doi:10.2533/chimia.2020.303 Chimia 74 (2020) 303–304 © Swiss Chemical Society

Conference Report

2nd Anglo-Swiss Symposium on 'Using Chemical Biology to Identify New Targets for Medicinal Chemistry', Basel, 4th February, 2020

Sevan Habeshian* and Mischa Schüttel*

*Correspondence: S. Habeshian, M. Schüttel, E-mail: sevan.habeshian@epfl.ch, mischa.schuttel@epfl.ch; Institute of Chemical Sciences and Engineering, Ecole Polytechnique Fédérale de Lausanne (EPFL), Laboratory of Therapeutic Proteins and Peptides, BCH 5201, Av. F.-A. Forel 2, CH-1015 Lausanne

The 2nd Anglo-Swiss Symposium – jointly organized by the Division of Medicinal Chemistry and Chemical Biology (DMCCB) of the Swiss Chemical Society (SCS) and the Biological & Medicinal Chemistry sector of the Royal Society of Chemistry (RSC) – took place earlier this year at the University of Basel. This second edition of the Anglo-Swiss Symposium aimed to reinforce the links between chemical biology, medicinal chemistry and agricultural chemistry. The audience was comprised of an equal number of participants from industry and academia. Of the 135 attendees, 75% were members of the SCS or RSC.

Eight keynote speakers showed how chemical biology can be used to identify new targets for medicinal chemistry, with exciting topics such as drug discovery platforms, technologies to identify potential therapeutic targets, drug conjugates and pharmacophore-directed retrosynthesis.

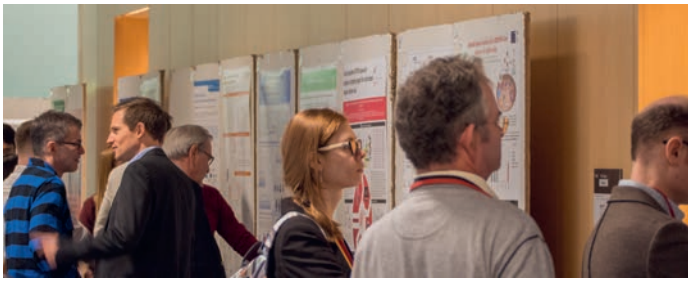
The opening talk was given by ***Dr. Jonas V. Schaefer*** (Novartis), a research investigator in Chemical Biology & Therapeutics (CBT) focusing on encoding library technologies (ELT). He offered insights into major challenges in drug development, discussing the long timeframes, cumulative costs of up to 3 billion dollars, and complex diseases, summing up with "let's face it, low hanging fruits are gone". Instead, finding new therapeutic solutions requires a cross talk between disciplines. Currently, his ELT technology challenges the gold standard 'high-throughput screening' with its one well, one compound strategy, since dozens of parallel target screens may be performed by simultaneously screening significantly higher numbers of compounds (1.7 billion) with one single DNA-encoded library test tube. These libraries have found their application in target validation, assay development, pharmacophore mapping and in the identification of alternative modes of action. Nevertheless, a few limitations were mentioned by Dr. Schaefer, such as restricted target choices (no DNA/RNA-binding targets), screening set-up (functional/phenotypical read-outs), and solubility issues during the hit validation process.

Prof. Yimon Aye (EPFL) followed with a talk about electrophile signalling in cells, which can be exploited to find pathways that shed light on biological function. While highly reactive electrophilic species behave promiscuously in cells, her lab has developed a strategy called T-REX (targetable reactive electrophiles and oxidants) that allows for the selective modification of proteins. The technique can be applied to bacterial and mammalian cells, and in organisms such as *Caenorhabditis elegans* and zebrafish. Professor Aye demonstrated the utility of the method by highlighting research on the multiple sclerosis drug Tecfidera (dimethylfumarate) and its modulation of immune cells, as well as the downregulation of AKT3 by modification with endogenous electrophiles.

After a brief coffee break, ***Prof. Maja Köhn*** (University of Freiburg) described the work of her lab in the area of phosphatase enzymes, which remove phosphate groups from proteins and are important for a variety of biological processes. While kinases, which phosphorylate proteins, have been heavily researched, phosphatases have received far less attention. The group developed a selective peptide activator for the Ser/Thr phosphatase PP1 and used it to investigate the dephosphorylation of two kinases, MEK and ERK. They found that PP1 directly dephosphorylates MEK and indirectly dephosphorylates ERK through a Tyr–phosphatase-mediated pathway. PP1 is also important in cardiomyopathy, where receptors in heart cells are hyperphosphorylated, thus leading to a large flux of Ca^{2+} ions. PP1 activation was shown to normalize calcium cycling, and therefore could be a useful target for the treatment of heart conditions.

