Swiss National Centre of Competence in Research

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NCCR TransCure
Excellence in Membrane Transport Research

Dear readers and colleagues,

Summer greetings from the National Centre of Competence in Research (NCCR) TransCure! Supported by the Swiss National Science Foundation, the NCCR TransCure is currently in its 7th year and, as you will read here, research developments and network activities are in full swing.

In addition to exciting research projects and results (see article on p. 2 and publication highlights on p. 7), the NCCR TransCure also involves strategy development. Currently, the network is in an intensive reporting phase, since both the annual report and the pre-proposal for the third and last phase (2018-2022) are due at the end of July. The latter document is a strategic milestone for the next years, as it defines the Phase 3 project portfolio and the developments foreseen in every action field of the NCCR. Maintaining excellent research activities and an interdisciplinary character will continue to be the main aims. To this end, the Institute of Biochemistry and Molecular Medicine (IBMM) at the University of Bern is glad to strengthen its interdisciplinarity by welcoming Martin Lochner (TransCure PI) in July 2017 as a tenured lecturer in chemistry.

Interdisciplinarity was also a keyword at the NCCR TransCure Annual Retreat, which took place on 11-12 May 2017. This well-established event is dedicated to scientific exchange and networking across disciplines and groups. Moreover, fellows have the chance to improve their communication skills at the poster session and this year, for the first time, by holding short oral presentations. The retreat was also the perfect occasion to officially congratulate Cristina Manatschal and Julia Kowal, recipients of the first NCCR TransCure Young Scientist Award (p. 6).

NCCR TransCure researchers will also be able to profit from several other activities (see events on p. 7). The summer break will be short; the 10th Biomedical Transporters Conference in Lausanne starts on 6 August 2017, with a rich scientific program, rounded out by several networking opportunities. On 4 October, the NCCR TransCure Symposium, focusing on membrane transporters and cancer, will take place in Bern. As usual, part of this event will be dedicated to equal opportunity themes. In between these two events, a specialised course in drug discovery (22 September) and soft skills training in career development (26-27 September) will be available to the fellows.

A special outreach event is the Night of Research, which will take place at the University of Bern on 16 September 2017. The NCCR TransCure will participate with interactive lectures for the general public on transporters.

All of these events foster communication inside and outside the network. As reported on p. 4, developing appropriate communication measures in large interdisciplinary networks is a challenge faced by all NCCRs. The NCCR TransCure is putting effort into providing modern communication channels, such as the website and social media. Moreover, we have recently started the development of a video gallery to showcase the NCCR TransCure projects. We look forward to the completion of the gallery and hope to get many views!

The NCCR TransCure wishes everybody a sunny and pleasant summer!

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

Natural products in drug discovery

Prof. Karl-Heinz Altmann, NCCR TransCure PI, is a leading expert in natural products chemistry. Here, he presents an insight into the history and relevance of natural products in drug development.

The use of natural remedies for the treatment of human diseases dates back thousands of years to the beginning of recorded medical history. Traditionally, (attempted) natural product-based therapeutic intervention involved mostly plant-derived extract mixtures, while isolating natural products as medical agents only appeared on the scene at the beginning of the 19th century, notably with the isolation of morphine from opium by the German pharmacist Friedrich Wilhelm Sertürner in 1804. Ever since, natural products have proven to be a unique and highly prolific source of lead structures for drug discovery and development. While the specific numbers in different analyses differ, mostly due to the scope of the natural product definition used, it has been estimated that between 25% and up to 65% of FDA-approved drugs are derived from a natural product (Fig. 1). Natural products engage in a multitude of interactions with proteins, either in the context of their biosynthesis and degradation or when exerting specific cellular activities. It has been suggested that the exquisite lead potential of natural products for drug discovery reflects their inherent capacity for protein binding.

The impact of natural product-based drug development has been most profound in the area of bacterial infections, where every fourth antibiotic in use today is derived from a natural product (!) but important natural product-based drugs have been developed for all the major diseases. There is, however, no generic strategy for turning a bioactive natural product into an actual drug. While a natural product has emerged as the final drug in many cases—examples are numerous antibiotics or the cancer drugs vinblastine, taxol, or doxorubicin—structural modification of the natural product by semisynthetic derivatisation was required in others, as exemplified by the rapamycin derivative everolimus (Fig. 2). The example of rapamycin also highlights the unique potential of natural products as enabling tools for biological pathway elucidation and (drug) target validation. The unravelling of rapamycin's mode of action led to the discovery of the central cell growth regulator mTOR (mechanistic target of rapamycin), which has become an important drug target in oncology and transplantation.

