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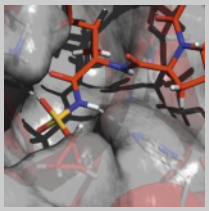

# Medicinal Chemistry and Chemical Biology Highlights

## Division of Medicinal Chemistry and Chemical Biology

A Division of the Swiss Chemical Society

## Peptide Therapeutics Forum 2023

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On September 4th and 5th, 2023 the Peptide Therapeutics Forum 2023 took place at the University Hospital Basel. The conference, organized under the umbrella of the Division of Medicinal Chemistry and Chemical Biology (DMCCB) of the Swiss Chemical Society (SCS), is an annual event with the aim of highlighting important new findings in peptide drug research as well as examples of successful development candidates.

The first day of the conference started with opening remarks from the scientific organization committee, consisting of Prof. Melpomeni Fani (University of Basel), Prof. Nina Hartrampf (University of Zurich), Prof. Roderich Süssmuth (Technische Universität Berlin) and Dr. Thomas Vorherr (Technische Universität Berlin). Then, ***Dr. Frank Osterkamp*** (3B Pharmaceuticals) presented the development of fibroblast activation protein (FAP)-targeting radiopharmaceuticals. He introduced 3B's technology platform and gave insights into the development of FAP-2286, a FAP-binding peptide coupled to a radionuclide chelator, which is currently in phase I/II clinical trials. Afterwards, ***Dr. René Thürmer*** from the Federal Institute for Drugs and Medical Devices (BfArM) gave an overview on current European regulatory expectations for synthetic peptides. He specifically emphasized the special role that peptides, which are positioned between synthetic small molecules and recombinantly expressed proteins, play from an analytical and regulatory perspective. ***Dr. Hans Maric*** (University of Würzburg) then presented on his group's approach to achieve proteome-wide specificity in ligand development by systematically mapping entire proteomes of intrinsically disordered protein regions and then leveraging naturally occurring endogenous proteome-wide target selectivity of linear binders. He introduced their microarray-based screening platform as well as a method for quantification in solution and demonstrated their application in multiple case studies. In the final presentation of morning, ***Prof. Ali Tavassoli*** from Curve Therapeutics and University of Southampton introduced their platforms for the intracellular generation and high-throughput screening of cyclic peptide libraries. Here, genetically encoded 'Microcycle' libraries are generated in cells and in microfluidic droplets, and the generated libraries are then tested in several high-throughput assays for the direct identification of functional inhibitors of various protein-protein and protein-DNA interactions. Several of those cyclic hexapeptides could be scaffold-hopped into more drug-like small molecules.

The afternoon session commenced with four presentations from students and postdocs. First, ***Héloïse Bürgisser*** (University of Zurich) disclosed a synthesis tag (SynTag) which enabled the chemical synthesis of the MYC transactivation domain, a very challenging and biologically relevant synthesis target. Afterwards, ***Dr. Elyse Williams*** (University of Zurich) presented on the development of (poly)phosphorylation methods using flow chemistry, which permitted the chemical synthesis and investigation of a synthetic MYC[1-84] library to allow correlation of PTMs with binding interactions. ***Dr. Xinjian Ji*** (EPFL) reported on novel methods for the synthesis and subsequent screening of large cyclic peptide libraries for addressing intracellular protein-protein interactions. Following up on the topic of cell permeability, ***Dr. Franz Waibl*** (ETH Zurich) presented computational modelling for membrane permeation of cyclic peptides and gave an introduction to *in silico* approaches such as conformer generation and molecular dynamics to study the conformations of cyclic peptides.

In the next invited lecture, ***Prof. Markus Kaiser*** (University of Duisburg-Essen) introduced peptide natural products as a starting point for the development of chemical probes. He illustrated this approach in three applications including the development of


Fig. 1. Dr. René Thürmer (left), Dr. Hans Maric (middle) and Prof. Ali Tavassoli (right) presented in the morning session of the first conference day.

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BacPROTACs from cyclomarins. Afterwards, ***Prof. Paramjit Arora*** (New York University) presented on the development of a Pan inhibitor for oncogenic Ras. His group designed a conformationally-defined proteomimetic that resembles a key binding surface of Sos, an effector protein of Ras. In the last presentation of the day, ***Dr. Virgínia Castillo Cano*** (Peptomyc) gave an overview of their development of the MYC dominant negative, cell-permeable mini-protein OMO-103. The potential anti-cancer therapeutic OMO-103 is the first MYC inhibitor to successfully complete a Phase I clinical trial. The first day of the conference ended with a very well-attended poster session as well as an apéro for all conference participants.

