Swiss National Centre of Competence in Research

Newsletter No. 9 / Jun 2018

NCCR TransCure
Excellence in Membrane Transport Research

Dear readers and colleagues,

The National Centre of Competence in Research (NCCR) TransCure is getting close to the end of Phase 2 (2014-2018) and is ready to enter the last four-year phase (2019-2022) with renewed enthusiasm. Indeed, as you will read in this issue, the network continues to put energy into many fields, ranging from pure basic research to technology commercialisation.

Interdisciplinarity has characterised the NCCR TransCure from the beginning and remains fundamental to tackle future challenges. Our scientific output continues to demonstrate this interdisciplinary effort of the network (p. 7). In the main article (p. 2-3), Martin Lochner, NCCR TransCure PI and chemistry expert, highlights the importance of interdisciplinary research in the field of chemical biology. Here, the synergy across disciplines enables major advances in the development of novel compounds that target transport proteins.

An even broader interdisciplinary effort is asked of those researchers pursuing an entrepreneurial career. In order to launch a spin-off company, scientists need to work with business experts, patent attorneys and colleagues from very different fields. To support academics in the early entrepreneurial stages, the NCCR TransCure hosted the "SwissCompanyMaker pre-seed workshop" in Bern (Apr 2018). An interview with the workshop founder, Mark Wilson, gives some insights into this aspect of academia (p. 4-5).

So far this year, the NCCR TransCure has organised several educational events spanning various aspects of a researcher's life. The "Career Pathway Lecture" (Mar 2018) provided useful information about the academic path to a professorship in Switzerland. The annual retreat (May 2018) was again appreciated by the fellows as an excellent occasion to learn about the network's advances and to profit from discussions among peers. Looking ahead, TransCure fellows will have a wide choice of courses after the summer break. The specialised scientific courses for this year (Aug-Sep 2018) will focus on single particle cryo-electron microscopy and on the genetics of transporters. The soft skills workshops (Nov 2018) will address the challenges of leadership tasks and time management during a PhD. Soft skills will be put to good use at the main outreach event of the year, the "Kids Lab Day" (Aug 2018). On this occasion, a group of Bernese TransCure researchers will open their laboratory doors to a younger generation and entertain them with the beauty of science.

Finally, the whole network is invited to join two large events taking place in autumn: the "4th Endocannabinoid Pharmacology Meeting" and the "End-of-Phase 2 Symposium" (Oct 2018). The latter is intended to close the second phase of the NCCR TransCure and, at the same time, to say goodbye to those who will be retiring during Phase 3.

Before letting you leaf through the pages of this issue, we would like to remind you about the “Meet the NCCR TransCure Fellows” section (p. 6). The short portraits of our researchers and alumni are excellent showcases of the interdisciplinarity of the NCCR TransCure projects. Moreover, you can discover the names of the 2nd NCCR TransCure Young Scientist Award winners!

The NCCR TransCure Directorate wishes everybody a sunny and exciting summer time!

H. Abriel and J.-L. Reymond,
NCCR TransCure Directorate

Chemical biology in transporter research: Molecules to the rescue?

Chemical biology approaches use small molecules to study and manipulate biological systems. The field has come a long way from simple blockers that perturb the function of a protein to small bespoke molecular tools endowed with useful biophysical tags.

Manipulating the function of biological macromolecules, in particular proteins, by using small organic molecules is not a new idea. Chemical biology has scientific roots in pharmacology, medicinal chemistry, bioorganic chemistry, biochemistry, metabolic engineering and genetics. Due to major advances in synthetic and analytical techniques, chemical biology has branched out into many subfields (e.g., proteomics, protein engineering, molecular sensors and bioorthogonal chemistry).

It is fair to say that chemical biology approaches nowadays complement the arsenal of basic biomedical research tools, such as molecular biology, electrophysiology and structural biology methods. Many elegant examples of chemical biology approaches have been reported in the literature, mostly concerning cytosolic proteins, ion channels and receptors. However, transport proteins have been somewhat neglected. Developing small molecule probes against poorly characterised targets is challenging and requires an efficient interaction between synthetic chemistry and biochemistry teams. An interdisciplinary research environment such as the NCCR TransCure therefore offers a unique opportunity to discover and optimise such molecular tools in order to achieve step changes in transporter research.

