The NCCR Chemical Biology just completed its sixth year of operation of a maximum of twelve years. Being halfway through our existence is a good time to reflect on what we have accomplished so far and define the challenges that remain for the future.

The results from our last site visit by the Swiss National Science Foundation (SNSF), although still only delivered orally, were highly positive. A panel of international scientific experts recognized the progress made over the last two years in all aspects of our mission and confirmed that we are on the right track towards building an internationally recognized center of excellence in chemical biology.

Our initial goal was to create a network of scientists from different disciplines - chemistry, biochemistry, cell biology, and physics - that collaborate with each other to create novel technologies and address important biological questions. This strategy clearly provides part of the added value that is expected from an NCCR. In the last couple of years, we have some very good examples of this exchange and how increased communication can guide us to find solutions. These collaborations are not just scientists from each discipline doing their part, but a deeper exchange that leads to a high educational and training benefit.

NCCRs are funded through three 4-year periods and when we entered into our second phase, we decided to concentrate our efforts on five projects and our main technology platform, ACCESS. As you will read in this newsletter with the interview of our project leaders or investigators, all our projects are progressing very well.

Next year, we will submit a pre-proposal for the final 3rd phase of the NCCR, including a plan to sustain our progress, improve our visibility and innovation. Furthermore, we will develop a long-term vision of how our efforts will be maintained when we will no longer receive funding from the SNSF. These challenges will be met by our leadership, including our project leaders, our new co-Director, Christian Heinis, and the new steering committee.

Personally, I am very sad to see Kai Johnsson, NCCR co-Director until the end of November 2016, leave us in a few months. He has been a fantastic collaborator and friend over the years. I want to thank him for the tremendous investment of time and energy he has put into setting up this NCCR realm.

I would like to sincerely thank all of you for your dedication and hard-work doing creative science, which is what makes us successful. Best wishes for a wonderful holiday season!

Howard Riezman
Director of the NCCR Chemical Biology
Professor at the Department of Biochemistry, University of Geneva
**BIOORTHOGONAL CHEMISTRY**

Five research teams join efforts to use bioorthogonal chemistry answers to develop novel chemistries to specifically modify or influence biological processes, as well as to deliver novel molecules to expand the chemical diversity of small molecules.

**Interview with Professor Jérôme Waser, Principal Investigator**

Hypervalent iodine compounds are not found in biological systems and combine high reactivity with stability in presence of water and most functional groups present in biomolecules. We therefore consider that they have an important potential to make a strong impact into the field of biomolecule functionalization.

**WHAT DO YOU SEE AS THE MAJOR ACHIEVEMENTS OF THIS PROJECT OVER THE PAST 6 YEARS, AND FOR THE LAST YEAR IN PARTICULAR?**

The first key breakthrough was in fundamental chemistry in 2013-2013. At that time, we discovered that the Ethynylbenziodoxole (EBX) reagents used in our laboratory were reacting extremely fast with thiol anions to give the corresponding thioalkynes. This transformation was finished in a few seconds and was selective for sulfur nucleophiles in presence of many other reactive functional groups, such as amines, alcohols or electron-rich aromatic rings. We were also able to elucidate an unprecedented concerted reaction mechanism which rationalized the high rate of the reaction.

Whereas this first breakthrough was done exclusively in our laboratory (LCSO), the NCCR Chemical Biology network was truly instrumental to bring this project to the interface between biology and chemistry. Indeed, we were indeed very interested in testing the method for the functionalization of cysteines in proteins, but were lacking the expertise for working with biomolecules. In this respect, an important proof of concept was first realized by the van der Goot group, which demonstrated that EBX reagents were indeed highly efficient to block cysteines in proteins. However, using EBX reagents only as "proteotyping" reagents was a little bit disappointing. The first truly exciting application was then developed by the Adibekian group in 2015, who used one of the synthesized reagents (JW-RF-020) for the proteome-wide profiling of targets of cysteine-reactive small molecules. This reagent, which bears also a reactive azide group for further functionalization, was superior both in selectivity and efficiency to state-of-the art iodoacetamide-based reagents. It allowed the identification of a unique set of cysteine-reactive proteins. One of them, casen kinase I gamma could be subsequently identified as a target of the natural product curcumin, which could help to better understand the anti-cancer activity of this compound as this protein is phosphorylating Akt, a known oncogene.

