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Conference Report

The Swiss Summer School in Chemical Biology 2016 in brief

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The Swiss Summer School 2016 in Chemical Biology of the Swiss Chemical Society (SCS) was held in Villars sur Ollon from August 21st to August 25th. This year, the Summer School brought together five outstanding speakers, Profs ***Scott Snyder*** (University of Chicago), ***Reza Ghadiri*** (Scripps Research Institute), ***Ling Peng*** (University of Marseille), ***Jonathan Hall*** (ETHZ) and ***Xiaoyu Li*** (The University of Hong Kong). Their research interests span a broad spectrum of chemical biology, namely natural product synthetic, cyclic peptides, dendrimers for medical applications, RNA-targeting and oligonucleotide-based drugs and as well as DNA-encoded chemistry. Each speaker had three 75 min talks to present the state of the art and their own research in each area. Around 40 students attended the summer school. Poster sessions and short talks sessions allowed the students to present their own work.

Reza Ghadiri

Prof. Reza Ghadiri opened the meeting Sunday evening with an increasingly hot topic, the microbiome. Indeed, more and more studies show that our microbiome acts like a complete organ in itself, it is related to very unexpected aspects of human health such as mood and it might be involved in the origin of some diseases. As a corollary of this talk, Prof. Ghadiri presented the influence that cyclic D,L-α peptides can have in the microbiome. These peptides were shown to be able to retune the microbiome of overweighed mice,[1] by modulating the levels of the different bacteria present in the microbiome. In his next talk, Prof. Ghadiri showed how to reprogram enzymes by using small molecules. Indeed by attaching a small molecule inhibitor through an oligonucleotide strand to an enzyme of interest, his group was able to switch on and off an enzyme by addition or removal of the complementary oligonucleotide strand. Since this method relies on enzymes that act catalytically, signal amplification gives a wide range of detection. Furthermore, since inhibitors can be found for most enzymes, this method is widely applicable to detect or reprogram an enzymatic activity.[2] The last talk focused on protein nanopore-based DNA sequencing. Prof. Ghadiri took us through the history of the technology, while highlighting the key experiments, which proved the method to be viable. Nanopore-based sequencing offers the advantage to read native sequence without any PCR amplification and proceeds also faster than technologies presently employed.[3] With this technology he hopes that genome sequencing, which costs about $1000 today, will become even cheaper and that many new applications will arise. High-throughput DNA sequencing has become a game-changer in many fields and has allowed for new technologies to emerge.

Xiaoyu Li

Prof. Xiaoyu Li takes advantage of the encoding power of DNA and uses it to encode chemical libraries. The first lecture of Prof. Li drew a quick portrait of the state of the art in terms of encoding methods for DEL (DNA encoded chemical libraries). During this talk, he covered the whole field, starting with the first ideas by Brenner and Lerner, reviewing all the DNA encoding strategies, which include pre-encoding or direct encoding where building blocks are already DNA-labeled. This first talk was closed with a summary on dynamic DNA encoded chemical libraries developed by his group,[4] where DNA encoding is based on reversible dynamic reactions. The second talk focused on protein labeling and DEL-selection. A general method used for target identification is to do a pull-down experiment using a reactive probe and a tag. Prof. Li presented a technology named DPAL (DNA programmed affinity labeling) where a short DNA sequence is responsible for photo crosslinking to the protein and another DNA sequence bearing the desired tag.[5] This technique brings versatility (tags can easily be exchanged and even multiplexing is achievable) and can be used in DEL selection. Prof. Li developed a versatile method to screen DEL against native proteins and therefore overcome the limitations of other DEL selection method only based on affinity selection with recombinant proteins.[6] In a last presentation, Prof. Li presented his group's latest efforts in target identification working on Terazosin using methods developed in his lab.