Traditionally, natural products (e.g., plant and animal toxins) were used to specifically block the function of a protein of interest and to investigate the impact on the biological system. Due to evolutionary selection, these natural products often exhibit high potency and specificity for their target. Conversely, and probably true for most human transport proteins, finding a potent and specific modulator for a less well-defined protein target is not trivial.

In the last few years, there have been some spectacular advances in the elucidation of the 3D-structures of transport proteins, especially by means of cryo electron microscopy (cryo-EM). Transport proteins cycle through several conformational states during the transport mechanism and therefore these 3D-models, which represent only one of these states, are of limited use for the rational design of new probes. Using transport substrate structures (e.g., amino acids, sugars, inorganic anions and cations) as starting points for synthetic alterations is also not ideal and, in many cases, even small structural changes result in complete loss of biological activity. One might also argue that compounds that do not interact with the substrate binding site, but rather exert their effect by acting at another site (i.e., allosteric modulators), are more desirable, as they allow more subtle modulation of transport function. Transport function is reduced in many diseases and positive allosteric modulators could also be an interesting option to bring transport activity back to normal levels in these cases.

Some human transporters are known to be affected by non-natural compounds that were discovered by accident. In most cases, such compounds have low potency and low selectivity for the human transporter. Conducting a structural-activity relationship study by generating synthetic analogues might produce tool compounds with better properties but is also very time-consuming.[1] Tens of thousands of medicinal chemistry-type compounds are now commercially available. If the proper logistics, infrastructure and robust assays are in place, screening of large random compound libraries against transporter targets can identify better starting points for synthetic optimisation. A more focussed approach is to use low potency transporter modulators as input structures in ligand-based virtual screening exercises (Fig. 1). Similarity algorithms can identify hits in commercially available libraries, which can be purchased and assessed in biological assays. Compounds with interesting biological activity undergo further rounds of virtual screening and synthetic exploration might ultimately deliver novel compounds with high potency and selectivity for the human transporter target.[2,3] Importantly, final compounds have to be profiled against other cellular targets and validated in complex biological systems (tissue or animals). Whilst compounds are mostly optimised to achieve maximum potency and selectivity, other properties such as solubility and stability in cellular media should not be neglected.

A selective and potent transporter blocker or activator is a very valuable research tool in its own

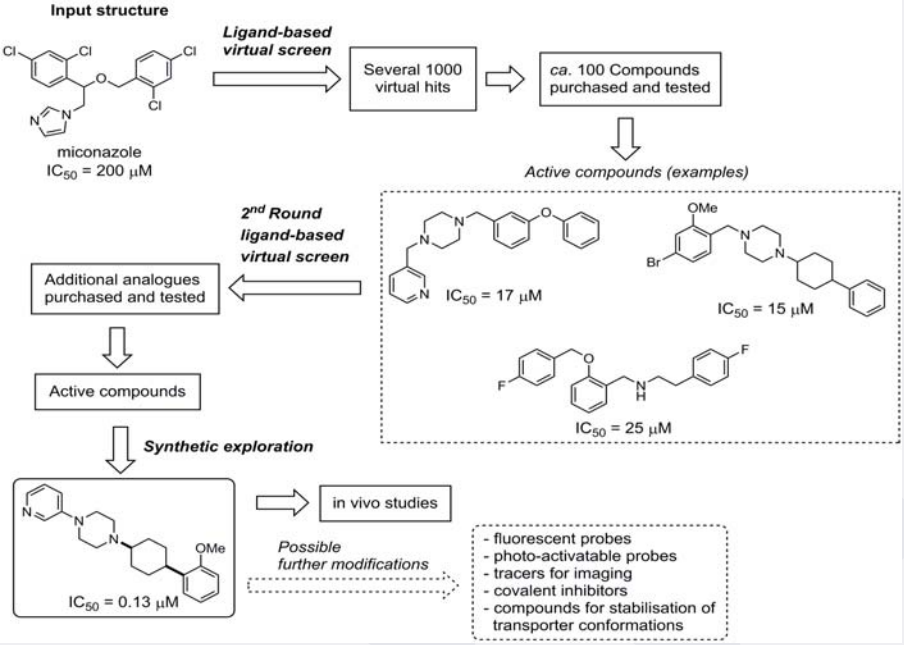

Figure 1: Virtual screening/synthetic approach to developing novel TRPV6 inhibitors.

right, however, such active compounds can be further developed into useful probes. Very often, existing structure-activity relationship data from previous compound optimisation helps to decide where to attach linkers and biophysical tags. Commonly used tags comprise fluorescent dyes (for fluorescence microscopy studies and fluorescence-based binding assays), photo-cleavable and photo-crosslinking groups[4] (for proteomics and binding site identification), isotopes (e.g., for PET and SPECT studies) and biotin groups (for protein target capture and concentration). The synthetic possibilities are almost endless.