With the proof of concept established for the use of EBX reagents for biomolecule functionalization, this last year has been focused on new exciting directions. Our laboratory has continued to work on new reagents and the understanding of the reaction in collaboration with the Fierz group. Water soluble reagents are now available. Together with the Adibekian group, we are now also developing EBX reagents as selective inhibitors of proteins instead of broadly reacting reagents. Applications of biomolecules can only be extended to the functionalization of biomolecules. Indeed, any transformation involving the functionalization of sulfur atoms can profit from the amazing reactivity of EBX reagents. For example, the Matte group recently used EBX reagents as terminators for the polymerization of cell-penetrating polypeptides.

**HOW WAS THE PROCESS OF THE CONCEPTION AND DEVELOPMENT OF THE HYPERVALENT IODINE REAGENTS? DID IT START OUT FROM AN IDEA OR WAS IT AN ACCIDENTAL FINDING? WHAT WERE THE ROADBLOCKS AND HOW DID YOU DEAL WITH THESE?**

As often in science, a mix of luck and design led to success. The project started purely on paper, with a fundamental challenge: can we transform an alkyne, an inherently nucleophile entity, into a electrophile? That was the first fundamental question of reactivity, which are those my group is most fascinated with. However, it was only in 2011 that we found potential for applications, as alkyynes are frequently used in synthetic chemistry, materials science and chemical biology. Before our work, only less stable alkynyliodonium salts have been used for this purpose, but we were not able to develop useful new transformations with these very sensitive compounds. It is then that we first used more stable cyclic reagents. After that, Dr. Reto Frei had the idea to use it to functionalize thiol, and it worked like a charm. Kick-off for the biomolecule functionalization was a presentation by Matthieu Blanc from the van der Goot group working on palmitoylation during a NCCR meeting, after which we just decided to try it! Luck, unexpected opportunities, design and surprises continue since then to bring the project forward.

**WHAT DO YOU SEE AS THE PRIME ADVANTAGES OF THESE REAGENTS?**

The unique combination of high reactivity with good stability, and the extreme "love" for sulfur, which make them ideally suited for the functionalization of biomolecules.

**WHERE DO YOU SEE THE MAJOR APPLICATIONS OF THESE REAGENTS, AND WHERE COULD THEY HAVE THE BIGGEST IMPACT?**

In synthesis, biomolecular labelling or functionalization.

Small molecules have always been of interest in chemistry and biology because of their ability to exert powerful effects on the functions of macromolecules that comprise living systems. This project work package focusses on the development and implementation of novel chemistries to access uncharted diversity space, develop novel novel reagents and methods that can be applied to interrogate or manipulate biologically relevant systems.

A central theme of "Bioorthogonal chemistry" is to develop on the one hand innovative strategies in organic synthesis to expand small molecules structural/ functional repertoire and on the other hand explore commercially available space and to provide the required synthetic chemistry expertise to follow up on identified hits, identify inhibitors and perform medicinal chemistry follow-ups. Within that frame, a DNA-encoded chemical library (DECL) automated screening platform, complimentary to the high throughput screening (HTS) platform ACCESS, has been developed and is in use.

Reactions that are suitable to modify proteins with chemical reporters have attracted significant attention over the past decade and this project aims to advance bioorthogonal reactions to tag cysteines or to report on biochemical process through luminescence and templated reactions, so as to provide a window into the function of these proteins through biophysical and mechanistic studies. Technological breakthroughs such as the expressed protein ligation have enabled the introduction of fluorophores, NMR probes and other reporters into complex proteins directly or permitted the targeting of a functionality in a chemoselective manner.

The scope and limitations of current technologies vary significantly in terms of bioorthogonality, compatibility with complex cellular environment, yield and selectivity. Indeed, compared to the situation with native purified proteins, the repertoire of chemical transformations is dramatically reduced in more complex settings such as lysates and even more in live cells. These techniques are well entrenched in ongoing projects: the labs of Adibekian and Wissinger recently reported the synthesis and cellular targets of decoyephosphatins, a natural product with anticancer properties and the González-Talalt and Wissinger labs reported imaging of miRNA in live vertebrates (zebrafish). These examples illustrate the potential of existing methodologies but also represent clear opportunities that arise from broadening the scope of bioorthogonal reactions.

**WHAT WOULD BE YOUR NEXT "DREAM" COMPOUND OR REACTION?**

We want to push the dream in two extreme directions: develop on the one hand reagents with very high general reactivity which are useful to functionalize extensively biomolecules and on the other hand highly selective reagents, which will target a single protein in the cell. Preliminary results obtained by the Adibekian group indeed indicate that such a dream may become reality one day.
**CELLULAR ENTRY AND NOVEL MEMBRANE PROBES**

With a focus on methods development with regard to biomembranes, five research teams strive to establish conceptually innovative approaches to cross membrane barriers and enter cells, and to image biologically important properties of biomembranes that are otherwise difficult to detect.

