Swiss National Centre of Competence in Research

Newsletter No. 8 / Dec 2017

NCCR TransCure
Excellence in Membrane Transport Research

Dear readers and colleagues,

The 8th year of the National Center of Competence in Research (NCCR) TransCure started on 1 November 2017. This is the last year of the second phase (2014-2018) and is an important transition to the next and final phase (2019-2022). As you will read in this issue, scientific advances and perspectives for the future make this time particularly exciting.

Already on p. 2, we present an intriguing scientific perspective – "Transporters and cancer: Rise of a new field?" This is the question that Roch-Philippe Charles, NCCR TransCure PI, addresses with an overview of current therapies and the possible role of transporters in the fight against cancer. This year, the network dedicated particular attention to this topic by choosing membrane transporters and cancer as the focus of the annual symposium (4 October 2017, Bern). Speakers from all over Europe contributed to this event with excellent and inspiring talks.

In addition to the annual symposium, the 10th BioMedical Transporters Conference (6-10 August, Lausanne) provided another occasion for scientific exchange at international level. Academic researchers and industry representatives gathered to discuss SLC transporters and ion channels in drug discovery and preclinical development. One of the conference sessions was dedicated to TransCure research.

The opportunities for interdisciplinary dialogue among experts at a national and international level are part of the research activity of the network, often resulting in outstanding papers. In the past months, two publications have appeared in high impact journals (see Publication highlights, p. 7). The groups of Kaspar Locher and Henning Stahlberg determined the structure of the human multidrug transporter ABCG2, while Jürg Gertsch's group achieved outstanding results on the inhibitors of endocannabinoid cellular reuptake.

The industriousness of TransCure researchers also goes beyond laboratory boundaries. As reported on p. 4-5, the network was recently involved in a series of outreach initiatives supported by TransCure fellows and PIs. The NCCR TransCure had the pleasure of interacting with an enthusiastic and interested public at the Bern Botanic Gardens (thematic day on the chemistry of plants) and at the Night of Research of the University of Bern. Moreover, the video gallery of the NCCR TransCure projects has now been officially launched and is available on YouTube. Based on these positive experiences, the network will continue with further outreach during Phase 3.

Finally, the NCCR TransCure strongly encourages fellows with an entrepreneurial spirit to participate in the April 2018 SwissCompanyMaker Pre-Seed Workshop. This event, in which the network has been involved for a couple of years, is a unique training opportunity to help innovative early-stage ideas turn into concrete entrepreneurial plans. The 2018 edition will take place in Bern and will be hosted by the NCCR TransCure, in collaboration with the NCCR RNA & Disease and the NCCR PlanetS. The call for idea champions is already open!

The NCCR TransCure Directorate wishes everybody a relaxing winter holiday season and a brilliant start of the new year!

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

Transporters and cancer: Rise of a new field?

Cancerous cells are driven by aberrant expression of genes that are usually tightly regulated. These oncogenes have been the focus of drug development for decades. With the resistance of cancer cells to oncogene targeting therapies, new solutions need to be found. Can the field of transporter research come to the rescue?

Cancer research sprouted from the virology field. Indeed, the first oncogenes were found in viruses and the pioneers of the field, like Mike Bishop, awarded a Nobel Prize for his discovery of the very first oncogene, v-Src, were virologists. After the discovery and characterisation of oncogenes, huge efforts have been undertaken to block the kinases responsible for the aberrant proliferation of cancer cells. This work was based on the oncogene addiction theory (Fig. 1). It was proposed in the early 2000s that cancer cells were 'junkies', addicted to the signalling generated by the mutant kinases. Therefore, the loss of this signal would induce a massive imbalance, which would ultimately lead to apoptosis. Cancer research thereby became an issue of biochemistry. A case in point is the receptor for the epidermal growth factor that sits upstream of the canonical MAP-kinase pathway that is involved in cell cycling. For example, cetuximab, a humanised monoclonal antibody, blocks the receptor's activation.

When growth receptors are targeted, non-cancerous cells are also affected, resulting in serious side effects. A major advance in this area has come from the field of structural biology. Plexxicon pioneered an approach using co-crystallography to develop inhibitors for mutant versions of oncogenes. They co-developed vemurafenib, a kinase inhibitor selective for a mutant version of BRAF that is found in 60% of melanoma patients. The tumour regression obtained was so striking that vemurafenib became the FDA's most rapidly approved drug to date. Unfortunately, with time most of the targeted therapies face drug resistance. Tumour cells are highly plastic, able to adapt to signalling pathway modulations and 'cure' their oncogene addiction.