***Prof. Stephan Pless*** (University of Copenhagen) opened the second conference day with his group's work on membrane protein semi-synthesis using protein trans-splicing to investigate the impact of post-translational modifications on their regulation and function. They translated their techniques to live-cell experiments to investigate the functional and pharmacological consequences of phosphorylation on cardiac sodium channels. Next, ***Prof. Christian Ottmann*** (Eindhoven University of Technology), who joined us virtually, gave insights into their efforts to target 14-3-3 protein-protein interactions, which are involved in many devastating diseases such as cancer, Alzheimer's and Cystic fibrosis. More specifically, he reported on their efforts to develop molecular glues for protein-protein interaction stabilization. ***Dr. Søren Østergaard*** (Novo Nordisk) then presented state of the art methods for diabetes and obesity peptide drug development. While dual and triple agonist peptides are a recent trend in this field, he also presented on new array and screening technologies for binding assays and to achieve half-life extension. Following up on anti-obesity peptides, ***Prof. Krishna Kumar*** (Tufts University) then presented on modification of the incretin hormones GLP-1 and GIP, which are key regulators of glucose homeostasis. Both peptides are rapidly hydrolyzed by a DPP4 protease, and N-alkylation was presented as a strategy to overcome this deactivation mechanism. Remarkably, his group also developed small molecules capable of repairing the truncated, inactive GLP-1 peptide and restore the full-length functional bioactive compound. In the last presentation of the morning session, ***Dr. Gao Shang*** (MSD; Merck Sharp and Dohme) presented their remarkable 115 kg scale GMP campaign of the structurally complex cyclic peptide drug MK-0616. He described the discovery, development and manufacturing progress, and highlighted synthetic (large scale) challenges as well as solutions originating from novel synthetic approaches, biocatalysis and protein engineering. After the lunch break, ***Prof. Yu-Shan Lin*** (Tufts University) kicked off the afternoon session with an engaging presentation on a combination of molecular dynamics and machine learning for structure prediction of cyclic peptides. Using their novel approaches, they significantly reduced the computation time and can now provide simulation-quality cyclic peptide structure predictions in seconds, thereby eventually enabling a structure-based study of (cyclic) peptide properties.

Next, another four contributed lectures, which were selected from submitted abstracts, were presented: ***Dr. Mirja Harms*** (Ulm University) reported on the development of the CXCR4 antagonist EPI-X4 for therapy of cancer and inflammatory diseases through computational approaches and rational drug design. ***Dr. Rumit Maini*** (PepLib Boston) then presented on PepLib's Peptide Information Compression Technology (PICT) for the production of large cyclic peptide libraries for application in GPCR drug discovery. Afterwards, ***Prof. Young Do Yoo*** (Korea University) presented on their development of a new antimicrobial peptide (AMP), which was derived from the mitochondrial protein Romo1 and is reported to possess broad antimicrobial activity. Following up on the topic of cyclic peptide library technologies, ***Prof. Alessandro Angelini*** (Ca' Foscari University of Venice) introduced their novel combinatorial peptide platform for rapid selection and characterization of cyclic peptide structures, which is complementary to existing *in vitro* high-throughput technologies.

The closing, and keynote, lecture of the Peptide Therapeutics Forum was presented by ***Prof. Kim Lewis*** (Northeastern University), who joined us virtually. To combat the antimicrobial resistance crisis, new antibiotics have to be developed that avoid resistance development, and are active against dormant persister cells. To accomplish these goals, his group works on the development of new antibiotics with novel modes of action, such as teixobactin, clovibactin and darobactin.

The keynote lecture was followed by another conference highlight: the announcement of the 'Best Short Talk' and 'Best Poster' prizes. ***Dr. Mirja Harms*** (Ulm University) and ***Héloïse Bürgisser*** (University of Zurich) were both honored with the Helvetica Best Short Talk award. In addition, ***Dr. Tam Dang*** (Technische Universität Berlin) and ***Adeline Schmitt*** (ETH Zurich) were awarded *ChemBioChem* and *ChemMedChem* poster prizes by Chemistry Europe. Congratulations to all award winners! The organization committee (Prof. Melpomeni Fani, Prof. Nina Hartrampf, Prof. Roderich Süssmuth, Dr. Thomas Vorherr, and Céline Wittwer) would like to thank all sponsors and speakers, as well as poster and short talk presenters who contributed to the success of this two-day symposium.

Finally, as we look back on a successful Peptide Therapeutics Forum 2023, we already started planning the next event, which will take place on August 22nd and 23rd, 2024 at the Biozentrum Basel. We already look forward to seeing you there! Photographs were taken and provided by Nina Hartrampf.



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