Next, ***Prof. Kristian Strømgaard*** (University of Copenhagen) discussed the inhibition of PDZ domains of intracellular auxiliary proteins of surface receptors. The first example given was for PSD-95 protein, for which many high-throughput screens failed to produce any inhibitors. A weak peptide inhibitor was eventually found. When two molecules of the peptide were tethered together with a flexible spacer, the dimeric molecule could bind to two adjacent PDZ domains of PSD-95, and low nanomolar inhibition was possible. The compound was further optimized to be stable in plasma and permeable through the blood-brain barrier. A similar approach was then used for other PDZ–domain-containing proteins Mint2 (potential Alzheimer's target) and Syntenin (oncological target), wherein low nanomolar inhibitors were again found. These inhibitors were able to elicit the desired biological responses in the respective disease models.

Following Prof. Strømgaard's talk, lunch was provided, during which time attendees were able to visit the poster session. Roughly 20 posters were presented, covering a variety of chemi-



cal biology topics, ranging from the development of inhibitors for proteins of therapeutic interest to the synthesis of various building blocks for screening libraries.

Starting off the afternoon session, ***Prof. Stephan Sieber*** (Technical University Munich) detailed his work in the development of tools to fight multiresistant bacteria. The group developed pyridoxyl phosphate (PLP)-based probes to mine the bacterial proteome for potential protein targets. Using four analogues of the probe, they were able to identify 73% of the known PLP targets in *Staphylococcus aureus*. Alanine racemase and IU9 were chosen as model enzymes for investigation and characterization. In a separate project, known human kinase inhibitors were screened for antibacterial activity. An optimized hit, PK150, was able to kill resistant bacteria, reduce biofilms compared to rifampicin, and showed no resistance development. A reactive probe based on the inhibitor was developed, and its targets were identified as MenG, which is inhibited, and SpsB, which is stimulated, in the presence of the compound.

The second industry speaker, ***Dr. Mark Frigerio*** (Abzena), spoke about the strategy of antibody drug conjugates (ADC) and its goal of expanding the therapeutic window between the maximum tolerated and minimum effective dose of drug. As indicated throughout his presentation, current challenges in developing new ADCs are the choice of suitable targets and payloads. Further challenges are heterogeneity, stability, poor safety profiles and suboptimal pharmacokinetics. To counter some of these, he introduced technologies that allow site-specific conjugation of the payload with a narrower distribution. Additionally, other strategies, such as steric shielding within the FcγR region, may improve toxicity outcomes. "ADC is still a maturing field" he said, and this technology may yet find its application in oncology as well as other fields such as Alzheimer's disease.

After the second coffee break, ***Dr. Filip Roudnicky*** (F. Hoffmann-La Roche) presented his team's work on human pluripotent stem cells (hPSCs) and genome editing. CRISPR/Cas9 technology was applied to introduce a claudin 5 (CLDN5) transcriptional reporter in high resistance retinal endothelial cell barrier as a surrogate marker. This allowed the identification of the gene and protein involved in causing the high barrier resistance in endothelial cells (ECs). This finding was validated by applying a combined approach of genomics, proteomics *in vitro*, and the follow up *in vivo* functional assay using a chemogenomic library (SPARK). This revealed potent chemical compounds that improve barrier integrity in ECs and opened the door for a therapeutic program against retinal vascular leaked disease, where no cure currently exists.

The closing presentation of the conference was given by ***Prof. Daniel Romo*** (Baylor University), who shifted from biology-orientated topics towards the total synthesis of natural products. Traditionally, the total synthesis of a compound is first developed before the generation of new derivatives with more potent biological activity. His approach focuses on the opposite by following a pharmacophore-driven retrosynthesis (PDR), which "brings function to the forefront of synthesis." This idea develops structure-activity relationship studies through the natural product synthesis process. With their PDR approach, his group was able to identify active products that were simpler in structure compared to the initial natural product. The target natural products were never actually synthesized, since the simpler precursors already identified the necessary pharmacophores.

After the talks, the winners of the poster prizes were announced. ***Simon Schnell*** (University of Zurich) won for his poster entitled '3-bromotetrazine: Labelling of Macromolecules via Monosubstituted Bifunctional s-Tetrazines', and ***Chiara Borsari*** (University of Basel) won for 'Targeted Therapy for Neurological Disorders: A Novel, Orally Available, and Brain-Penetrant mTOR inhibitor (PQR626)'. As a prize, both will receive free admission to the EFMC-ISMC conference in September 2020, each worth 410 Euros. A networking aperitif followed, where conference attendees were able to socialize while enjoying food and drinks.

The second edition of the Anglo-Swiss Symposium, attended by over hundred attendees from academia and industry, was a great success. Many thanks should be given to the organizing committee, the Swiss Chemical Society, the Royal Society of Chemistry, as well as to the corporate sponsors, for assembling a group of interesting speakers and making such a successful conference possible.

Received: March 7, 2020