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Editorial

NCCR Chemical Biology: Interdisciplinary Research Excellence, Outreach, Education, and New Tools for Switzerland

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Abstract: Funded by the Swiss National Science Foundation to promote cutting edge research as well as the advancement of young researchers and women, technology transfer, outreach and education, the NCCR (Swiss National Centre of Competence in Research) Chemical Biology is co-led by Howard Riezman, University of Geneva and Kai Johnsson, École Polytechnique Fédérale de Lausanne (EPFL).

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Visualisation and Control

What is chemical biology?[1] How is it different from chemistry or biology? Chemical biology is more than traditional chemistry alone, although it does make use of chemical synthesis. It is also more than biology alone, although it does make use of living cells and genetic manipulation. Chemical biology is an evolution of the fields to visualize and control biological processes in living cells using chemistry. The end point may be new tools for researchers, elucidation of signalling pathways, probes for membrane structure or lead compounds for therapeutic ends.

Researchers at the NCCR Chemical Biology will now take a step into the future to visualize and modulate what's happening inside individual cells as they continue to function. New tools will be needed to address ongoing challenges in biology, which include separation of indirect from direct effects of proteins, regulation of protein activity, and pinpointing spatial and quantitative information about reactions within cells.

The Power of Multidisciplinarity

What does this multidisciplinarity mean for research in the field of chemical biology? The fusion of disciplines through expertise from cellular and molecular biology, biochemistry, biophysics and chemistry sets this center of excellence apart from the research conducted within the traditional disciplines alone. Cross-disciplinary approaches not only bring a new, fresh perspective to basic and applied research, but also train the next generation of scientists to employ many more tools to adroitly ask – and answer – the nagging questions researchers face today. Questions such as, what is going on in the endosomal milieu? Where and when exactly is Notch active during cancer progression? How does the order of the membrane environment affect protein function? Researchers in the NCCR Chemical Biology will be developing novel chemical approaches to observe and manipulate biochemical activities in living cells. They will use these tools to resolve important and pertinent challenges in cell biology and biological medicine. Projects within the NCCR Chemical Biology are innovative, varied, and intertwined.[2]

Teams, Projects and Goals

The generous funding from the Swiss National Science Foundation, along with significant contributions from both host institutions, is enabling the cross-disciplinary teams at the NCCR Chemical Biology to launch a multi-pronged approach to tackle, on a long-term basis, riskier research more likely to produce transformative results. There are seven diverse projects and a technology platform in the works for the first four-year funding period.

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Project 1, 'Chemical Interference' draws from different areas such as organic synthesis, organometallic chemistry, or natural products chemistry, and combines biological and predictive computational approaches. Project leader ***Karl Gademann*** and his colleagues generate and discover small molecules that interfere with key biological processes to better understand their mechanism of action. Natural product libraries, scaffolds of organometallic origin, and bicyclic peptides will be prepared and evaluated for biological function. Virtual screeing and subsequent organic synthesis or purchase will complement these approaches.

Project 2, 'System-Level Chemical Interference' ingeniously exploits state-of-the-art high throughput screening resources developed in the NCCR Chemical Biology, thereby supporting breakthroughs in molecular biology. Project leader ***Robbie Loewith*** and colleagues establish generic protocols to discover novel, potent, cell-permeable small molecule inhibitors for defined targets using a yeast model, *S. cerevisiae*, which can be easily modified genetically and is also useful for metabolic engineering. This project encompasses the discovery of novel inhibitors of the target of rapamycin (TOR) kinase complexes, novel inhibitors of histidine kinase 'two-component' systems, ceramide synthase inhibitors, sphingolipid metabolism inhibitors and CDC48 inhibitors.

Project 3, 'Chemical Biology of Membranes: Localization and Endocytosis' identifies small inhibitors of protein and lipid trafficking/sorting in mammalian cells. To avoid adaptive responses associated with genetic manipulations, this project identifies compounds that interfere with endosomal functions on a real-time scale. Project leader ***Jean Gruenberg*** and colleagues develop innovative strategies to probe both the aqueous and membrane environments. Chemical libraries will be used in high throughput (HTP) screening to identify compounds that interfere with endosomal lipid homeostasis and localization (lysobisphosphatidic acid, cholesterol, phosphoinositides). Once the membrane composition screen is completed, a second HTP, high content screening will be used to identify compounds that interfere with receptor sorting. Together with project 7, this project develops sensors to probe the microenvironment encountered by signaling receptors during transport.

Project 4, 'Chemical Biology of Signal Transduction: Monitoring and Manipulating Aurora-A Kinases in Living Cells', led by ***Pierre Gönczy***, involves a team of researchers to develop new approaches to analyze and interfere with the function of Aurora-A, a Ser/Thr kinase that plays a critical role in mitosis across eukaryotic evolution. In *C. elegans*, the Aurora-A ortholog AIR-1 will be studied using fluorescent sensor proteins that visualize the activation of Aurora-A in living cells. Localizing active versus inactive kinase will be critical to elucidate kinase-dependent and kinase-independent functions. Using caged inhibitors, the researchers will attempt to modulate Aurora-A activity in time and space.