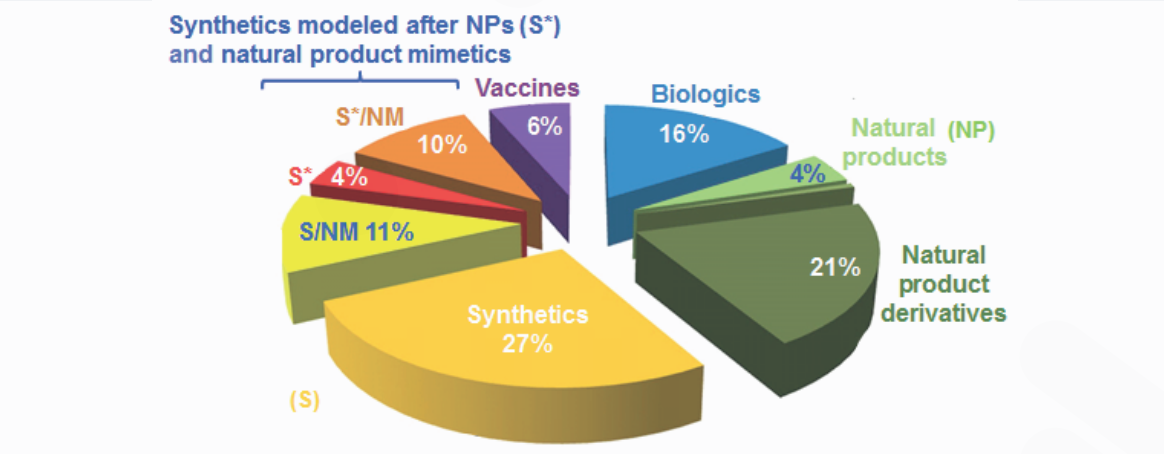


Figure 1: Sources of FDA-approved drugs 1981-2014. Graphic modified from D. J. Newman & G. M. Cragg, J. Nat. Prod. 2016, 79, 629. Note that the definition of the term "natural product" by Newman and Cragg also includes metabolites from human physiology, such as lipids, peptide hormones, steroid hormones, eicosanoids, nucleosides and neurotransmitters.

Finally, natural products may be developed into new synthetic drugs with distinct structural properties, a scenario that is illustrated by the development of the lipid-lowering agent atorvastatin (Lipitor®), the multiple sclerosis drug fingolimod (Gilenya®), and opioid-like analgesics such as tramadol (Tramol®). Natural product-based drugs that act on membrane transporters have also been developed, although their number is somewhat limited. The plant-derived indole alkaloid reserpine, which is a potent inhibitor of the vesicular monoamine transporter 2 (VMAT2), was employed in the 1950s as an antihypertensive and antipsychotic, but is only rarely used today.