Jonathan Hall

Prof. Jonathan Hall started his lecture series by presenting RNA as a target but also as a potential drug. The talk started by emphasizing the fact that oligonucleotide-based drugs have been first mentioned in PNAS[7] in 1978. The disclosure of RNAi in 2001 relaunched the hope to see an oligo drug on the market since it induces a very precise cleavage of mRNA. Nevertheless, pharmacokinetic properties of oligonucleotides remain problematic and make them problematic as drugs. Despite these hurdles, oligos are still used and remain cheaper than new generation small molecule inhibitors and are therefore still being investigated as potential drugs.[8] Prof. Hall's following talk demonstrated how to expand the possibilities of an oligonucleotide drug. Indeed by targeting the same RNA at different stages of its maturation, various effects can be achieved and the outcome of the inhibition can be very different.[9] During his last presentation he went beyond simple oligonucleotide interactions, as oligonucleotide-based drugs can also target proteins. Prof. Hall's lab is currently working on such cases where an oligonucleotide disrupts a protein–oligonucleotide interaction, rather than working through an antisense mechanism.[10] They also recently obtained the same effect using a small molecule.[11]

Prof. Ling Peng presented in her first lecture the major concepts of dendrimers and their synthesis as well as the advantages of dendrimers as drug delivery agents. Then, she

Ling Peng

presented an overview of siRNA as new therapeutic agents concluding with her work on encapsulation of siRNA in dendrimers for cancer treatment.[12] During her second talk she spoke about the advantages of synthesizing dendrimers by self-assembly to facilitate formation of nanomicelles. She then showed that siRNA could be encapsulated in the inner space of the nanomicelles given rise to a much greater RNAi response than that produced with conventional siRNA. She concluded this talk by showing that it is possible to encapsulate drugs in the inner space of the nanomicelles for specific drug delivery.[13] Her final talk focused on functionalization of the aforementioned nanomicelles for multimodal imaging and teranostics applications.

Scott Snyder

Prof. Scott Snyder showed how to build diversity in the synthesis of natural products, Each of the lectures was organized around one family of natural products from molecules synthesized in his lab. The first lecture focused on the generation of halogenated natural products. Prof. Snyder started his presentation with the total synthesis of (–)-napyradiomycin A1. While trying to form napyradiomycin B by a chloronium-induced cyclization[14] they discovered a new reagent for bromonium-induced polyene cyclizations.[15] He presented several total syntheses of the *Laurencia* family using this new methodology. In his second lecture he presented methods to access different families of alkaloids, showing how sometimes the most intuitive disconnections do not always lead to the expect products as in the formation of some unexpected dimeric compounds.[16] And for his final intervention, Prof. Snyder presented synthetic approaches for the formation of oligomeric natural products.[17] The emphasis was put on how to design suitable starting materials to access as many final products as possible. One easy way to achieve this goal is to take inspiration from nature and build oligomeric entities, Prof Snyder showed here a wide range of compounds that would not be considered as oligomeric at first sight but that can be accessed through oligomerisation. The use of oligomers allows for quick generation of diversity, which is of major interest for the generation of natural product inspired chemical libraries.

The week was concluded with a dinner around a typical Swiss raclette, where the Best Presentation Award and Best Poster Awards were given. The best presentation award was given to ***Jérémy Boilevin*** (Reymond Lab, University of Bern) for his talk on lipid linked oligosaccharides. The Best Poster Awards were both given to pairs of students working on related projects: ***Vanessa Carle*** and ***Camille Villequey*** (Heinis Lab, EPFL) for their work on phage-encoded peptide libraries, as well as to ***Jacques Saarbach*** and ***Eric Lindberg*** (Winssinger Lab, University of Geneva) for their work on templated chemistry. The gratitude of the participants was warmly conveyed to the Organizing Committee and the sponsors of the event and to the NCCR in Chemical Biology, which sponsored the registration of one student. The travel grant of the Division of Medicinal Chemistry and Chemical Biology (DMCCB) of the Swiss Chemical Society allowed the participation of Jacques Saarbach. This summer school was financially supported by the Interuniversity Graduate Program in Chemistry Bern-Zürich, the EPFL, the University of Fribourg, the KGF (BASF, Syngenta, Novartis, Roche) and Actelion Pharmaceuticals Ltd.

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[1] a) Y. Zhao, A. S. Black, D. J. Bonnet, B. E. Maryanoff, L. K. Curtiss, L. J. Leman, M. R. Ghadiri, *J. Lipid Res.* **2014**, *55*, 2053; b) Y. Zhao, T. Imura, L. J. Leman, L. K. Curtiss, B. E. Maryanoff, M. R. Ghadiri, *J. Am. Chem. Soc.* **2013**, *135*, 13414.

