entsprechend sind die individuellen Kühleinheiten CFC-frei. Das elegante Design rundet die bewährten technischen Raffinessen wie TED-Dreifachexcenter-Antrieb oder den kohlenbürstenlosen Elektromotor so ab, dass Sie auch noch noch Jahren Ihre Freude daran haben.

Ihre Kulturen werden es Ihnen zu danken wissen.

- IG
  Instrumenten-Gesellschaft AG
  Räffelstrasse 32
  CH–8045 Zürich
  Telefon 01 456 33 33
  Telefax 01 456 33 30
  Das gesamte Lieferprogramm finden Sie auch im Internet unter www.igz.ch

Leserdienst Nr. 23

Mehr Sicherheit – mehr Freizeit IQ und OQ in der Schmelzpunktbestimmung

Die Qualifizierung von analytischen Messgeräten in der pharmazeutischen Industrie und Feinchemie gewinnt immer mehr an Bedeutung. Neu erlaubt die Dienstleistung zur Installationsqualifizierung (IQ) und funktionalen Qualifizierung (OQ) des Schmelzpunkt Gerätes Büchi Melting Point B-545, wertvolle interne Ressourcen zu sparen und bietet Gewähr für ein erfolgreiches Audit.

Von herausragender Bedeutung in einem IQ und OQ ist die Erstellung eines vollständigen Prüfplanes, die Vorbereitung von Qualifizierungs-SOP's, sowie eine GMP/GLP konforme Dokumentation der durchgeführten Arbeiten. Vertiefte Gerätekenntnisse und intensive Vorarbeiten sind notwendig, um die Auflagen offizieller Stellen sicher zu erfüllen.

Das komplette Dienstleistungspaket für IQ und OQ erlaubt es, von jahrelanger Herstellererfahrung zu profitieren. Die gesamte Dokumentation, bestehend aus Logbuch, Prüfplänen, Zertifikaten und abschliessenden Reports, steht vorab zur Verfügung. Die Dokumentation garantiert die lückenlose Erfassung aller durchgeführten Arbeiten. Die praktischen Arbeiten der Gerätequalifizierung werden beim Kunden durch einen speziell ausgebildeten Qualifizierungstechniker durchgeführt. Zum Einsatz kommen exklusive Kalibrier- und Verifikationssets, welche die Rückführung der Schmelzpunkte auf die internationale Temperaturskala ITS-90 gewährleisten. Darüber hinaus bietet die Schulung von Mitarbeitern im Kundenlabor zusätzliche Gewähr für ein sicheres Audit.

- Büchi Labortechnik AG
  Postfach
  CH–9230 Flawil
  Telefon 071 394 63 63
  Telefax 071 394 65 65
  www.buchi.com

Leserdienst Nr. 24

Zusammenführung von Arbeitsschutz und Umweltschutz

Die 27. A+A, Internationale Fachmesse und Kongress Arbeitsschutz und Arbeitsmedizin, und die 10. ENVITEC, Internationale Fachmesse für Ver- und Entsorgung mit Fachkongress, werden vom 14.–17. Mai 2001 zum ersten Mal gemeinsam auf dem Düsseldorfer Messegelände stattfinden.

Mit dieser Entscheidung, die die Messe Düsseldorf zusammen mit ihren Messepartnern getroffen hat, wird den Bedürfnissen des Marktes entsprochen. Die Entwicklungen der letzten Jahre in den Unternehmen und Organisationen zeigen, dass vor allem die Bereiche Arbeitsschutz und Umwelttechnik viele Parallelen aufweisen. In den meisten Betrieben sind diese Themen in einer Abteilung zusammengefasst. Die sich daraus ergebenen Synergien können sowohl die Besucher als auch Aussteller beider Messen nun zu ihrem Vorteil nutzen. Sie haben die Chance, ihre Gespräche als Basis für erfolgreiche Geschäfte an einem Ort und zum gleichen Zeitpunkt zu führen.

A+A und ENVITEC werden dennoch ihren eigenen Charakter, bestehend aus branchenspezifischen Elementen, behalten. Die ENVITEC hat den Wandel von der Messe des nachsorgenden Umweltschutzes zur Ver- und Entsorgungsmesse vollzogen und wird sich 2001 neu positionieren. Wie bereits zur letzten ENVITEC 1998 wird es zur ENVITEC 2001 wieder einen begleitenden Kongress zum Thema 'Eco-Efficiency' geben, der vom Wuppertal Institut für Klima, Umwelt, Energie GmbH organisiert wird. Neben dem Bereich der Umwelttechnik werden bei der A+A 2001 die Themen Persönliche Schutzausrüstungen, sowie Technische Sicherheitseinrichtungen für den Arbeitsplatz und die Arbeitsmedizin im Mittelpunkt des Interesses stehen. Unterstrichen wird das A+A-Angebot durch den seit Jahren erfolgreichen A+A-Kongress, der unter Trägerschaft der Bundesarbeitsgemeinschaft für Sicherheit und Gesundheit bei der Arbeit e.V. (Basi) ein interessantes Informations- und Kommunikationsforum für die Branche schafft.