An interesting issue with chemotherapy is that cancer cells tend to adapt and pump out xenobiotics, even with chemotherapy drugs that rarely diffuse freely through membranes (Fig. 2a). For instance, the multidrug resistance 1 (*ABCB1* gene) is responsible for the export of many drugs like doxorubicin. Since it is often upregulated in cancer cells, blocking this pumping system has been proposed as an anti-cancer approach, holding a lot of promise for potentiating current therapies. The challenge however resides in the plethora of transporters and their potential overlap, making drug development extremely challenging. The prevailing trend is the design of multi-transporter inhibitors.

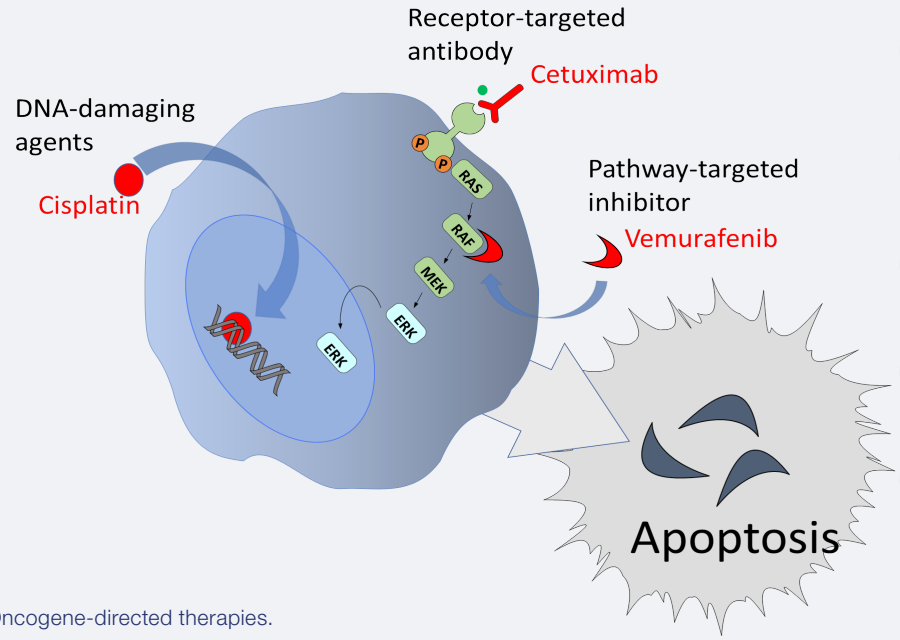


Figure 1: Oncogene-directed therapies.

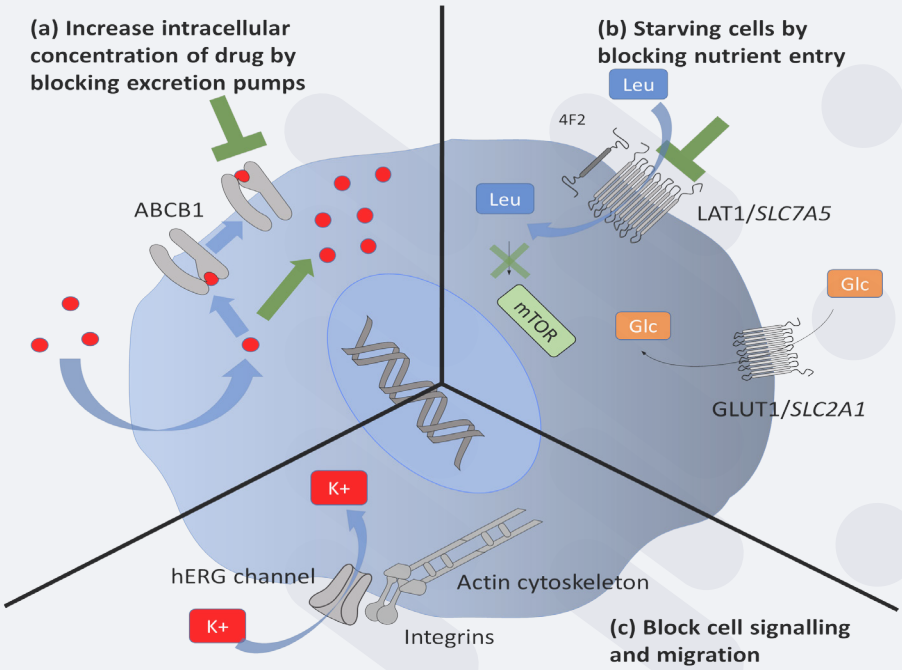


Figure 2: Transporters and cancers – multiple possibilities for tackling cancer cells.