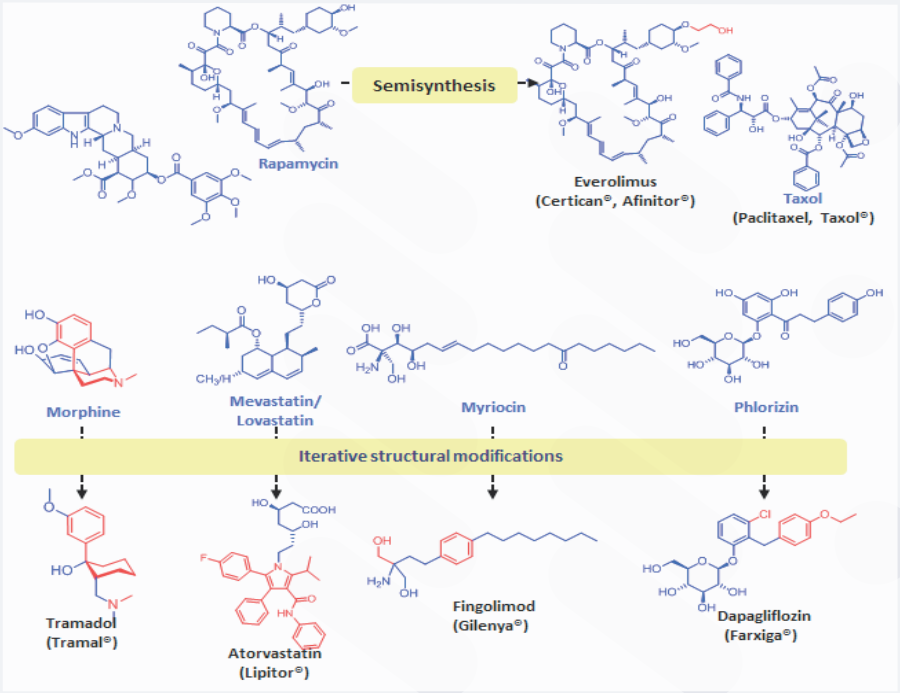


Figure 2: Selected examples of bioactive natural products and derived drugs.

More recently, the glycosylated dihydrochalcone phlorizin has served as the starting point for the development of gliflozins, an important new drug class for the treatment of type 2 diabetes (Fig. 2). Gliflozins are inhibitors of the sodium/glucose co-transporter SGLT2 (SLC5A2).

Over the last two decades, the importance of natural product-based drug discovery in the pharmaceutical industry has steadily declined. This is largely but not exclusively due to the reliance on high-throughput screening of large synthetic compound collections as the preferred hit and lead discovery platform. There is, however, a growing (re)recognition that natural products comprise a unique pool of structural diversity and unusual bioactivities and offer exceptional opportunities for the discovery of new drugs and drug targets. Thus, natural products will continue to play an important role in drug discovery in the years to come.

Karl-Heinz Altmann,
NCCR TransCure PI

How it works: Endocannabinoid system

Unlike neurotransmitters, which are stored in vesicles, endocannabinoids appear to be generated upon demand by most tissues. Although equally lipophilic, endocannabinoids are chemically different from tetrahydrocannabinol (THC) in cannabis or synthetic cannabinoids. They are generated through specific enzymes (e.g., lipases) from major membrane lipid precursors, including diacylglycerols and phosphatidylethanolamines containing arachidonic acid. In mammals, endocannabinoids not only selectively activate the G protein-coupled receptors (GPCRs) CB1, CB2 and GPR55, they also activate or modulate ion channels, such as TRPV1, GABAA and potassium channels. In the brain, CB1 receptors are among the most widespread GPCRs and their physiological roles have been studied extensively in the last decade. Endocannabinoids target presynaptic neurons, where they act as key retrograde messengers, inhibiting the release of both excitatory (glutamate) and inhibitory (GABA) neurotransmitters. They also inhibit inflammatory signals from microglial cells (via CB2 receptors). Endocannabinoids promote a major anti-stress signalling network that restores homeostatic imbalance related to inflammation, metabolism and synaptic transmission. It is possible to block the cellular reuptake of endocannabinoids in the brain, leading to analgesic and anxiolytic effects.

Jürg Gertsch,
NCCR TransCure PI

Communication in NCCRs: Learning from experience to face common challenges

In their daily effort to ensure optimal communication inside and outside the network, NCCRs make positive and negative experiences. Valuing all of them is possible and helps to improve the communication activity – also by sharing them.

On 23 March 2017, the Swiss National Science Foundation (SNSF) organised a meeting for NCCR Communication Officers entitled "Share your experience". Representatives from 18 NCCRs, together with SNSF officers, participated with enthusiasm in this event. After an introduction by Thomas Griessen (Science Officer, SNSF Programmes Division) and Daniel Saraga (Head of Science Communication, SNSF) on science communication and the relevance of failures as learning opportunities, the event was in full swing. Eight selected NCCR officers each shortly presented two illustrative cases—one positive and one negative. These served as the basis for lively discussions, which were moderated by the science communicator Andreas Trabesinger (Reinschrift Science Communication).

The variety of audiences and languages

A clear fact emerging from the presentations, regardless of the NCCR, was the diversity of audiences that NCCRs target with their communication activities. On the one hand, internal communication is the pillar that supports the entire information exchange among the large networks of collaborating groups. This encompasses scientific dialogue among fellows as well as the administrative information flow between management and researchers. Technical jargon, scientific vocabulary and NCCR-specific terms are the daily language of internal communication.