Interview with Professor Stefan Matile, Project Leader

Can you shed light on the project and describe the selected approaches used? For imaging, we have introduced fluorescent probes that change color like lobsters during cooking or the chemistry of vision. We were thus surprised to realize that this winning approach had not been used before to create new fluorescent probes and just thought we should try and see what we can get.

For uptake, we aim to apply lessons from proteomics analysis from the Adibekian group. This could be a game-changer, we will see.

Did you face any experimental or technical roadblocks? How did you deal with it? With ambitious and innovative research, there is always plenty of this. For example, some time ago we realized that both bright and mechanosensitive probes would have to be introduced in our lab.

New adventures always start with the design, the great ideas, with input from everyone, from all directions. Then comes synthesis, the creation of new matter, with organic chemists taking the lead. The evaluation of the new tools then requires expertise from biorganic chemistry, membrane biophysics, device engineering, molecular modeling and ultrafast photophysics to ultimately move on toward cellular biology. It is just so cool to have most of these expertise unified in one NCCR and see students from different background working together to ask the really important questions, learning from each other. It is this added value that makes the NCCR so special. We are all immensely grateful to be part of it, enjoy so much what we are doing and couldn’t do it without the NCCR.

What do you think is going to be the greatest impact or possible applications of the project for life sciences? Currently I would bet on strain-promoted uptake, but you always expect most from what is newest. General, reliable and efficient cellular uptake is one of the central current challenges in chemistry and biology. It would be just wonderful if we would find the transporters everybody will use for delivery in the future, also with regard to public health. Although most exciting and timely, mechanosensitive membrane probes target a clearly smaller community.

What is your vision about the next generation of biomembrane probes? All I can say at this point is that we plan to apply the lessons learned to fluorospheres that have marked the history of Switzerland, with regard both science and economy, literally contributing to our current quality of life. Pertinent literature implies that they have all it takes to also land a big hit as flipper probes.

**CELLULAR ENTRY AND NOVEL MEMBRANE PROBES**: WHAT IS THIS PROJECT ABOUT?

This project aims to establish conceptually innovative approaches to cross membrane barriers and enter cells. The chemistry of cell-penetrating poly(disulfide)s (CPDs) that can grow directly on substrates of free oligomers to cross the cell membrane under conjugation, are studied to maximize the potential to solve this problem. Namely, the “fluorescent flippers”, a new concept that allows to insert large and bright molecules into oligomeric probes to really feel the environment and also shine when twisted out of conjugation, are studied to maximize mechanosensitivity and to be used to study the mechanism of TORC1 activation in vivo.

Echphants is also given on novel membrane probes including molecules such as planarizable push-pull probes, ceramide mimics and protein-based probes. Notably, planarizable push-pull probes explore, for the first time, the molecular principles of the color change of labets upon cooking or the chemistry of vision. To image biologically important properties of biomembranes represent the 2nd main theme of this project. The detection of membrane tension is so far difficult to achieve but the chemical and biological approaches present in the labs involved in the project have the potential to solve this problem. Namely, the “fluorescent flippers”, a new concept that allows to insert large and bright molecules into oligomeric probes to really feel the environment and also shine when twisted out of conjugation, are studied to maximize mechanosensitivity and to be used to study the mechanism of TORC1 activation in vivo.

Other topics of interest include the sensing of membrane phases and microdomains ("rafts") and also membrane potentials. In addition, new methods focusing on free-standing lipid bilayers not supported and named "electrofluorescent imaging" and compressible Langmuir monolayers (2D system model of biomembranes) are developed to comprehensively characterize new and old fluorescent membrane probes.
UNDERSTANDING THE CELL AS A PHYSICAL OBJECT

Using chemical sensors and biophysical tools, seven research groups address a much neglected issue: the cell as a physical object, which is subject to forces, pressures and tensions. In 2016, the NCCR Chemical Biology reinforced this research project with the hiring of Prof. Karsten Kruse, a specialist in Theoretical Physics applied to Biology.

Interview with Professor Karsten Kruse, Principal Investigator

Since 2016, Karsten Kruse is Full Professor in Theoretical Physics Applied to Biology at the University of Geneva. His arrival will greatly enhance the NCCR capabilities in quantitative biology and approaches to understanding complex mechanisms in cell biology.

You are a theoretical physicist studying dynamic biological systems. How did you become interested in biology?