Besucher können mit einem Messe-Ticket beide Veranstaltungen besuchen. Aussteller können an der A+A und an der ENVITEC jeweils zum gleichen Preis teilnehmen.

- Messe Düsseldorf GmbH
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Leserdienst Nr. 25

National Instruments erweitert Lösungen zur Instrumentensteuerung unter Linux

Erste Standards der VXI- und VME-Steuerungslösungen für Linux

Ingenieure und Wissenschaftler, die für Ihre Mess- und Automatisierungsanwendungen VXI oder VME verwenden, können dies nun auch im Betriebssystem Linux programmieren. Als einer der führenden Hersteller von leistungsfähigen Instrumentensteuerungs-Systemen bietet National Instruments nun komplette Linux kompatible VXI- und VME-Steuerungslösungen, die LabVIEW™, GPIB, Embedded und verteilte Systeme enthalten. Um der wachsenden Nachfrage nach dem freien Betriebssystem in Hochschulen, Forschungseinrichtungen und der Industrie nachzukommen entwickelte National Instruments Linux-Lösungen für die Produkte VXIpc™-870 und MXI™-2.

Über Linux in der VXIpc-870-Serie

Die VXIpc-870-Serie, die die schnellsten VXI-Embedded Controller von National Instruments umfasst, verwendet ein innovatives, mechanisches Design, um die Mikroprozessoren des Intel Slot I, Pentium II und Pentium III in eine Einheit von zwei Slots der Grösse C umwandeln zu können. In einem kleinen Format ist der VXI-pc-870 komplett mit CD-ROM, Ultra DMA 33 Laufwerk, PC Card Steckplatz und einer Vielzahl von leistungsfähigen Peripheriegeräten erhältlich. Zudem verwendet VXI-pc-870 neueste Intel Chipsatz-Technologien, sowie die Highperformance-Produkte MITE™ und MANTIS™ ASICs von National Instruments, um bestmögliche VXI- und PC-Performance gewährleisten zu können. Mit der Architektur eines einzigen Slots können Anwender das VXIpc-870 CPU auf jeweils schnellere Versionen der Mikroprozessoren von Intel aktualisieren.

In Kombination mit Controllern der VXIpc-870-Serie bietet die NI-VXI™/VISA™-Software Linux-Anwendern die Leistungsfähigkeit des schnellsten VXI Embedded Controllers von National Instruments.

Über Linux in MXI gesteuerten VXI- und VME-Systemen

Der Multisystem eXtension Interfaxe (MXI)-Bus ist eine leistungsstarke Kommunikationsverbindung, die Geräte durch Kabel miteinander verbindet. Mit MXI-2 können nun die Möglichkeiten moderner Bussysteme mit angeschlossenen Kommunikationsanbindungen verbunden werden, um hohe Kommunikationsraten zwischen alleinstehenden PCs und VXI- oder VME-Systemen erlangen zu können.

Die VXI/VME-PCI8026 Schnittstelle gestatten den Anwendern den Wechsel zu PCI-basierten Desktop-Systemen unter Linux, da die Software NI-VXI/VISA auf allen Betriebssystemen standardisiert ist. Das Paket der VXI-PCI8026 Busschnittstelle zur VXI-Steuerung beinhaltet PCI-MXI-2, VXI-MXI-2, ein Kabel und NI-VXI/VISA für Linux. Das Paket der VME-PCI8026 Busschnittstelle zu VME-Steuerung enthält PCI-MXI-2, VME-MXI-2, ein Kabel und NI-XI-VISA für Linux.

Über NI-VXI/VISA Software

Die Software-Busschnittstelle NI-VXI/VISA ist ein umfangreiches, rückwärts kompatibles Software-Paket zur Konfiguration, Programmierung und zum Debuggen von VXI/VME-Systemen. Sie beschleunigt die Entwicklung durch ein kom-

STELLENMARKT

plettes Set von von Highperformance-Routinen für industriestandardgemässe Programmiersprachen und intuitiv bedienbare Werkzeuge zur Bearbeitung und Problemlösung von VXI- und VME-Systemen. Anwender, die Ihre VXI/VME-Systeme mit NI-VXI/VISA und einem Paket der VXI-PCI8000 Serie oder mit Embedded Controllern erstellen, können den verwendeten Code ohne Modifizierung in Linux portieren, indem Sie das VXI/VME-PCI8026-Kit oder den VXIpc-870 Controller verwenden.