On the other hand, external communication is essential in order for the scientific knowledge generated to reach the academic environment and society. For the former, the communication style is scientific but is adapted to be understood by a broad community. For the latter, a further simplification of the vocabulary is needed. The general public is very interested in understanding research outcomes and is eager to hear answers to basic questions in an accessible language: How will a certain disease be cured, how can a new planet be discovered, or how will robots help us in our daily lives?

Finally, it is important not to forget the interaction with the media relations offices of the universities. Falling between internal and external communication, they are in charge of writing press releases that enhance the visibility of the achieved results. But, as the example of the NCCR PlanetS illustrated, *"C'est l'enfer sur la planète HD23101"* (scientist's favourite sentence) is not the same as "*Il fait plus de 1000 degrés sur l'exoplanète HD23101*" (University of Geneva press release). Different points of view on language, subject and timing of press releases can represent a real communication challenge.

The variety of measures: successes and failures

Internal communication aims for efficient information exchange and optimal involvement of the NCCR members. Events, opinions, scientific news and management communication are usually spread via email, newsletters and a variety of online tools, ranging from websites to social media. Advanced internal social platforms such as Yammer are rarely used due to the demanding management and collective participation effort. However, if well established, these tools can significantly improve internal collaboration, as the NCCR On the Move confirmed. They presented their experience with Yammer, which was used from the very beginning of the network. For scientific information exchange, network meetings involving smaller or larger sections of the NCCR (e.g., project meetings, retreats) are widespread. Nevertheless, even these common measures do not implicitly imply success and may need adaptations. NCCR Digital Fabrication, for example, faced poor participation in their weekly internal meetings that were coordinated by the management team. Based on feedback from their researchers, these events now take place monthly and are coordinated by fellows at different NCCR locations. The meetings include scientific presentations, discussions and an evening social event. Participation has increased dramatically.

Communication towards the general public often includes participation in public events organised by institutions or cities, such as University Research Days, Museum Nights, Children's or Seniors' Universities. Such events provide the opportunity to explain and discuss complex topics with lay people, as the NCCR RNA & Disease experienced at Scientifica (Zurich Science Day) in 2015. Thanks to dedicated scientists and excellent technical support from the organisers, the interaction with the wider public (25,000 total visitors) was definitely satisfactory. However, in planning outreach events, stumbling blocks may sometimes be encountered that need to be overcome. As the NCCR Affective Sciences explained, institutional disagreements or conflicting goals can sometimes interfere with

Communication in focus – the plenary room at the SNSF was a perfect environment for inspiring discussions on shared experiences.

planned activities. Creative solutions needs to be found. NCCRs also often have contact with schools by offering tailored courses. These are typically welcomed by the pupils. NCCR LIVES reported on the high level of satisfaction of both students and teachers with the "Kalendaro workshop", a game-based series of teaching sessions on life cycles and social inequalities, which reached 800 pupils (14-17 years old) between 2015 and 2017. Such activities nevertheless can be very demanding in terms of finances and personnel.

Know your story and audience and tell it like it is

In order to tip the scales from failure to success, the NCCR management team and the scientists have to work hand in hand in every phase of a communication activity—from the planning to the realisation. Considering the practical aspects, one major challenge is to find the right balance between available financial and time resources, and the need (or pressure from outside) to develop a specific measure. Scientists should not be distracted too much from their main focus, namely to carry out their research, however, they are the main players who own the core material of science communication. A challenging task of communication officers is to utilise researchers' potential for knowledge transfer and excitement for science in communication activities, while taking into account their busy schedules.

At the basis of efficient interaction between scientists and officers is careful planning of the communication measures. As Andreas Trabesinger explained to meeting participants, the main tasks of science communicators can be summarised in three points: *(1) know your story, (2) know your audience, and (3) tell it like it is*. The basic principles of communication theory should always be taken into account and used as a guide in the development of any activity. Moreover, participants were warned about the risk of implementing too many measures at the expense of quality. A few well-designed, targeted activities can have a much higher impact than several badly designed efforts.

Good theory and practice in communication should support the NCCRs in tackling the overarching challenge of developing an NCCR identity. Internally, this can translate into fostering a feeling of community among researchers, which is beneficial to their scientific collaboration. Outside the network, an NCCR identity is important in order to promote the relevance of these funding instruments and the impact they can have on society. This 'brand' recognition can also happen through simple actions such as the correct attribution of the NCCR affiliation in papers or newspaper articles, and in dealing with the press. Foreign journalists in particular might be interested in learning about national centres that pool the expertise of several universities in excellence networks.