I became scientifically attracted to biological systems towards the end of my PhD. It was the time when the first collective effects of molecular motors were studied from a physical point of view. It was absolutely fascinating to see motors, which move directionally along cytoskeletal filaments as single entities, spontaneously oscillate when coupled together. In situations, when coupled motors interact with flexible filaments, they can generate bending waves that are for example used by sperm cells for swimming.

What has been the most surprising finding in your scientific career so far?

The possibility that networks of molecular motors and cytoskeletal filaments can spontaneously generate traveling waves. These waves could orchestrate the cytoskeletal filaments during cell migration. This in turn offers evolution a handle for changing migration patterns to optimize search processes in topographically structured environments.

Where do you see the power of theoretical physics contributing to the field of chemical biology?

It provides concepts and tools for understanding cooperative behaviours that result from the interaction of many molecules. Furthermore, it can also be instrumental for analysing the readouts of mechanical sensors. As a slightly more unconventional aspect, I would like to mention information theoretical aspects that are tightly linked to concepts from statistical physics. It is the combination of these three aspects that has a great potential for advancing our understanding of cellular signalling.

What has been the most interesting experience so far since you arrived to Geneva this summer?

The people. They comprise a large number of outstanding and enthusiastic scientists as well as most supportive and competent administrative staff. Together they create a scientifically most stimulating environment.

What do you see the power of the NCCR contributions to teaching?

Furthering the NCCR also contributes to teaching. Project students might open the way to test theoretical ideas, for example, about signalling efficiency. The NCCR also contributes to teaching. Which lectures are you planning to organize in the future?

I will offer courses on nonlinear dynamics and introductions to the field of theoretical biophysics.

Much of our understanding of the cell focuses on the biochemical properties; however, mechanics of the compounds present in living matter: most prominently proteins, lipids, sugars and nucleic acids. Inherently, this realm is subject to a chemical biology: indeed, chemical biology approaches can generate both sensors and reagents to interfere with their abundance and function.

The general goal of this project is to use chemical sensors and biophysical tools to address the cell as a physical object, which is subject to forces, pressures and tensions. These physical constraints have a major impact on the shape and function of cells and tissues, ultimately feeding back and determining the biochemistry of living matter.

Within this frame, assays and reagents are generated to detect and study the physical properties of three key objects: the plasma membrane, the cytoskeleton and the endosomal pathway. Strategically, mitosis is highlighted as a subject where cell dynamics are most obvious, with an emphasis on asymmetric cell divisions, during which two daughter cells are generated with different properties, as this scenario of broken symmetry offers an optimal system to test innovative tools.

Project’s members develop sensors, calibrate reagents and establish assays to elucidate the role of membrane mechanics in endocytosis and cytokinesis, during cell size control in asymmetric division, epithelial morphogenesis and/or epithelial buckling (via the use of STORM, fluorescence probes, flipper probes in different cell types and tissues, CPD probes as a cell delivery system, quantum dot delivery, optogenetics, SNAP-tag and high spatial resolution).
Among the NCCR, four research groups have as common theme the use of protein engineering to generate protein-based tools for visualization and manipulation of biochemical activities. One of them develops versatile small antibody mimics (monobodies) as tools for chemical biology.

Interview with Professor Oliver Hantschel, Principal Investigator

Oliver Hantschel is Tenure Track Assistant Professor at the EPFL School of Life Sciences. He was awarded the first ISREC (Swiss Institute for Experimental Cancer Research) Foundation Chair in Translational Oncology and in 2016 an ERC Consolidator grant.

Could you give us an insight in the project and the approaches that are being pursued?

The main aim of this project is to use protein engineering to generate new tools for studying and manipulate biological processes. There is a considerable synergy between as well as complementation of the great expertise in chemical synthesis, proteomics and cell biology that has been built up during the first funding phase (2010-2014) of the NCCR Chemical Biology. In the different subprojects, we are developing engineered monobody proteins that bind with high affinity and specificity to the centriolar SAS-6 proteins or to proteins involved in tyrosine kinase signaling for subsequent mechanistic studies. In addition, expressed protein ligation is used to generate tubulin proteins with defined post-translational modifications to study their role in asymmetric vesicle trafficking and in centriole formation. Finally, we aim at developing a fluorescence sensor for acetyl-CoA to study acetyl-CoA homeostasis.

What are the main scientific advances achieved by your project after 6 years of research and during this past year in particular?