Cancer cells also undergo a major change in metabolism, switching from aerobic to anaerobic metabolism (Fig 2b). This effect, first described by Otto Warburg and named after him, is also accompanied by an increased need for metabolites like glutamine and other amino acids. Starving cancer cells by blocking essential amino acid entry has anti-tumourigenic potential, especially when a membrane transporter like LAT1/*SLC7A5* is the main port of entry for leucine in several cancer types. The craving of cancer cells for glucose has also raised some interest, for example ^{18}F-FDG PET is currently used for imaging tumours. However, since GLUT-1 is ubiquitous, blocking glucose uptake in cancer cells is not possible because of potential toxicity.

Several ion channels play a role in cancer. Some are required for volume control and therefore for mitosis and proliferation. Most notably, ERG potassium channels have been found to influence cell signalling and to interact with the cytoskeleton. A binding between hERGB1 and integrin β, involved in signalling modulation and cytoskeleton re-arrangements, was observed in cancer cells. The idea would be to block the hERG/integrin scaffolding interaction with new agents (Fig 2c), to obtain an anti-cancer effect without affecting channel activity and avoiding potential arrhythmias.

The cancer field is a lively area at the intersection of several specialities. With the recent discovery of several transporters involved in cancer, there is definitely some room to develop a "transporters and cancer" field.

Roch-Philippe Charles,
NCCR TransCure PI

How it works: Placenta - the interface between mother and foetus

During pregnancy, the foetus depends completely on the mother for its nutrient supply, waste elimination and gas exchange. By the end of the first trimester, the placenta serves as a bridge between the maternal and the foetal blood circulation. The main functional units of the human placenta are the chorionic villi. These are protuberances of the placental tissue that provide maximum contact with the maternal circulation. The villi are covered by a layer of specialised placental cells called trophoblasts, which are the major functional components of the placental barrier. This layer is composed of an outer and inner surface characterised by distinct types of trophoblast cells. The outer surface is in direct contact with the maternal blood circulating in the space between the villi. The cells of the inner surface are closely aligned against the villous capillaries carrying foetal blood. As with other cell membranes, the placental barrier is rich with membrane transporters that are involved in the communication between the maternal and foetal environments. A malfunctioning of these transporters can lead to impaired growth of the foetus. NCCR TransCure researchers in the Albrecht group study the function of membrane transporters involved in amino acid, iron and lipid exchange, and their possible roles in diseases of pregnancy.

Christiane Albrecht,
NCCR TransCure PI

Science in the spotlight: When academia meets the public

When talking about science, researchers' jargon and formulas hardly support the thirst for knowledge of lay people. Public outreach is an effort to overcome this problem by improving the dialogue between academia and society. Read how the NCCR TransCure plays its part in this challenge.

"We live in a society absolutely dependent on science and technology and yet have cleverly arranged things so that almost no one understands science and technology…" *Carl Sagan, 1994*

Science communication is primarily in the hands of scientists. Their communication efforts have the potential to help the public understand the basics of science – something that can have a strong impact on society. However, scientific ideas can be complex and riddled with jargon, and as such, difficult to pass on to a lay public. Effective communication outside academia is a challenge for many researchers. One way to facilitate an understanding between scientists and society is to organise outreach activities. Going beyond the laboratory gives scientists the opportunity to improve their pedagogical skills, e.g., in simplifying their language when speaking to a lay audience. Along these lines, the NCCR TransCure recently participated in several public events and developed a video gallery. This article provides a brief report of our latest experiences with public outreach.

