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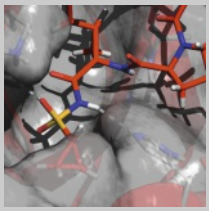

Medicinal Chemistry and Chemical Biology Highlights

Division of Medicinal Chemistry and Chemical Biology

A Division of the Swiss Chemical Society

News from the DMCCB – Congress Report from the Virtual EFMC-ISMC 2021

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The XXVI EFMC International Symposium on Medicinal Chemistry (EFMC-ISMC 2021), the largest congress of medicinal chemistry in Europe, took place as a virtual event, from August 29th to September 2nd, 2021. The congress was hosted by the Division of Medicinal Chemistry and Chemical Biology (DMCCB) of the SCS together with the European Federation for Medicinal Chemistry and Chemical Biology, EFMC. The involvement of the DMCCB goes back to the EFMC Council Meeting 2016 in Manchester, at which the application for hosting the event in Switzerland was presented and received a majority of votes. Basel was planned to be the host city in 2020 but it was finally decided, due to the pandemic situation, to postpone the congress to 2021 and run it as a virtual event – with a small in-person opening ceremony (Fig. 1) that was broadcast to all participants.

Fig. 1. Prof. Karl-Heinz Altmann (ETHZ) opening the virtual EFMC-ISMC 2021 from the Gehry auditorium at Novartis in Basel.

Despite the virtual format, the program remained largely unchanged with more than 80 lectures run in three parallel streams: Chemical Biology, Technologies and Drug Discovery Projects. The program was complemented by plenary lectures including six first disclosure lectures, eight prize lectures of EFMC awards, four lectures of invited speakers as well as poster sessions. All presentations were recorded and made available for a month after the event to registered participants. The organizers were delighted that more than 850 scientists registered and benefitted from the excellent program. A few highlights from the three presentation streams are described below.

Chemical Biology

The sessions in the Chemical Biology stream covered various topics ranging from ***Imaging tools*** over ***photochemistry*** to ***chemical approaches*** to ***stem cell differentiation***, but also ***carbohydrate recognition*** and ***RNA targeting by small molecules***.

Gonçalo Bernardes (University of Cambridge, UK) discussed in his talk novel probes for selective covalent modifications of specific amino acids in proteins. For example benzoylacrylamide reagents being able to selectively react with only one of several cysteines present in a protein, or sulfonylmethacrylate derivatives labelling only the most basic lysines in a given protein. These methodologies can serve to construct novel antibody-drug conjugates, or to study the function or interactions of proteins in vitro.

Pablo Rivera-Fuentes (ETHZ/EPFL, CH) presented chemical tools to study the redox potential of various organelles such as mitochondria (having an oxidizing potential) or the endoplasmic reticulum (with its reducing potential). The probes are fluorescent sensors of glutathione concentration and useful to study the stress response pathways that are activated upon disruption of redox homeostasis in these organelles.

Glycosylation plays a critical role in determining protein structure, function and stability. Carbohydrate binding enzymes recognize very specifically certain sugar residues and modulate their function. These carbohydrate-receptor interactions are often weak and the carbohydrate binding site shallow and difficult to inhibit with small molecules. Ulf Nilsson (Lund University, Sweden) described the discovery of potent carbohydrate-based inhibitors of Galectin-3 with oral bioavailability. The potency of the compounds was based on halogen bonds (the interaction of a halogen atom, *e.g.* Cl or Br, with a carbonyl amide of the protein backbone). Biophysical methods to study the thermodynamics of binding showed that halogen bond solvation and water assistance are important. The rational use of such halogen bonds in solvent exposed binding pockets might be applicable in other situations where classical methods are insufficient.

Technologies

The sessions in the technology stream covered various topics ranging from ***novel strategies and methods for drug discovery and development*** over ***cryo-electron microscopy as an emerging tool*** to ***innovative synthesis for medicinal chemistry***, but also

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artificial intelligence in drug discovery, prodrug strategies, biocatalysis** and **late-stage functionalization.

The Technology session focused on cryo-EM as an enabling tool for medicinal chemistry opened with the contribution of Stacey Southall (Sosei Heptares, UK) on G-protein coupled receptors (GPCRs) drug discovery. The advancements in the field of X-ray crystallography and, more recently, cryo-EM structure determination, contributed to the success of structure-based design in the GPCRs field. GPCRs structures are increasingly accessible by cryo-EM, which has become the go-to technique for active state receptors and is synergistic to X-ray crystallography for structure-base design. The two techniques support drug discovery by providing multiple high-resolution receptor structures that offer complementary insights into GPCR-ligand binding modes and structure-activity relationship.