My lab has been able to set-up an efficient screening platform for the generation of monobodies using phage- and yeast-display screening. Besides several high-affinity antagonists that target protein-protein interactions involved in cell signaling, we are particular excited about the first monobody clones binding to the centriolar SAS-6 protein that we are currently characterizing with the Gönczy lab. We have also started collaborations with other NCCR labs on cellular delivery of monobody proteins (Matile lab) and to develop monobody binders to additional challenging targets (van der Goot and Manley labs).

You are interested in Tyr-kinases, their signalling, and in innovative manners to modulate these. How did the research of this project contribute to the progress of your research? What were the roadblocks on the way and how did you deal with these?

The support from the NCCR Chemical Biology has enabled me to set-up the monobody screening platform in my lab and catalyzed a number of collaborations that gave us access to expertise and methods that have helped ongoing projects. Most importantly, the successful set-up of the monobody screening platform has been a strong asset for the award of an ERC Consolidator Grant.

What do you see as major applications of the results of your research?

A common aim of most projects in my lab is to identify novel and unconventional targeting mechanisms for oncoproteins. We have demonstrated that monobodies can be used as versatile target validation tool in case small molecule inhibitors are (yet) available. So, aside from providing a strong rationale for the development of small molecule inhibitors to hitherto untargetable oncoproteins, we also explore if monobodies can be used as protein-based drugs. This requires that we overcome two major challenges: efficient delivery of monobody proteins and improvement of pharmacokinetics and immunogenicity.

What would be your “dream” discovery?

We hope to develop a monobody inhibitor that targets an oncogenic transcription factor, which could be efficiently delivered to the nucleus of cancer cells in a mouse model. This will be an important step towards a possible translation of this technology for cancer patients.

The first sub-project involves the establishment of a platform for the generation and characterization of monobodies against specific target proteins such as the proto-oncogene Src family kinases involved in various cancers and the centriolar SAS-6 proteins necessary for centriole duplication and function. Further mechanistic studies are pursued to characterise in depth some of the monoboody studied. At a larger scope, the establishment of a platform for the generation of monobodies is extremely valuable for various projects in the NCCR.

Sub-project 2 involves the development of strategies to switch on-off such monobodies and make these tools even more valuable.

In the third sub-project, expressed protein ligation methods are refined to produce proteins in a traceless manner with defined chemical modifications. These methods are used e.g. to generate α and β-tubulin proteins with defined post-translational modifications (PTMs) at their C-terminal tail and to characterize the importance of these modifications in asymmetric vesicle trafficking and in centriole formation.

Finally, the fourth sub-project involves the generation of new semi-synthetic fluorescent sensor proteins to measure with unprecedented precision and spatial-temporal resolution NADPH/NADP* ratios or NAD* concentrations within the cytosol or lumen of organelles in living cells. Next, general strategies for improving the dynamic range of such sensors are under continuous development.

Future changes

Kai Johnsson, Full Professor at the Institute of Chemical Sciences and Engineering of the EPFL and Project Leader of the NCCR Chemical Biology, will be leaving the NCCR and Switzerland in mid-2017 to take a Max Planck Directorship in Heidelberg, Germany. Kai Johnsson’s research interests are the development and application of chemical approaches to study and manipulate protein function. His past achievements include the introduction of different approaches to specifically label proteins in living cells; among these the SNAP-tag and CLIP-tag have become popular in the biological community.
Since 2013, Alexander Adibekian is Tenure Track Assistant Professor in the Department of Organic Chemistry at the UNIGE. How are the methods and technologies used in your lab helping to answer questions raised within this project? As a chemical proteomics lab, we are trying to contribute our part to the overall success of the NCCR, in particular by developing novel technologies to help with both research groups with the global identification of protein targets of small molecules of their interest. These molecules for example include hits identified in phenotypic chemical genetics screens or compounds with intriguing biological properties that were synthesized in their lab.

**Interview with Professor Alexander Adibekian, Principal Investigator**

This new methodology for proteomics allows detection and monitoring of up to ~3000 reactive cysteines in any given cellular proteome in one single experiment, thus providing a comprehensive proteome-wide picture of small molecule-cysteine interactions (Angew. Chem. Int. Ed. 2015, 54, 10852). This is achieved via strategic use of two clickable, cysteine-reactive chemical probes with complementary selectivity profiles, iodoacetamide alkyne and ethynyl benzodiazepine JN-RF-000. We have shown that JN-RF-000 alkylates cysteines in complex proteomes fast, under mild physiological conditions, and with a very high degree of chemoselectivity. We have also demonstrated the utility of alkyl benzodiazepines for chemical proteomics applications by identifying the proteomic targets of curcumin, a dipherthiodiaryl natural product that was and still is part of multiple human clinical trials as anticancer agent. Projecting forward, we would like to develop additional chemical scaffolds for cysteine-reactive probes that should, in principle, allow us to further expand the cysteome coverage.

