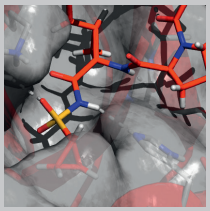
doi:10.2533/chimia.2025.272 Chimia 79 (2025) 272–274 



# Medicinal Chemistry and Chemical Biology Highlights

## Division of Medicinal Chemistry and Chemical Biology

A Division of the Swiss Chemical Society

## DMCCB Basel Symposium 2025: Strategies for Addressing Challenging Targets

Fides Benfatti, Nicola Compagnone, Federico Dapiaggi, Thomas Rossolini, and Simon Williams*

*Correspondence: Dr. S. Williams, E-mail: simon.williams@syngenta.com
Syngenta Crop Protection AG, Schaffhauserstrasse 101, CH-4332 Stein

Not all biological targets were created equal; this is a well-known, and often hard-learned fact for those working in drug discovery. Successful drugs typically target a relatively small subset of the disease-relevant proteome yet there are many more attractive targets that are simply not amenable to modulation with traditional approaches. Progress against these 'undruggable' targets requires out-of-the-box thinking and a multidisciplinary approach from across the biological and chemical sciences (and sometimes beyond).

This year's DMCCB Basel symposium focused on research that is enabling progress against such challenging drug targets. The symposium took place in the BioZentrum at the University of Basel and was attended by around 100 participants from across industry and academia, reflecting that research on this topic is both fundamental and applied but above all, collaborative. The scientific program spanned cutting edge chemical biology, new drug modalities and drug discovery with nine excellent talks and a poster session.

Session one focused on protein degradation and how this is rapidly becoming an essential tool to study disease pathways. Prof. ***Sascha Hoogendoorn*** from the University of Geneva kicked off the day presenting her group's work on unravelling the cellular target of HPI-1, an inhibitor of the Hedgehog signalling pathway. The compound was discovered by phenotypic screening over a decade ago but its molecular target in the pathway has remained elusive. By converting the compound into a protac (HHP-9) the group were able to demonstrate using proteomics that the targets of HPI-1 are the BET bromodomains (BRD2/3/4).[1] With the protac compound in hand they were able to study the role of BET bromodomains in Hedgehog signalling and understand the complementarity of HPI-1 and HHP-9 to existing inhibitors at other points in the pathway. Continuing the theme of studying drug mechanisms through the lens of protein degradation, Prof. ***Nicolas Thomä*** (EPFL) described studies on nuclear hormone receptors as a way to modulate transcription factors involved in cancer. The first example presented was selective estrogen receptor degraders (SERDs) that have drawn a lot of attention as a breast cancer therapy. Receptor signalling is mediated by a push-pull interaction between coactivator proteins and E3 ligases that degrade the receptor and SERDs act by shifting the equilibrium towards degradation. Using genetic screening, Prof Thomä's group are showing that this is in fact a much more complex picture with different SERDs perturbing the degradation pathway in different ways that can help explain their different performance in the clinic. Prof. Thomä's second example was that of Niclosamide, an old compound used to treat tapeworms that they were able to show triggers the degradation of Cyclin D1 by the E3 ligase AMBRA1. So far so simple but, in an unexpected twist to the story, it appears that Niclosamide does not act as a molecular glue degrader but instead depolarises the mitochondrial membrane which is the trigger for enhanced degradation.

Overall, the takeaway from this session was that studying protein degradation offers a treasure-trove of new insights into disease pathways.

Session two featured three short talks from students at local universities. First, ***Laura Poller*** from the Wennemers group at ETH Zurich presented her PhD studies on the development of fluorescent probes to evaluate lysyl oxidases (LOX) activity. The newly described coumarin-based probes allowed detection of LOXL2 activity at nanomolar level in serum and organ homogenates with high selectivity over other amine oxidases. They offer significantly improved performance compared to standard HRP assays and constitute a powerful diagnostic tool towards the direct monitoring of impaired tissue function. Dr. ***Lukas Schneider*** then described his PhD studies in the Spingler group at the University of Zurich and disclosed the potential of novel BODIPY-based compounds as photothermal agents for cancer treatment.[2] These compounds aggregate in cells and, upon light irradiation, exhibit remarkable photocytotoxicity towards various cancer cell lines in an oxygen-independent manner. Consequently, these photosensitizers also demonstrated their efficacy under hypoxic conditions, potentially overcoming limitations of traditional photodynamic therapy (PDT) employing conventional ROS generating agents. Finally, Dr. ***Zuzanna Kozicka***, currently at Harvard University but previously of the Thomä group at FMI, presented her studies on molecular glue degraders. By examining relationships between E3 ligase expression in cancer cells and small-molecule cytotoxicity, CR8 a CDK inhibitor, was identified as a molecular glue degrader that induces degradation of cyclin K.[3] CR8 promotes key interactions between CDK12 and the E3 ligase DDB1 *via* a solvent-exposed pyridyl moiety. Various chemical scaffolds were shown to exploit similar interactions, modification of such surface-exposed moieties could emerge as a new approach for discovery of molecular glues.[4]