[2] a) N. C. Gianneschi, M. R. Ghadiri, *Angew. Chem. Int. Ed. Engl.* **2007**, *46*, 3955; b) A. Saghatelian, K. M. Guckian, D. A. Thayer, M. R. Ghadiri, *J. Am. Chem. Soc.* **2003**, *125*, 344.

[3] a) N. Ashkenasy, J. Sanchez-Quesada, H. Bayley, M. R. Ghadiri, *Angew. Chem. Int. Ed. Engl.* **2005**, *44*, 1401; b) J. Chu, M. Gonzalez-Lopez, S. L. Cockroft, M. Amorin, M. R. Ghadiri, *Angew. Chem. Int. Ed.* **2010**, *49*, 10106; c) S. L. Cockroft, J. Chu, M. Amorin, M. R. Ghadiri, *J. Am. Chem. Soc*. **2008**, *130*, 818; d) J. Sanchez-Quesada, A. Saghatelian, S. Cheley, H. Bayley, M. R. Ghadiri, *Angew. Chem. Int. Ed. Engl.* **2004**, *43*, 3063.

[4] G. Li, W. L. Zheng, Z. T. Chen, Y. Zhou, Y. Liu, J. R. Yang, Y. Y. Huang, X. Y. Li, *Chem. Sci.* **2015**, *6*, 7097.

[5] Y. Liu, W. L. Zheng, W. Zhang, N. Chen, Y. Liu, L. Chen, X. Z. Zhou, X. S. Chen, H. F. Zheng, X. Y. Li, *Chem. Sci.* **2015**, *6*, 745.

[6] P. Zhao, Z. Chen, Y. Li, D. Sun, Y. Gao, Y. Huang, X. Li, *Angew. Chem. Int. Ed.* **2014**, *53*, 10056.

[7] X. Liu, C. Liu, C. Chen, M. Bentobji, F. A. Cheillan, J. T. Piana, F. Qu, P. Rocchi, L. Peng, *Nanomed. Nanotechnol. Biol. Med.* **2014**, *10*, 1627.

[8] H. L. Lightfoot, J. Hall, *Nucleic Acids Res*. **2012**, *40*, 10585.

[9] B. Guennewig, M. Roos, A. M. Dogar, L. F. Gebert, J. A. Zagalak, V. Vongrad, K. J. Metzner, J. Hall, *RNA* **2014**, *20*, 61.

[10] M. Roos, M. A. Rebhan, M. Lucic, D. Pavlicek, U. Pradere, H. Towbin, G. Civenni, C. V. Catapano, J. Hall, *Nucleic Acids Res.* **2015**, *43*, e9.

[11] M. Roos, U. Pradere, R. P. Ngondo, A. Behera, S. Allegrini, G. Civenni, J. A. Zagalak, J. R. Marchand, M. Menzi, H. Towbin, J. Scheuermann, D. Neri, A. Caflisch, C. V. Catapano, C. Ciaudo, J. Hall, *ACS Chem. Biol.* **2016**, *11*, 2773.

[12] X. Liu, C. Liu, C. Chen, M. Bentobji, F. A. Cheillan, J. T. Piana, F. Qu, P. Rocchi, L. Peng, *Nanomed.* **2014**, *10*, 1627.

[13] X. Liu, J. Zhou, T. Yu, C. Chen, Q. Cheng, K. Sengupta, Y. Huang, H. Li, C. Liu, Y. Wang, P. Posocco, M. Wang, Q. Cui, S. Giorgio, M. Fermeglia, F. Qu, S. Pricl, Y. Shi, Z. Liang, P. Rocchi, J. J. Rossi, L. Peng, *Angew. Chem. Int. Ed*. **2014**, *53*, 11822.

[14] S. A. Snyder, Z. Y. Tang, R. Gupta, *J. Am. Chem. Soc.* **2009**, *131*, 5744.

[15] S. A. Snyder, D. S. Treitler, *Angew. Chem. Int. Ed.* **2009**, *48*, 7899.

[16] T. C. Sherwood, A. H. Trotta, S. A. Snyder, *J. Am. Chem. Soc.* **2014**, *136*, 9743.

[17] a) S. A. Snyder, A. M. ElSohly, F. Kontes, *Nat. Prod. Rep.* **2011**, *28*, 897; b) S. A. Snyder, A. Gollner, M. I. Chiriac, *Nature* **2011**, *474*, 461.