Martin Lochner,
NCCR TransCure PI

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[2] Simonin C, Awale M, Brand M, van Deursen R, Schwartz J, Fine M, Kovacs G, Häfliger P, Gyimesi G, Sithampari A, Charles RP, Hediger MA, Reymond JL (2015) Angew Chem Int Ed 54: 14748.
[3] Ozhathil LC, Delalande C, Bianchi B, Nemeth G, Kappel S, Thomet U, Ross-Kaschitza D, Simonin C, Rubin M, Gertsch J, Lochner M, Peinelt C, Reymond JL, Abriel H (2018) Br J Pharmacol, doi: 10.1111/bph.14220.
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How it works: Bioelectricity

In the early 1770s, the Italian scientist Luigi Galvani was conducting experiments with his assistant on static electricity using frogs. When by chance they touched an exposed nerve of a frog's leg with a metal scalpel, they saw a spark and the frog leg contracted as if it were alive. Galvani thought he had discovered a new kind of electricity, which he called "animal electricity", or "bioelectricity", as we call it now. Electrical potential in living organisms is mainly driven by the controlled flow of ions (Na^+, K^+, Cl^-, Ca^{2+}) across the cell membrane through specialised membrane proteins called ion channels. Differences in the ionic concentration on either side of the cell membrane leads to a voltage called "electric membrane potential". All cells use this membrane potential to assist or control metabolic processes. Some specialised cells such as neurons and muscles can additionally develop "action potential" through the well-orchestrated opening and closing of ion channel gates. Biomedical recording techniques such as electrocardiography, electroencephalography or electromyography are used to measure action potentials in the heart, brain and muscle, respectively. An alteration in ion channel function can lead to disorders known as channelopathies. Ion channels have also gained attention from pharmaceutical companies as hotspots for targeting specific diseases. With access to whole human genome sequences and advanced technologies, the field of bioelectricity has achieved credibility in human physiology and may help clinicians to better understand, diagnose and develop novel therapeutic strategies.

Lijo Ozhathil,
NCCR TransCure postdoctoral researcher

Academia and Entrepreneurship: friends or foes?

Researchers with marketable ideas often do not dare to move beyond lab borders into the start-up system, thus reinforcing the image of academia and entrepreneurship as conflicting worlds. Mark Wilson, founder of the "SwissCompanyMaker" (SCM) workshop, provides an insight into this topic and possible ways to change the mind-set.

Interviewer: Valentina Rossetti

The SCM workshop is taking place at the moment in Bern. What is the atmosphere like?
Electrifying! This is partially due to the number of participants (about 90) but more so to the design of the workshop – positive enthusiasm for new ideas is mixed with the anxiety of conflicting opinions, and assignments have very tight time limits. At the same time, the atmosphere is non-threatening. There is no formal competition and no wrong answers. In fact, most people at the workshop are there to help the Idea Champions*. This sets up the perfect atmosphere for the right amount of critical thinking.

Where are our Idea Champions finding out they need further thought the most?
Overall, they are learning that they have a lot to learn about business. There is nothing very difficult in the SCM workshop but the Idea Champions are being asked questions that most have not thought about very much because they have been focussed on their science. I believe they are realising that science is only one aspect of producing a product that society wants.

Idea Champions typically come from academia. During this workshop, do they express their academic or entrepreneurial 'souls' more?
SCM puts Idea Champions into a situation in which they are stressed. In any stressful situation, natural attitudes tend to come out. Overall, SCM Idea Champions come from science and have a background in the scientific method. They naturally prefer to analyse problems long enough to become confident of a single answer. In technology commercialisation however, this is counterproductive. Business decisions cannot be prescribed by a formula, especially early on in the concept stages. The entrepreneurial soul is frustrated by too much analysis (or sometimes by ANY analysis). Entrepreneurs often don't care WHY something should happen or about evaluating options. They feel an innate panic that doing ANYTHING is better than sitting around analysing. Exaggerating to make the point, entrepreneurs are haphazard and quick to act, and scientists are afraid to make a decision until all the facts are in. This is a healthy tension that must be understood and it is a deliberate aspect of the SCM to help scientists and business people understand each other.