In recognition of their excellent contributions to the field of anticancer research during their studies Dr. Lukas Schneider and Dr. Zuzanna Kozicka were awarded the Cancer Drug Discovery Research Award, supported by RGCC International.

In addition to the student lectures there was a poster session and the prizes for the best posters were awarded to Claire Griggl-stone from the Hartrampf group at UZH who presented a method for the controlled synthesis of phosphopeptides and Nathan De Sadeleer of the Heinis group at EPFL who is developing membrane permeable cyclic peptides.

Session three focused on the development and application of new enabling technologies, to this end Prof. ***Pablo Rivera-Fuentes*** from the University of Zurich presented his team's work on

**Can you show us your Medicinal Chemistry and Chemical Biology Highlight?**
Prof. Dr. Nathalie Grob, Dept. of Chemistry and Applied Biosciences, ETH Zurich, Vladimir-Prelog-Weg 1-5/10, CH-8093 Zurich, E-mail: nathalie.grob@pharma.ethz.ch


Dr. Zuzanna Kozicka

the design of fluorescent chemical probes. In the realm of redox biology, they created advanced sensors to characterize the glutathione redox state in the Golgi apparatus, an organelle that had been understudied in this context.[5] Their findings revealed the Golgi to be a highly oxidizing environment with surprisingly low glutathione concentrations, providing valuable insights into cellular redox homeostasis. In the field of chemigenetic imaging, Prof. Rivera-Fuentes's team introduced a groundbreaking approach to create fluorogenic polymethine dyes spanning a wide range of wavelengths, including the near-infrared region.[6] By applying organic chemistry principles (Baldwin's rules) to design favourable cyclization reactions, they developed switchable fluorogenic carbocyanine derivatives suitable for no-wash, live-cell imaging. These new tools demonstrated excellent compatibility with various cellular targets and existing imaging technologies, including super-resolution microscopy and multicolor imaging. This work not only advances our understanding of cellular redox states but also provides powerful new tools for studying dynamic cellular processes with improved signal-to-noise ratios and expanded colour options.

Prof. Pablo Rivera-Fuentes

Moving on to more applied research Dr. ***Stefanie Flohr*** (Novartis) presented her team's work on the identification and optimization of novel positive allosteric modulators (PAMs) for GPR126, an adhesion receptor critical for Schwann cell function in peripheral nerve regeneration. A high throughput screening campaign identified several GPR126 PAMs, unprecedented in the literature, but characterized by high logD values (>5) and consequently low solubility. These initial hits, while potent in the micromolar range, posed challenges for *in vivo* use due to their suboptimal properties. A cryo-EM structure at 3 Å resolution revealed the binding site at the interface of TM5-7 to the lipid bilayer. Notably, PAM binding induced a significant conformational change in TM6, from linear to kinked. Knowledge-based computational methods then identified hotspots for weakly polar groups in the PAM binding site, guiding further optimization efforts. The team used chromatographic human serin albumin binding measurements to overcome challenges posed by the highly lipophilic compound series. This approach, combined with strategic modifications to improve solubility, led to compounds with better physicochemical profiles. Ultimately the team successfully developed the first orally active GPR126 PAMs with nanomolar potency, high alpha shifts, and logD values below 4. The presentation highlighted the challenges of optimizing highly lipophilic compounds and demonstrated the value of integrating structural biology, computational methods, and property-based design in modern drug discovery.

The conference closed by showcasing two cutting-edge approaches to tackle difficult drug targets. Prof. ***Joseph Rogers*** from the University of Copenhagen presented a novel approach for discovering *de novo* cyclic peptides.