In the session devoted to 'Expanding the chemical space through AI', Ola Engkvist from Astra Zeneca reported the impact Artificial Intelligence (AI) has in exploring the chemical space. He explained how generative models overcome the limitations of the traditional virtual screening approaches based on the enumeration/selection of large sets of molecular structures. Generative models efficiently navigate vast regions of chemical space owing to an efficient sampling strategy. They generate, on-demand, only small numbers of molecular structures that match user-defined multi-objective criteria. The exploration of chemical space is thus guided by bespoke multi-objective scores, encompassing predicted molecular properties and 3D molecular structure scores (*e.g.* docking). Overall, generative models address both efficiency and effectiveness of chemical space exploration, providing suitable molecular structures faster.

Behind the recent advances of AI in drug discovery is a 'perfect storm' of concurrent technological and social factors: exponentially increasing computational power, new neural network algorithms for modeling, and a general open-source approach to software development. Innovations developed in very distant fields, such as PyTorch from Facebook and TensorFlow from Google, could successfully be repurposed to chemistry applications. One outstanding example is natural language processing, a modeling technique developed initially for language translation and now used in synthesis prediction software[1] and generative algorithms.[2]

However, to realize the full potential of the AI-driven inverse design, a generative algorithm should appropriately consider synthetic feasibility. Although some solutions have been proposed in this regard, the synthesis-aware inverse design represents the next frontier of AI-driven chemical space exploration in the quest for novel drugs.

Drug Discovery Projects/First Disclosures

The sessions in the Drug Discovery stream covered multiple disease areas, including ***antivirals, antibiotics, drugs for neuroinflammation, heart failure, fibrosis and cancer***, as well as principles for ***inhaled drugs and tissue-specific delivery***. As always, the ***first disclosure session*** was a closely followed session, with the presentation of six new drug candidates:

Susanne Röhrig (Bayer) presented the elegant optimization of Asundexian (BAY 2433334), a potent inhibitor of Factor XIa (FXIa) currently in phase II clinical trials for the prevention and treatment of thromboembolic disorders, and involving more than 4000 patients.[3] The program started in 2010. As screening approaches did not deliver promising chemical starting points, an interesting protein structure-based *de novo* design approach based on tool compounds with undesired properties was used to generate a chemical hit structure with favorable physicochemical properties. Optimization guided by structure-based design led eventually to the identification of the highly potent first clinical candidate, which advanced to phase I clinical studies. Unfortunately, the compound showed a short half-life, a characteristic possibly related to the carboxylic moiety. Subsequent efforts were then focused on non-acidic moieties targeting the P2' pocket and resulted in the discovery of **BAY 2433334**.[4] The presentation elegantly illustrated the complexity of drug discovery requiring the parallel optimization of multiple parameters, and that a blend of creativity, strategic planning, experience and perseverance are necessary for being successful.

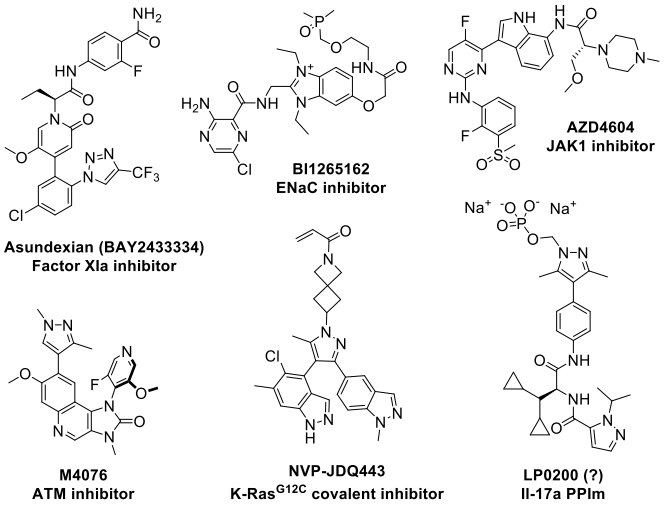

Fig. 2. Structure of clinical candidates presented at the First Disclosure session.

Jörg Kley (Boehringer Ingelheim) presented **BI1265162**,[5] an inhaled Endothelial Sodium Channel (ENAc) inhibitor that reached Ph. II clinical trials for cystic fibrosis. ENaC inhibition in these patients dilutes mucus and facilitates mucociliarly clearance, limiting the risk of bacterial infection and relieving symptoms. A low dose, low permeability, very high aqueous solubility and hydrolytic stability were key parameters for optimization. **BI1265162** was evaluated clinically as an add-on to CFTR modulators. Despite adequate safety and tolerability, a phase 2 study with 200 µg inhalations twice daily did not show efficacy and development was discontinued.