**Chemical Systems Biology: What is This Project About?**

One of the major goals of this project is to exploit model organisms (yeasts and higher eukaryotes) amenable to chemical/genetic techniques to dissect disease-related signalling pathways and pathophysiologic.

A second theme is to support clever, dedicated and novel screening approaches, often based on synthetic biology or genetic interactions, to furnish novel reagents for the study of signalling pathways involved in, for example: modulation of lipid metabolism in Niemann-Pick C disease, protein palmitoylation, TOR signalling, or response to hypoxia. The availability of pathway inhibitors, orphan or otherwise, provides the opportunity to probe, at a system-wide level, the temporally defined cellular consequences of perturbation of these pathways. These system-level studies, including Mass Spectrometry-based Quantitative Mass Spectrometry approaches, are supported by innovative chemistry, exploiting, for example, isotopically labelled probes, which greatly facilitates quantification of proteins, lipids and other metabolites.

A third and increasingly more prominent aspect of this project is the development of generic approaches to identify the molecular targets of orphan compounds. These compounds range from natural products used in traditional medicine to hits that come out in our screening efforts described above. Here too, we rely on innovative chemistry, exploiting for example novel “warhead” to selectively enrich particular classes of proteins. One such warhead contains a hypervalent iodine moiety that efficiently labels thousands of proteins containing reactive cysteines, residues often targeted by small molecule inhibitors. Target identification is often rate limiting in drug screening campaigns and we are gearing up to meet this important challenge.

**The Concept**

Facing a camera, a young researcher presents his/her work and gives emphasis on the physical problem behind it. Another one comments with a few lines to explain the biological approach used to solve the problem. They are from different disciplines but meet through chemical biology.

**The Audience**

Scientists from different disciplines rapidly learn how to think in a chemical biology way, i.e. how tools taken from chemistry can help solve problems in biology.

**The Protagonists**

Lina Carlin, Postdoctoral fellow in Manley’s lab, EPFL, Biophysics lab. Tatjana Kleee, Synergy young investigator postdoctoral fellow in Manley’s lab, EPFL, Biochemist.

**Go Further!**


**SUMMER SCHOOL ON CHEMICAL BIOLOGY**

Organized by the Swiss Chemical Society, the NCCR School on Chemical Biology held last August 2016 in Villars-sur-Ollon brought together five outstanding speakers, whose interest span across the whole discipline. Each speaker presented the state of the art in their domain and shared on their own research.

Prof. Reza Ghadiri, from Scripps Research Institute in California, presented amazing cyclic D-L peptides that can remodel the gut microbiome, re-engineering and also DNA sequencing through single nanopore. Prof. Scott Snyder from the University of Chicago came to shape strategies to create diverse collection of natural products, through examples of synthesis carried out in his lab where he managed to cover halogenated natural products, alkaloids and multimeric natural compounds. Dr. Ling Peng from the University of Manneselle presented the dendrimers synthesized in her lab, and the development of a diverse medical application she manages to use them for, spanning from encapsulation for siRNA delivery to using them as imaging agents. Oligonucleotides is also an important topic and Prof. Jonathan Hall from ETH Zurich and NCCR RNA and Disease focused his presentations on RNA, first as a drug target but also as a potential drug itself. Continuing with oligonucleotides, Prof. Xiaoyu Li from the University of Hong Kong showed different methods to encode chemical libraries with RNA and its application in protein labeling or target identification in drug discovery.

Forty students from all the Swiss Universities and some international participants were present to listen to these inspiring talks. In addition to lectures, poster sessions were organized and the PhD students presented the whole week to encourage interactions at any given time. Students also had the chance to present their own results during short talk sessions.

The week was concluded with a dinner around a typical Swiss raclette, where one Best Presentation Award and Best Poster Awards were given. We are very proud that all Best Poster Awards were won by NCCR Chemical Biology members: Vanessa Carle and Camille Villequey (both Heins Lab PhD students) for their work on phage-encoded peptide libraries, as well as Jacques Saarbach and Eric Lindberg (respectively Winsinger Lab PhD student and postdoc) for their work on imaging using templated chemistry.

Many thanks should be addressed to the Organising Committee including NCCR member Prof. Christian Heinish and to the NCCR PhD students who sponsored the registration of one PhD student.