The value of learning from experience

In all these communication processes, the SNSF remains a background reference point. They welcome discussions about new initiatives or special needs of the NCCRs as they arise. They plan to organise similar events again, to support this important attitude of sharing experiences, including both successes and failures. As all the participants learnt, this encourages broader communication and is an excellent way to understand problems and find better strategies, and to gain inspiration from success stories. Importantly, communication among communicators shows that many challenges are common amongst NCCRs, regardless of the research area, and the way problems are solved builds a valuable experience for the NCCR community. Because, as Steven Wright's words recalled by Andreas Trabesinger suggest, *"Experience is something you don't get until just after you need it."*

Valentina Rossetti
NCCR TransCure Scientific Officer &
Communication Delegate

Meet the NCCR TransCure Fellows

Roberta de Ceglia

I joined Prof. Andrea Volterra's laboratory at the University of Lausanne in February 2016 as a postdoc, after finishing my PhD in neuroimmunology at San Raffele Institute in Milan. Our lab investigates the role of astrocytes in physiological and pathological conditions. By using exclusive conditional cell-specific transgenic mouse lines, my project aims at understanding the astrocytic role of vesicular glutamate transporters (VGLUTs) in neuropathologies, e.g., epilepsy. The NCCR TransCure allows us to establish collaborations to develop specific astrocytic linkers against VGLUTs and demonstrate their importance in pathologies. The NCCR TransCure is an inspiring platform that encourages horizontal communication with peers and interactions with excellent scientists from other fields.

Pascal Häfliger

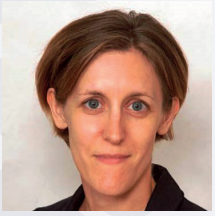
I joined the laboratory of Prof. Roch-Philippe Charles at the University of Bern in May 2013 as a PhD student. During my PhD, I had the opportunity to work in different NCCR TransCure projects. These collaborations offered me new insights into the field of chemistry, trained my networking skills and resulted in some interesting discoveries. In collaboration with the groups of Jean-Louis Reymond and Matthias Hediger, we described a new TRPV6 inhibitor that reduces proliferation of a breast cancer cell line in the low micromolar range. A recent finding, in collaboration with the groups of Karl-Heinz Altmann and Jürg Gertsch, is that the pharmacological inhibition of the L-type amino acid transporter LAT1 reduces tumour growth in vivo in a genetically engineered mouse model of thyroid cancer. This study revealed that the inhibition of LAT1 might be a new treatment option for thyroid cancer patients. I will finish my PhD soon and am looking forward to new challenges as a postdoc in the USA.

Anna Börgstrom

I joined Prof. Christine Peinelt's group at the University of Bern as a postdoc in 2016. My NCCR TransCure project focuses on the calcium-activated non-selective TRPM4 channel in prostate cancer. Thanks to close collaborations between the TransCure research groups of Hugues Abriel and Jean-Louis Reymond, we have access to a number of TRPM4 blockers. In my project, I am testing these blockers for inhibition of TRPM4 currents and their potential to alter cancer hallmark functions (e.g., inability to induce apoptosis, increased migration). Furthermore, we plan to investigate the contribution of TRPM4 in prostate cancer progression and metastasis by comparing wildtype and TRPM4-knockout rats in collaboration with Prof. Rudi Vennkens. With the use of electrophysiology, molecular and cell biology methods, I hope to gain valuable insights into the role of TRPM4 in prostate cancer.

NCCR TransCure Alumni

Lise Parmentier (Brethous)