As you just mentioned, an academic career and entrepreneurial success may be seen as incompatible. Are they really 'foes' of one another?
If I have to give one clear-cut answer: Yes, they are foes; they are opposites. Consider why each is excited to get up in the morning and go to work. Scientists are inventors. They want to figure out something that never worked before. They want to contribute to society's overall knowledge. Scientists get excited to explain and define things in a increasingly better way and prove regressions with less noise and stronger r^2. They are drawn toward large, complex, unsolvable problems. They accept long time horizons to help humanity. Scientists do not expect anything back from the beneficiaries of their ideas, and therefore look to the government to pay them today for something that may be helpful a long time in the future. These traits are in contrast to what excites entrepreneurs. Entrepreneurs are frustrated by perfection and theories. They are not inventing; they are implementing. Implementing means using project management skills to get to 'good enough' milestones in a short time horizon. Very few entrepreneurs have the resources to worry about solving society's problems in 10 or 20 years. They need to solve a few people's problems well enough today that those folks will pay them today. However, if I can go beyond the one simple answer, then scientists and entrepreneurs also have similarities. They always need more money than they have, and they continually need to figure out where to get more. Moreover, they both compete against an extensive pool of applicants within their own small pools of funders. Both need to recruit people who will work with them and who will believe in them and their ideas.

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Scientists and business experts need to understand each other in order to benefit from a fruitful exchange of ideas.

Finally, scientists and entrepreneurs both need to build reputations; a difficult 'chicken and egg' problem. Until you are a respected scientist, no one respects your science. Until you have established a successful business, no one believes in your start-up idea.

How can we help researchers and enable academia and entrepreneurship to become 'friends'?
They have to learn each other's language and find people with whom they want to work. Researchers have to find business people who appreciate hard science, have patience, understand and have sufficient financial resources for more radical platform development. Science-based start-ups take a long time to fly but once successful, can become large companies that employ many people. Science commercialisers may as well avoid business people that want to hear a new idea Friday evening, expect a working prototype by Saturday morning that has been tested on 30 people in a shopping mall by Saturday night, and pick a 'winner' after hearing the shark-tank pitches on Sunday. There is solid rationale for why the smart-phone internet realm gets so much investment attention but these folks are not aligned with hard-science commercialisation. To help accelerate research out of the lab, it would do wonders if every science student were exposed to the fundamentals of technology commercialisation. SCM, Innosuisse and other programmes, especially at an early stage, are very good for this. Scientists need to have an appreciation for how difficult it is to actually launch a product and what the challenges are that typically stunt progress down that long road. The responsibility to bridge this gap lies mainly on the science side, strictly because of the laws of supply and demand. The reality is that it takes millions of Swiss francs to launch the average science-based start-up and statistically 70% of them will fail. Therefore, investors with large funds who are willing to take high risks are in the driver's seat.

Is the situation very different in the USA? If yes, to what extent?
No, it is not at all different. Everywhere I go, the same types of challenges are discussed by the same types of people.

In Switzerland, do you see any factor that might particularly favour the development of spin-offs and start-ups?
I only have data on four Swiss cities across six years; and I've been interacting with a self-selected group of science-business advocates. Hence, I am not answering with very diverse data. Nonetheless, from what I've seen, Switzerland is an idyllic, wonderful country with a heavy emphasis on science, higher education and technology. There is a very good infrastructure and transportation and manufacturing work well. Moreover, there are focused government programmes (NCCRs, SNF, Innosuisse). This gives Switzerland a big advantage in mechanising technology commercialisation with respect to other countries where government programmes are diluted due to the various problems of their societies. This does not mean that every scientist in Switzerland will become an entrepreneur, nor should they, but the small percentage of researchers going in that direction will be supported by a very efficient mechanism.

You will soon be back in the USA but we hope to welcome you again to SwissCompanyMaker 2019! What is your wish for next year regarding the workshop and the Swiss start-up ecosystem in general?
I hope that the Idea Champions wanting to move forward will receive the funding and investments they need to advance their prototypes and capture beta-customers. And I hope that those Idea Champions who are finding out they do not like the business aspects of starting a business will cheer on commercialisation from the lab and continue a fruitful and fulfilled life in academic science. In both cases, I hope they see SCM as a meaningful turning point in their lives. As to Zurich 2019, I look forward to an exciting new cohort of Idea Champions and another strong army of support team members!