**Go Further!**

May C. Morris

May C. Morris obtained her PhD in Biology and Health Sciences at the University of Montpellier, France, in 1997 and completed her postdoctoral training at the Scripps Research Institute, La Jolla, USA. In 2000, she was hired by the CNRS and returned to the Centre of Research on Macromolecular Biochemistry in Montpellier. In 2005, she established her own research group and in 2010, she was promoted CNRS Research Director. In 2014, she moved to the Institute of Biomolecules Max Mousseron, where she is currently in charge of the “Cell Cycle Biosensors and Inhibitors” group within the Department of Amino Acids, Heterocycles, Peptides and Proteins for Health. She was awarded the CNRS Bronze Medal in 2006 and the “Scientist of the Future” award from Languedoc-Roussillon Region in 2009. Dr. Morris is also a Council Board Member of the French “Women in Science” association and has established a Mentoring Programme for Doctoral students of the Biology & Health Doctoral School of the University of Montpellier. She is an Editorial Board member of ChemBioChem and of Frontiers in Chemistry.

https://bmm.unmontpellier.fr

Most intense moment of discovery.

The ability to turn on fluorescent biosensors in living cells, by screening a library of compounds, and by monitoring the expression of variants directly in situ by high-throughput analysis.

Why are you active in the field of chemical biology?

Because I enjoy the interface between biology and chemistry – developing synthetic or biomimetic tools made by mankind to address unresolved questions in life sciences.

Describe the most intense moment of your career.

I have had several moments of pure joy when obtaining a result of significant importance for a given scientific project and enjoyed times of recognition by my peers. But the most intense moment of my career was probably when I published my first independent piece of work.

Which is the best idea you ever had?

To develop and apply fluorescent biosensor technologies to cancer diagnostics.

Do you have a role-model or a driving-force?

Several female scientists have encouraged me in moments of doubt and difficulty in the past. I look up to Barbara Imperiali and the late Cécile Pickart for their sense of creativity and rigour.

The philosophy along which lines you lead your lab?

Teach the basic skills to my students and give them “guided” freedom so they can develop their sense of creativity and build their own experience through their questions and mistakes. In return I expect the best and a sense of respect for what has been taught and given.

Pick a piece of advice you’d like to give to the young generation of researchers.

Don’t be afraid to make mistakes – but learn from them. Don’t accept dogmas – question them. Risk new ideas to break boundaries – it takes a dose of courage but makes a good scientist.

A book, song, poem, music or painting that you spot out and get inspiration from?

“Song: Me and Bobby McGee – Janis Joplin” from “A SELECTION OF GOOD READS”. This book of “articles and thoughts” by good scientists is really inspiring! It takes a dose of courage but makes a good scientist.

Publications and patents

64 publications in peer-reviewed journals contributions to scientific volumes

1 special issue (Biotechnology Journal)

8 PCT patent applications

Total citations: 1971

A-factor: 27 (ISI Web of Science)

Editor of 1 volume (Elsevier Press)

Special Issue Editor “Fluorescence-Based Biosensors – concepts and applications”, 2010


Editor M.C.Morris, ISBN: 978-0-12-381477-3

Editor MC.Morris & M.Blondel (2014)

M.C.Morris & M.Blondel.


Visit: http://www.nature.com/nchembio/journal/v12/n10/full/nchembio2150.html

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DNA-ENCODED SMALL MOLECULE LIBRARY

The encoding of small chemicals by DNA has enabled the screening of enormously large collections of small molecule compounds. A highly fascinating strategy for synthesizing DNA-encoded chemical libraries named YoctoReactor is developed by the small start-up Vipergen in Denmark. Three DNA strands loaded each with a chemical building block are brought into close proximity by hybridization to form a tiny “reaction volume” of 1 yoctoliter (≈10⁻⁹ L). The building blocks react with each other and the attached DNA encodes the final product. After several years of development, the team of Niels Hansen has published a first article in which they describe the identification of a small molecule ligand to a therapeutic target. From a library of more than 12.6 million compounds, the authors have identified a novel negative allosteric modulator capable of strongly suppressing GABA-induced chloride currents.

Define research in just three words.

Brainstorming – Hard-work – Pleasure (of discovery).

How do you match the words beauty and science?

If you derive pleasure from the art of science, it is because you see and feel its beauty in its design and application.

A piece of advice you’d like to give to the young generation of researchers.

Don’t be afraid to make mistakes – but learn from them. Don’t accept dogmas – question them. Risk new ideas to break boundaries – it takes a dose of courage but makes a good scientist.

A portrait to inspire young researchers and female scientists in particular.