Strolling through molecules. On 9 September 2017, the NCCR TransCure groups of Jean-Louis Reymond and Jürg Gertsch presented several interactive stands at a day dedicated to "The chemistry of plants: drugs, scents & colours", organised by the Bern Botanic Gardens. Visitors took part in guided tours in the gardens, observing medicinal plants and listening to explanations about their use. In addition, they could try out various hands-on activities, such as the identification of substances by their scent, the extraction of colours from natural products, the distillation of essential oils and chemical separation techniques. One of the highlights was a virtual reality game. Equipped with special goggles and a joystick, visitors could move through a virtual garden where they had to find plants, which then transformed themselves into molecules when touched with a laser pointer. The software was designed by Daniel Probst, a PhD student in the Reymond group. This game allowed many people – who may have never seen a molecule before –to discover the atoms and bounds that constitute the geometrical structure of the molecules from a cannabis plant, a banana or an orange. *"I think the researchers here are doing a great job because everything they explained to me was very easy to understand, and I will remember what I have learnt today,"* commented an enthusiastic visitor. Interesting was also to hear that the cliché of the scientist as a bookworm is still alive: *"For me, scientists are people who read many books and have a lot of time for that,"* explained an old botany lover.

Et voilà, a cell made of Lego! This year, the Night of Research at the University of Bern on 16 September 2017 attracted about 9,000 visitors who took part in a broad spectrum of activities. The NCCR TransCure participated in this event by offering talks and interactive activities for kids, organised by the groups of Hugues Abriel, Christiane Albrecht and Martin Lochner. The didactic talks were accessible to the lay public and covered themes such as basic cell structure, natural drug development and medicinal plants, psychotropic drugs and neurotransmitters, and the functioning of the human placenta. During the discussion time, the audience actively participated, asking many questions. Kids had the opportunity to build cells with Lego bricks, observe living placenta cells under the microscope and learn how to identify plants. They could also participate in a lottery and with some luck win a book voucher. The researchers organising the activities reported receiving excellent feedback. *"The public is interested in research. For them, seeing all this is surprising. For us, it is rewarding to experience their interest,"* observed Sampada Kallol, a PhD student in the Albrecht group. Thuvarga Kalakaran, a Masters student in the same group, explained a placenta model to visitors: *"A lot of people are interested in the subject of pregnancy and I think we were able to improve their understanding."*

With instructions and a bit of imagination, kids built cells made of Lego bricks (Night of Research, Bern).

A virtual stroll through a garden of molecules gave visitors a chance to learn about chemistry in a very innovative and attractive way (Botanic Gardens, Bern).

With a camera in the lab. An important aspect of an NCCR is to increase visibility outside the network. One way to do this is by sharing the research that each group is pursuing. Videos, with their straightforward format to convey a message, are a useful tool to reach a large audience. In 2016, the NCCR TransCure began its video gallery project to share its research activities expertise and achievements with the scientific community, prospective students and the interested public. A short video for each NCCR TransCure project is planned. The video production team, composed of Valentina Rossetti (NCCR TransCure Scientific Officer and Communication Delegate) and Patricia Teixidor (Scientific Officer at the Univ. of Bern), worked in close collaboration with the researchers to define the video plot and identify suitable scenes. This preliminary work was fundamental to successful shooting sessions and a smooth editing process. The resulting videos take the viewer through the science and the labs, and introduce the many people who make the NCCR TransCure a lively, interdisciplinary research environment. The videos are available on the NCCR TransCure website, on Vimeo and YouTube – follow us!

For the researchers, the challenge was twofold: Condensing a large amount of information into a very short time, and breaking down a highly specialised terminology so that it was understandable to a general audience. The hard work paid off and resulted in a true learning experience – by addressing the lay public, researchers put themselves in a totally different mindset and were forced to think about their research from another perspective. This process of searching for simpler explanations can help to explore new aspects of the subject, previously not considered.

Show me science! Science communication is increasingly gaining relevance in a variety of academic and institutional environments. Both Rossetti and Teixidor received proof of this at "ScienceComm'17", the annual congress on science communication organised by the foundation "Science et Cité", the Swiss Academies of Arts and Sciences' competence centre for dialogue. This conference took place on 21-22 September 2017 in Solothurn and gathered together science communicators from all over Switzerland who are active in universities, museums, academic umbrella organisations and journalism. Under the motto "Show me science!", several workshops and dialogue sessions allowed the participants to get a glimpse of the latest trends. Ranging from virtual reality and visual story-telling in an educational context to creative skills learning and science camps for kids (just to mention a few), the Swiss science communication landscape is rich in innovative ideas. The congress was a source of inspiration for future work in the NCCR TransCure and an excellent opportunity for networking.