Project 5, led by ***Marcos González-Gaitán***, 'Chemical Biology of Notch Signalling' devises high throughput screening systems to identify novel small molecules and druggable targets which interfere with Notch signalling in cancer. The project uses complementary chemical approaches to study Notch signalling in physiological and pathological situations. Once compounds are identified the project develops secondary screens and validates the positive hits for their affect on model system development, especially in fruit flies and zebrafish. An early success has been the necessary establishment of conditions to deliver drugs to these model organisms.

Project 6, 'Quantification of GPCR-Mediated Signaling in Living Cells' is developing an imaging system to quantitatively visualize single molecules at nanoscale resolution. The team, led by biophysicist ***Horst Vogel*** along with chemists and biochemists, will develop methods that allow the quantitative characterization of the complex cellular network that detects extracellular signals *via* G protein coupled receptors (GPCRs) and transmits and amplifies these signals across the cell membrane to finally evoke a cellular response. In addition, the team will investigate, by mass spectrometry, cell membrane microdomains rich in GPCRs for their lipid and protein composition.

The general objective of project 7 'Chemical Biology of Membranes: Dynamic Fluorescent Probes and Cellular Uptake', led by ***Stefan Matile***, is to design, synthesize and use molecules that can i) tunnel through biomembrane barriers, and ii) report on their nature. Considering that the delivery of probes and drugs to their intracellular targets remains a central challenge in chemical biology despite decades of intense research in industry and academia, conceptual innovation will be unavoidable to achieve significant progress. Toward this end, lessons from dynamic covalent chemistry will be applied to gain rapid access to large libraries and screen for dynamic activators that enable siRNA or cell-penetrating peptides (CPP) to enter into otherwise problematic cells. New fluorescent membrane probes will be designed, synthesized and used to learn how the biophysical properties of membranes control these and related biological processes.

While all these projects are firmly anchored in fundamental research, when linked *via* the NCCR, together they address themes of strategic importance for the future of science, the economy and society of Switzerland.

ACCESS for all of CH

An academic chemical screening platform for Switzerland, ACCESS, established at EPFL will provide the scientific community with chemical diversity, screening facilities and expertise in chemical biology. Switzerland is host to important international pharmaceutical companies and biotechnology players in industry, but academic researchers need a facility to screen for small molecules that regulate the pathways they study in order to understand how these pathways work with cells and organisms. The entire academic community will benefit from the establishment of a diverse chemical library and know-how to apply the tools of chemistry to their biological systems.

Passion and Potential

Not only will the NCCR Chemical Biology team of scientists collaborate to develop new tools and insights, but also we are committed to training a new generation of interdisciplinary scientists, fluent in chemistry and biology. Industry and academia alike need future employees versed in tapping multiple disciplines to address today's complex scientific problems. Gone are the days of one discipline, one career – a plethora of careers await the diverse interests of students and postdocs of tomorrow who will devise creative solutions. Collaboration across disciplines, departments, schools, and institutions builds on existing strengths and resources to enable this sort of career training and help realize their potential. The NCCR Chemical Biology encourages all young scientists to excel in their career, paying special attention to advancement of women, through a mentoring program, career advice, and exposure to role models.

Knowledge and technology transfer is an additional mission of the NCCR Chemical Biology network. Knowledge transfer starts with making science understandable to broad audiences; even science communication between different disciplines sometimes requires translation. Through participation in community events and the development of the ***Chimiscope***, we will target public aware-

ness of the importance of chemistry in our everyday lives. The Chimiscope[3] is a platform to motivate young student interest in the sciences by providing an attractive and stimulating environment to engage in active learning through sharing our passion for the field, and is produced through a partnership with industry.

Long-term Vision

An understanding of life on a molecular level requires the characterization of all biochemical activities of an organism with spatial and temporal resolution. Progress toward this ambitious goal is thwarted by a shortage in technologies that permit a spatiotemporal quantification of biochemical activities in living cells and the lack of tools to rapidly and specifically intervene in biochemical pathways to investigate function *in situ*. The NCCR Chemical Biology will address these widely acknowledged needs by developing chemical approaches for the visualisation, quantification, and manipulation of biochemical activities through a collaborative and interdisciplinary effort. With the long-term support of the Swiss National Science Foundation, the University of Geneva and the École Polytechnique Fédérale de Lausanne, we expect breakthroughs in our understanding of biology and we are confident that the techniques and trained personnel developed in this NCCR will have an impact on biology and medicine in general.

[1] a) 'Chemical Biology: From Small Molecules to Systems Biology and Drug Design', Ed. S. Schreiber, T. Kapoor, G. Wess, Wiley, **2007**; b) W. Wells, 'Chemistry & Biology', Elsevier Science Ltd. **1999**, R209.
[2] *http://www.nccr-chembio.ch/research*
[3] V. Monnet, A. Vos, *Campus* **2010**, *102*, 10.

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