A portrait to inspire young researchers and female scientists in particular.

The screening of drugs capable of acting on GABA A receptors has been hampered by the existence of multiple ligand-binding sites and a lack of structural information. This paper by Isao Hamachi and co-workers describes the development of an innovative GABA A receptor biosensor on live cells and its application to high-throughput screening of a chemical library. As shown in the figure, a fluorescent dye is first linked covalently near an interesting ligand-binding site using a ligand-directed acyl imidazole chemistry. In a second step, a quencher-ligand conjugate is added. Chemicals that bind to the site of interest displace the quencher and in this way turn on the fluorescence in the biosensor. By screening a library of 1248 compounds, the authors have identified a novel negative allosteric modulator capable of strongly suppressing GABA-induced chloride currents.

NOVEL p93 MAP KINASE INHIBITORS IDENTIFIED FROM YOCTOREACTOR DNA-ENCODED SMALL MOLCULE LIBRARY
SwissCompanyMaker drives your idea to a start-up
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A fast-paced workshop for aspiring entrepreneurs in science and technology

March 20, 21 & 28, 2017
Campus Biotech, Geneva

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RECENTLY COMPLETED - OR ALMOST COMPLETED - PHD THESIS

- "Plantatable push-pull systems as mechanosensitive fluorescent probes for turn-on sulfide donors" by Quentin Verolet (Supervisor: S. Matile, UNIGE)
- "Analysis of paclitaxel/potato networks with kinetic modeling" by Tiziano Dallavilla (Supervisor: P. Dyson, EPFL)
- "Regulation of endoplasmic reticulum architecture by protein S-Palmitoylation" by Patrick Sor (Supervisor: G. van der Goot, EPFL)
- "Small molecules as tool compounds to probe Target of Rapamycin (TOR) signaling" by Karolina Nowak-Stożewska (Supervisor: Robbi Loweth, UNIGE)
- "Development of mass spectrometric methods to understand the mechanism of action of transition metal-based anticancer compounds" by Ronald Lee (Supervisors: P. Dyson and K. Johnson, EPFL)

PUBLICATIONS FROM AUGUST TO OCTOBER 2016


NOMINATIONS AND AWARDS RECEIVED BY NCCR CHEMICAL BIOLOGY MEMBERS OR ALUMNI

- The publication of Lascano S., Zhang K.-D., Wehlauch R., Gademann K., Sakai N., Matile S., "Third Orthogonal Dynamic Covalent Bond" (Chem. Sci., 2016, 7, 4720) was selected for the Swiss Science Concentrates, China, 2016, 70, no. 15.
- In celebration of Peer Review Week, with the theme of Recognition for Review, Stefan Matile has been selected by the editor as one of the top 10 reviewers for Chemical Science in 2016 for his significant contribution to the journal.

A selection of images that highlight topics in the field of Chemical Biology or are just meant for visual entertainment.

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NEW STEERING COMMITTEE

A new NCCR steering committee will be put in place on December 04, 2016 including past members Prof. Howards Leckman (Director), Prof. Pierre Gürsoy and Prof. Christian Heinis (new co-Director), Prof. Susana Marley, Prof. Nicolas Weisinger and Prof. Robbie Loweth are newly appointed, in replacement of Prof. Kai Johnson, Prof. Jean Grunberg who retires and Prof. Stefan Matile who does not wish to renew his mandate as he is the newly appointed President of the Chemistry Section (UNIGE). Prof. Kai Johnson remains as a Committee member but without the right to vote. The NCCR directorate is looking forward to this new dynamic composition and thanks warmly departing members for their important contribution to the NCCR strategic leadership over the previous six years.

SwissCompanyMaker is a joint initiative of
NEW NCCR BIOCHEMISTRY WORKSHOP AT EPFL’S SCIENCE OUTREACH DEPARTMENT

Is the grass green…or red? How do you make a living cell change color? And more… Last September and October, fifteen youngsters aged 11 to 13 dressed up in labcoats and became biochemists for three Wednesday afternoons. With the help of Tamara Maric, PhD student in Elena Dubkovskaya’s lab, and Nolwenn Chavan, Science Communicator for the NCCR Chemical Biology, the teenagers carried out fascinating experiments and stimulated their natural curiosity through science!

More info: Ateliers Polythèmes

OUTREACH NEWS

WE ARE MOVING TO A NEW LOCATION

From December 1st the NCCR Chemical Biology Office goes to the top! Room: 3-308 (3rd floor), Sciences II, UNIGE

Welcome!

www.youtube.com/watch?v=-UNaH_jbZIU