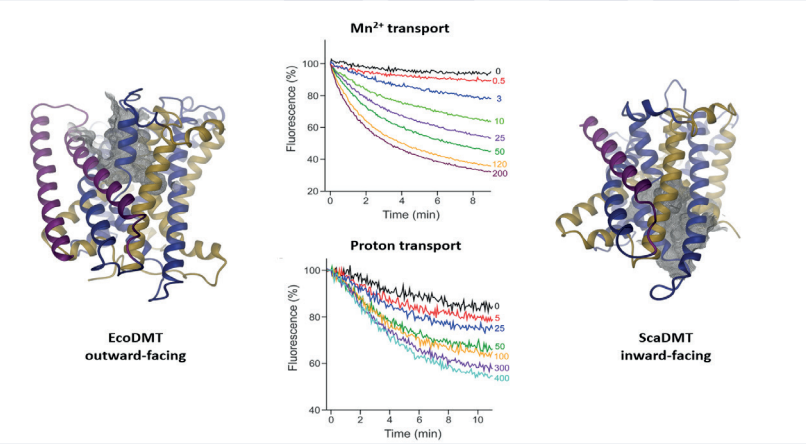
I recently joined a pharmaceutical company as a technical writer in regulatory affairs. My daily work consists of providing and updating the technical documentation for the application dossier for marketing authorisation of medicinal products. This documentation contains information such as the description of the manufacturing process, the analytical procedures and the characterisation of the drug. I joined Prof. Jean-Louis Reymond's group at the University of Bern in November 2009 and worked in the NCCR Transcure on new fluorescent transporters in 2011. This was a very good opportunity for me to work in a multicultural team with various experts (chemistry, computer science, biology, pharmacy). My experience in medicinal chemistry as well as in publication writing and my ability to interact with different experts helps me everyday.

1st NCCR TransCure Young Scientist Award

Launched in November 2016, the award supports the projects of outstanding TransCure fellows. A committee of NCCR TransCure PIs evaluated five applications and it is with great pleasure that we congratulate the two winners: Cristina Manatschal (Dutzler Group) & Julia Kowal (Locher Group). The second call for this award, which is open to all NCCR TransCure fellows, will take place in autumn 2017.

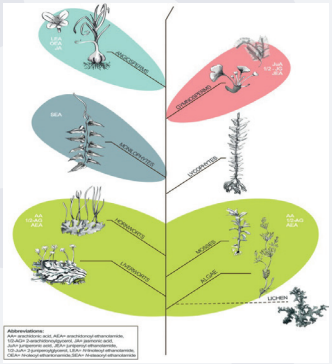
Publication highlights

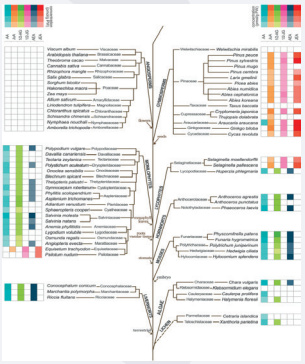
Ernsthofer IA, Manatschal C, Arnold FM, Laederach J, Dutzler R, "Structural and mechanistic basis of proton-coupled metal ion transport in the SLC11/NRAMP family", Nature Communications 8: 14033 (2017)



Transporters of the SLC11/NRAMP family transport essential trace elements such as the transition metals Fe^{2+} and Mn^{2+} and are highly conserved across all kingdoms of life. Thanks to a new structural and functional characterisation of prokaryotic SLC11 transporters, R. Dutzler and his team have provided significant advances in the understanding of transition-metal ion transport in the SLC11 family and important insight into its coupling to protons.

Gachet MS, Schubert A, Calarco S, Boccard J, Gertsch J, "Targeted metabolomics shows plasticity in the evolution of signalling lipids and uncovers old and new endocannabinoids in the plant kingdom", Sci Rep. 7:41177, 25 Jan (2017)





J. Gertsch and collaborators studied evolutionary relationships of signalling lipids in plants in nine plant groups and 71 plant species using targeted metabolomics. Their study is the first report on the molecular phylogenetic distribution of apparently ancient lipids in the plant kingdom, and reveals biosynthetic plasticity and potential physiological roles of endocannabinoid-like lipids in plants.

Upcoming TransCure Events

TransCure Lecture in Physiology
Armagan Kocer (Uni. of Groningen, NL)
21 June 2017 – Bern

10th Biomedical Transporters Conference
6-10 August 2017 – Lausanne

TransCure Lecture in Drug Design
Christopher Fowler (Umea University, SE)
8 September 2017 – Bern

TransCure Lecture in Biology
Laura Soucek (VHIO Barcelona, ES)
14 September 2017 – Bern

Night of Research, University of Bern
16 September 2017 – Bern

Course: Practical Drug Discovery in Chemical Space using Online Tools
22 September 2017 – Bern

Soft Skills Workshop: Career Opportunities in Science and Beyond
26-27 September 2017 – Bern

NCCR TransCure Symposium
4 October 2017 – Bern

Site Visit of the SNSF Review Panel
26-27 October 2017 – Bern

TransCure Lecture in Physiology
Milena Bellin (Leiden University, NL)
9 November 2017 – Bern

More on www.nccr-transcure.ch

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