**Idea Champions* *are the central participants who bring their own pre-approved ideas to the workshop. They are mostly at the early stage and there is typically only one Idea Champion per idea. When there are more than one, it is because these people are already working on this idea together. This year we had eight core ideas and a record number (17) of Idea Champions!*


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Mark Wilson has nearly 35 years of experience developing and launching a variety of new products from the napkin-sketch level, including navigational interactions with well over 500 pre-seed-stage research technologies and over $1 billion in new corporate product medical devices. Mark is also the founder of the pre-seed workshop. The NCCR TransCure hosted this workshop, co-facilitated on site by Mark, on 17, 18 and 25 April in Bern, within the framework of SwissCompanyMaker.

For more info: http://www.preseedworkshop.com/
https://swisscompanymaker.ch/

Meet the NCCR TransCure Fellows

Bartłomiej Augustynek

I joined the group of Prof. Matthias Hediger at the University of Bern as a postdoctoral researcher in April 2017. This group is engaged in several research projects and hence I was able to immerse myself immediately into a vibrant research environment. At its core is the NCCR TransCure network established under the leadership of Matthias Hediger in 2010, within which my colleagues and I have been especially involved in the project focusing on the iron transporter DMT1 and FPN. We aim to determine the structure and function of these proteins and to develop their specific modulators. Being part of the NCCR TransCure is a great opportunity for an early-stage postdoc like me to gain unique scientific expertise and a network of collaborators that will be vital for my independent academic career in the future.

Daniela Hanke

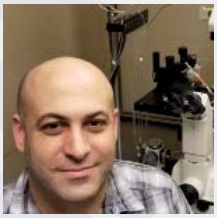
I have been a PhD student in the group of Prof. Daniel Fuster at the University of Bern for two years. The focus of my thesis lies in the study of membrane transporters, mainly cation/proton exchangers. This transporter family is studied in relation to widespread human diseases such as diabetes, osteoporosis and glioblastoma. Together with chemists, we aim to study the function and localisation of these transporters in vivo and in vitro, and to find compounds that act exclusively on them. These studies should explain the functionality of the transporters and lead to putative drugs for human diseases in which they are involved. The TransCure network allows me to work closely with collaborators from various fields and to be connected with a wide community of researchers working on similar topics. This is very important for studying our topics in the depth needed, getting feedback and exchanging ideas. The NCCR TransCure also helps PhD students to set project milestones and to present their progress to the community. In addition, we have the opportunity to acquire many skills through the NCCR TransCure courses and talks.

Ines Reynoso

I started as a postdoctoral fellow in the group of Prof. Jürg Gertsch at the University of Bern in September 2017. I obtained my PhD in Mexico by characterising the in vivo effects of a novel class of compounds called "selective endocannabinoid reuptake inhibitors" (SERIs), designed by the Gertsch group. The focus of my thesis was to explore the analgesic effect of the lead compound in mice models of acute and chronic pain. Currently, my research aims to elucidate the therapeutic potential of the SERIs in neuropsychiatric disorders, particularly in posttraumatic stress disorder. To understand the potential of SERIs as a valid approach, a mouse model with strong translatability is been generated. The behavioural outcome will be analysed in correlation with endocannabinoid levels in specific brain regions and markers of anxiety, such as corticosterone. I received one of the two NCCR TransCure Young Scientist Awards in 2017, from which I obtained funding for my research. Additionally, the “Mentor-Mentee Lunch” programme allowed me to meet Prof. Christine Peinelt, who advised me on career and oral presentation skills.