By utilizing the RaPID (Random Peptide Integrated Discovery) system, which combines mRNA display technology with a custom-reconstituted translation system to synthesize and screen trillions of unique cyclic peptide sequences, he addressed two major challenges in drug discovery: regulating protein folding and identifying molecules that bind to RNA-binding proteins. Prof. Rogers described how the RaPID system was used to discover cyclic peptides that bind to and stabilize the folded state of proteins. This approach was successfully applied to ASPA, a protein involved in Canavan disease, a severe neurological disorder caused by protein misfolding. Furthermore, Prof. Rogers demonstrated the system's ability to identify cyclic peptides with nanomolar affinity for RRM2, a key RNA-binding protein. This is particularly significant given that abnormal expression, malfunction, and aggregation of RNA-binding proteins are implicated in various human diseases, including neurological disorders, muscular atrophies, and cancer. Notably, these newly discovered cyclic peptides exhibited the capacity to displace RNA, potentially offering novel approaches for targeting RNA-binding proteins in pathological conditions.

Continuing the RNA theme Prof. ***Maria Duca*** (Université Côte d'Azur) presented an innovative approach to address challenging targets through the identification of small molecules that target oncogenic non-coding RNAs. With approximately 70% of the human genome encoding non-coding RNAs, this strategy could significantly increase the range of therapeutic targets. Prof. Duca's team employs rational design to develop RNA ligands for oncogenic miRNAs, which are overexpressed in cancer cells. By conjugating the C-terminal lateral chain of bleomycin A5 to diverse chemical motifs, several new RNA ligands were synthesised and evaluated for their *in vitro* affinity, selectivity, and inhibition activity against four oncogenic miRNAs: miR-21, miR-18a, miR-148a, and miR-373. The molecular determinants of ligand-RNA binding were elucidated through molecular docking studies, aligning well with the observed structure-activity relationship. Prof. Duca's research has yielded promising results in glioblastoma cell lines and cancer stem cells, which are typically resistant to conventional chemotherapy, whereby demonstrating the therapeutic potential of targeting non-coding RNAs.[7]

These talks concluded the excellent program that showcased high quality research taking place in Switzerland and beyond and highlighted the latest cutting-edge developments in the field. To return to the theme of the meeting, a target is only undruggable until someone finds the right way to drug it and this symposium demonstrated we have an ever-expanding toolbox of diverse methods to help us do so. The future is bright (and not just due to improved fluorescent chemical probes)!

Received: March 4, 2025

[1] M. Bagka, H. Choi, M. Héritier, H. Schwaemmle, Q.T. L. Pasquer, S. M. G. Braun, L. Scapozza, Y. Wu, S. Hoogendoorn, *Nat. Commun*. **2023**, *14*, 3893, https://doi.org/10.1038/s41467-023-39657-1.
[2] L. Schneider, M. Kalt, S. Koch, S. Sithamparanathan, V. Villiger, F. Kradolfer, E. Slyshkina, S. Luber, M. Bonmarin, C. Maake, B. Spingler, *J. Am. Chem. Soc*. **2023**, *145*, 4534, https://doi.org/10.1021/jacs.2c11650.
[3] M. Słabicki, Z. Kozicka, G. Petzold, Y-D. Li, M. Manojkumar, R. D. Bunker, K. A. Donovan, Q. L. Sievers, J. Koeppel, D. Suchyta, A. S. Sperling, E. C. Fink, J. A. Gasser, L. R. Wang, S. M. Corsello, R. S. Sellar, M. Jan, D. Gillingham, C. Scholl, S. Fröhling, T. R. Golub, E. S. Fischer, N. H. Thomä, B. L. Ebert, *Nature* **2020**, *585*, 293, https://doi.org/10.1038/s41586-020-2374-x.
[4] Z. Kozicka, D. J. Suchyta, V. Focht, G. Kempf, G. Petzold, M. Jentzsch, C. Zou, C. Di Genua, K. A. Donovan, S. Coomar, M. Cigler, C. Mayor-Ruiz, J. L. Schmid-Burgk, D. Häussinger, G. E. Winter, E. S. Fischer, M. Słabicki, D. Gillingham, B. L. Ebert, N. H. Thomä, *Nat. Chem. Biol*. **2024**, *20*, 93, https://doi.org/10.1038/s41589-023-01409-z.
[5] S. Emmert, G. Quargnali, S. Thallmair, P. Rivera-Fuentes, *Nat. Chem*. **2023**, *15*, 1415, https://doi.org/10.1038/s41557-023-01249-3.
[6] A. Martin, P. Rivera-Fuentes, *Nat. Chem*. **2024**, *16*, 28, https://doi.org/10.1038/s41557-023-01367-y.
[7] C. Maucort, M. Bonnet, J.-C. Ortuno, G. Tucker, E. Quissac, M. Verreault, S. Azoulay, C. Di Giorgio, A. Di Giorgio, M. Duca, *J. Med. Chem*. **2023**, *15*, 10639, https://doi.org/10.1021/acs.jmedchem.3c00797.