Magnus Nilsson (AstraZeneca) presented the discovery of **AZD4604**, a potent and selective Janus Kinase 1 (JAK1) inhibitor, as an inhaled treatment for respiratory disease. Optimization focused on selectivity to avoid the toxicity of pan-JAK inhibitors, and properties allowing administration *via* inhalation (crystallinity, melting point and lipophilicity) to avoid systemic immune suppression. **AZD4604** affinity is in the low-nanomolar range and it is >100 fold selective over a panel of 351 kinases. It displays good lung PK and target engagement, and will progress to Phase 1 clinical evaluation.

Kevin Dack (Leo Pharma) talked about the discovery of an orally active interleukin 17A (IL-17A) protein–protein interaction modulator for the treatment of psoriasis and other inflammatory diseases. While several anti-IL17a antibodies have been approved for the treatment of psoriasis, there are no orally bioavailable, small molecule IL-17A PPI modulators. The series was discovered by overlaying compounds from Leo Pharma and Pfizer, using structure-based design. Early hits were optimized into a clinical candidate, which was further elaborated into a more soluble and orally available phosphate prodrug of similar efficacy as anti-IL17A antibodies. The exact structure of the final clinical candidate (**LP0200**?) was not confirmed.

Thomas Fuchs (Merck KGaA) presented **M4076**, an ATM kinase inhibitor in Ph I clinical studies for the treatment of

cancer. ATM is a protein kinase that plays an important role in DNA damage repair and regulating the cellular response to DNA breakage. **M4076** is a stable atropisomer, and showed efficacy in several solid tumor models, especially when combined with radiotherapy.

Simona Cotesta (Novartis) presented the discovery of **NVP-JDQ443** a structurally unique, highly potent, selective and orally bioavailable $KRAS^{G12C}$ covalent inhibitor. KRAS is one of the most important oncogenes, but it is very difficult to target pharmacologically. The starting point of this program came from *de novo* design based on crystal structures of inhibitors bound to the inactive conformation of KRAS. Introduction of a spiro-piperidine resulted in an increased cellular activity while modulating the reactivity of the acrylamide warhead. **NVP-JDQ443** is under clinical evaluation in phase Ib/II clinical trials alone or in combination with SHP2 inhibitor or PD-1 blocker in patients with advanced solid tumors harboring the KRAS G12C mutation.

Another drug discovery highlight was the presentations of the two winners of the EFMC Prize for Young Medicinal Chemists or Chemical Biologists in Industry of 2020 and 2021.

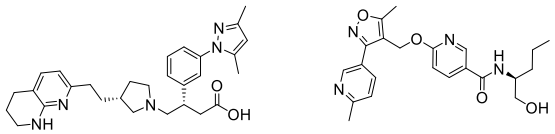

Fig. 3. Structures presented at the Prize Lectures for Young Medicinal Chemists or Chemical Biologists in Industry.

Niall Anderson (GSK, 2021 Prize Winner) presented the discovery of the inhaled small molecule **GSK3008348** (Fig. 3) which is a selective αvβ6 integrin inhibitor for the treatment of Idiopathic Pulmonary Fibrosis (IPF). The program used a pan αv integrin inhibitor as starting point and high integrin and hERG selectivity was achieved by several structural modifications including the introduction of a chiral pyrrolidine linker. **GSK3008348** was advanced to phase IIa clinical trials in patients with IPF and target engagement has been demonstrated by positron emission tomography (PET).

Giuseppe Cecere (Roche, 2020 Prize Winner) presented the discovery of selective $GABA_A$ α5 Positive Allosteric Modulators (PAMs). The program started from selective $GABA_A$ α5 Negative Allosteric Modulators (NAMs) originating from an internal program. Small structural variations led to an interesting 'NAM to PAM switch' while maintaining high selectivity and desired physicochemical properties. The actual clinical candidate RG7816 was not disclosed in the Prize Lecture, but the advanced lead compound **RO7015738** (Fig. 3) and its efficacy on repetitive behaviour in phenotypic and genetic models of ASD was shown.

The excellent highlights from the three work streams Chemical Biology, Technology and Drug Discovery Projects nicely demonstrate the broad coverage of topics as well as scientific excellence of the EFMC-ISMC 2021. This year there was no other option than to run the meeting in a virtual formal but luckily, there will be a second chance for Switzerland: The EFMC-ISMC 2026 will take place in Basel and the local organizing committee already looks forward to welcoming all participants in person.

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