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Leserdienst Nr. 26

Zeitgemässes Qualitätsmanagement nach der neuen ISO-Norm

Ende 2000 treten die Normen der neuen ISO 9000er Serie in Kraft: Das Praxishandbuch 'Qualitätsmanagement' des WEKA Verlages bietet wertvolle Informationen und klare Anleitungen zur raschen Umsetzung. Auf der CD-ROM sind die kompletten Prozessabläufe abrufbar – nach alter und neuer Nummerierung. Qualitätsmanagement erfüllt dann seinen Zweck, wenn es die ständige Bereitstellung fehlerfreier Produkte garantiert. Und genau dazu verhelfen die Normen der neuen ISO 9000er Serie. Im Unterschied zur alten systemorientierten Norm sind die neuen Normen prozessorientiert – in Struktur und Inhalt. Diesem Anspruch trägt das Praxishandbuch 'Qualitätsmanagement' des WEKA Verlages Rechnung. Es ist analog der neuen ISO-Norm aufgebaut und stellt folgende Fragen ins Zentrum: Was verlangt die neue ISO Zentrum: Was verlangt die neue ISO 9001:2000? Was hat sich gegenüber der alten Norm 9001:1994 geändert? Was bleibt gleich? Das Handbuch 'Qualitätsmanagement' liefert vorgefertigte Flowcharts, welche die Abläufe visualisieren und so die Umstellung auf ein prozessorientiertes QM-System erleichtern. Jedes Kapitel ist mit einer eigenen Checkliste versehen, sodass alle Änderungen gegenüber der alten Norm sofort ersichtlich sind. So lassen sich die Forderungen an ein Qualitätsmanagement-System bei jedem Prozessschritt effizient umsetzen. Zudem sind die kompletten Prozessabläufe auf der CD-ROM als Excel-Grafiken vorhanden – frei editierbar nach alter und neuer Nummerierung. Sämtliche Abläufe können also rasch und einfach an das einzelne Unternehmen angepasst und während der Einführung des neuen Systems beliebig verändert werden.

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Leserdienst Nr. 27

Anpassungsfähige Online Prozessanalytik

SENSORIX präsentiert an der Achema ihr neuartiges online Analysensystem auf der Basis von chemischen Sensoren und Biosensoren. Der patentierte modulare Aufbau bringt bisher unerreichte Flexibilität in die Prozessanalytik.

Kontinuierliche Messwerte von z.B. den wichtigsten Nährstoffen und Metaboliten in Fermentationsprozessen ermöglichen höhere Produktausbeuten bei kürzeren Produktionszeiten. 1–12 Sensoren können im Analysensystem eingesetzt und parallel betrieben werden. Sensoren für Glucose, Lactat und Alkohol sind zur Zeit erhältlich und nach Bedarf einzeln oder in beliebiger Kombination einsetzbar. Weitere Sensoren sind in Entwicklung und können auch später in den bereits in Betrieb stehenden Systemen verwendet werden.

Das Analysengerät wird über ein Probenahmesystem direkt mit dem Prozess verbunden. Die Resultate können nicht nur für die Prozessregelung verwendet werden, sondern auch bei unerwarteten Verlaufen einen Alarm auslösen oder Prozessdaten für die Qualitätssicherung liefern.

ACHEMA 2000:
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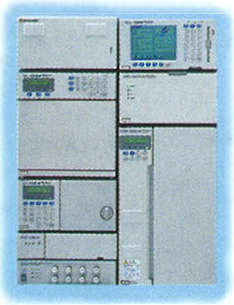
Leserdienst Nr. 28

SHIMADZU

800 an Bord. Wie unser LC10A*VP*

Wie bringt man mit gleichem Aufwand mehr Passagiere von A nach B? Durch Erhöhung der Transportkapazität.

Diesem Prinzip folgte Shimadzu bei der Entwicklung der LC-10A*VP* Serie mit der neuen CLASS-VP 5.0 Software. Sie vereint in die Hardware integrierte Validation-and-Productivity-Funktionen (VP), die die High-end-Analyse von Substanzen um ein Vielfaches wirtschaftlicher machen. Das heißt: mehr Durchsatz in gleicher Zeit, mehr Informationen bei geringerem Verbrauch an Testsubstanzen.
Wie ist das möglich? Unmittelbar nach der Selbstvalidierung des Systems, kann der Probenroboter bis zu 800 Testmedien in einem Durchlauf abarbeiten, wobei das Photodioden-Array für die hochempfindliche Auflösung der Substanzen sorgt.



VP
Validation & Productivity

Mikro-Titerplatten helfen bei der Einsparung von Probenmengen, und die CLASS-VP 5.0 Software ermöglicht die weitere Verarbeitung der gewonnenen Daten.

Durch die weitgehende Selbständigkeit der LC-10A*VP*-Serie können sich die Labormitarbeiter um andere Aufgaben kümmern. Oder Feierabend machen. Die Produkt- und Qualitätskontrolle bleibt auch über Nacht auf höchstem Niveau. Das ist unser Versprechen - und Ihre Garantie. Testen Sie uns.

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