NCCR TransCure Alumni

Nicolas Montalbetti



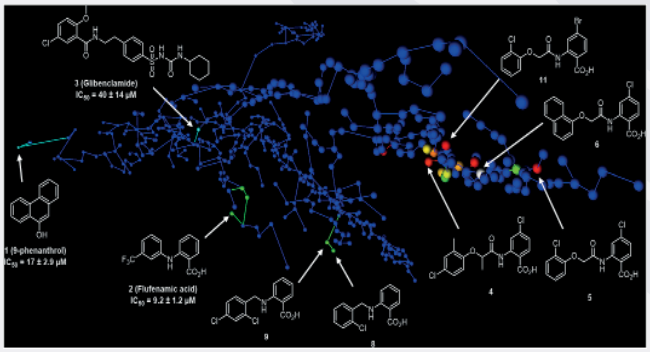
I joined Prof. Matthias Hediger’s lab at the University of Bern in 2011 after completing my PhD in Physiology at the University of Buenos Aires, Argentina. Currently, I have a faculty position at the University of Pittsburgh, USA. The goal of my project is to understand how changes in the permeability of urinary bladder epithelium lead to disease states. A central part of my project is to characterise the mechanism by which increased epithelial permeability sensitises bladder afferent neurons causing bladder hyperreflexia and pain. During my postdoc at the University of Bern, I was part of a multidisciplinary and multicultural team, which provided me with an excellent environment to expand my scientific horizons. I also enjoyed hiking in the Bernese Oberland and swimming in the Aare. Working in Switzerland was an outstanding experience!

2nd NCCR TransCure Young Scientist Award

The second round of this award that supports outstanding TransCure fellows was this time open to male as well as female scientists, and both are represented in the winning duo. From the four candidates, the selection committee composed of TransCure PIs gave the award to **Ines Reynoso** (Gertsch group) and **Lijo Ozhathil** (Abriel group). Congratulations and all the best for your projects!

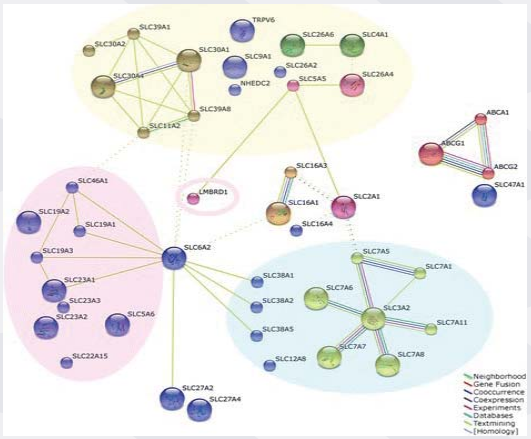
Publication highlights

Ozhathil LC, Delalande C, Bianchi B, Nemeth G, Kappel S, Thomet U, Ross-Kaschitza D, Simonin C, Rubin M, Gertsch J, Lochner M, Peinelt C, Reymond JL and Abriel H, *"Identification of potent and selective small molecule inhibitors of the cation channel TRPM4"*, British Journal of Pharmacology (2018), doi: 10.1111/bph.14220.



Due to the lack of suitable inhibitors, the cation channel TRPM4 has not yet been validated as a therapeutic target. Biologists and chemists in the Abriel, Peinelt, Lochner and Reymond groups discovered a potent and selective inhibitor of TRPM4 with an additional chemical chaperone feature. This discovery will lead to improved studies of TRPM4 and potentially to clinical drug candidates in the future.

Huang X, Anderle P, Hostettler L, Baumann MU, Surbek DV, Ontsouka EC, Albrecht C, *"Identification of placental nutrient transporters associated with intrauterine growth restriction and pre-eclampsia."* BMC Genomics (2018), Mar 2;19(1):173



Prof. Christiane Albrecht and collaborators recently identified three membrane transporters that are highly associated with transplacental nutrient deficiencies in intrauterine growth restriction and pre-eclampsia. This result represents a significant advance in the study of these gestational disorders, which commonly lead to poor perinatal outcomes worldwide.

Upcoming TransCure Events

Course: Single particle cryo-EM
Kaspar Locher (ETHZ) and Henning Stahlberg (UniBas)
22-24 August 2018 – Basel

Kids Lab Day 2018
26 August 2018 – Bern

Course: Genetics of transporters: a population-based perspective for non-specialists
Murielle Bochud (UniL)
20 September 2018 – Bern

8th Site Visit of the SNF Review Panel
University of Bern
9-10 October 2018 – Bern

End of Phase 2 Symposium
24 October 2018 – Bern

4th Endocannabinoid Pharmacology Meeting
25-26 October 2018 – Bern

Soft Skills Courses 2018
Taking over leadership tasks – with or without formal authority
Succeed in your PhD – thanks to good time management and organization
Kepos GmbH
6-7 November 2018 – Bern

More on www.nccr-transcure.ch

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