Out of the ivory tower. By collaborating in the recent NCCR TransCure outreach activities, researchers were able to be part of the exchange between science and society, enjoying the rewarding interactions but also learning the many challenges of this type of communication. The new generation of researchers, open to dialogue and ready to meet the public, has a big responsibility for the future. *"The notion of academia as an 'ivory tower' is on the way out, while science communication is rapidly gaining traction,"* explained Christophe Giovannini, Head of Communication Division, SNSF. *"Today more than ever, the taxpayer deserves to know how science benefits society and why basic research has fundamental implications, not only for the availability of knowledge but also for the future of education, the economy, and society as a whole,"* he continued. He also stated the importance of science communication for the SNSF itself, which is "*making a concerted effort to communicate and to encourage researchers to share their methods and results with the public.*"

This background, together with the positive results of the NCCR TransCure public communication efforts, are a strong motivation to continue our outreach – with one overarching aim: Let the excellent science of the NCCR TransCure flow out of the network and have an impact within and outside the academic field.

Patricia Teixidor (Scientific Officer, University of Bern)
and
Valentina Rossetti (NCCR TransCure Scientific Officer)

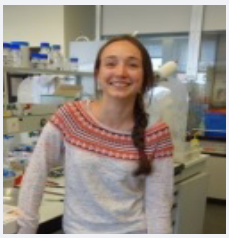
Visit the NCCR TransCure video gallery:
www.nccr-transcure.ch/communication/video-gallery/
https://tinyurl.com/y75ra6lr

Meet the NCCR TransCure Fellows

Karthik Ramanadane

I started as a PhD candidate in Raimund Dutzler's group at the University of Zurich in September 2016. Within the NCCR Transcure network, our laboratory investigates the structure and function of iron transporter proteins of the SLC11/NRAMP family. The members of this family are involved in frequent pathologies such as anaemia or haemochromatosis. Although our work has provided initial insight into the architecture of the family, the details of how SLC11 transporters catalyse the co-transport of protons and iron are still unknown. My project focuses on the mechanisms of selectivity and proton coupling within this family. For that purpose, I combine X-ray crystallography and functional assays using purified and reconstituted proteins.

Marion Poirier



In January 2015, I joined the group of Jean-Louis Reymond at the University of Bern as a PhD student, after my diploma in chemistry at the Engineering School of Chemistry of Rennes in France. I am currently working on VMAT2 in astrocytes and on the iron transporter DMT1. In both cases, I am interested in the synthesis of small molecule inhibitors of the target proteins. In the context of studying the structure and biological role of DMT1 in iron overload, collaborations with the groups of Matthias Hediger and Raimund Dutzler allow me to participate in the development of a potent and selective compound for this protein while working in a stimulating interdisciplinary environment. The NCCR TransCure gives me the opportunity to discover new approaches and widen my perspectives, which contributes to the success of my projects.

Hassan Melhem

I started my research on inflammatory bowel disease (IBD) as a PhD student at the Faculty of Medicine of Nancy in France. I studied the role of SIRT1 in endoplasmic reticulum (ER) stress regulation induced by methyl donor deficiency (MDD) during IBD. I showed that MDD aggravates colitis in animals using a SIRT1-mediated ER stress response. In my second post-doc, I studied the role of the antioxidant enzyme Prdx6 in IBD. Results showed that Prdx6-/- mice exposed to acute and chronic dextran sulfate sodium-induced colitis showed a significant decrease in clinical parameters and colon levels of pro-inflammatory cytokines compared to wildtype mice. In July 2017, I joined Christiane Albrecht's group at the University of Bern. I am currently studying the role of DMT1 and ferroportin in the placenta as well as the impact of diabetic conditions on placental iron homeostasis. In order to study the underlying mechanisms associated with hyperglycemia with altered placental iron homeostasis, we have generated novel BeWo trophoblast cell lines adapted to normoglycemic, hyperglycemic and hyperglycemic-obese conditions. In phase 3 of the NCCR TransCure, we plan to generate and characterise placenta-specific knock-out mice for iron transporters.

NCCR TransCure Alumni

Jennifer Hemmings

In 2012, I joined the NCCR TransCure as a postdoctoral fellow in chemistry thanks to the TransCure International Fellowship Program. I worked in Martin Lochner's group at the University of Bern on fluorescent agonists for the adenosine receptor. Following this, I joined the agrochemical industry working as a regulatory specialist and more recently as a regulatory manager. Through the NCCR TransCure, I gained experience working in a multidisciplinary team in an international environment. This is a skill that I now use every day. Working with the network also gave me a broad exposure to areas of science that were often unfamiliar to me. Being able to pick up and quickly understand new and diverse areas outside my expertise in chemistry is now an essential part of my work.

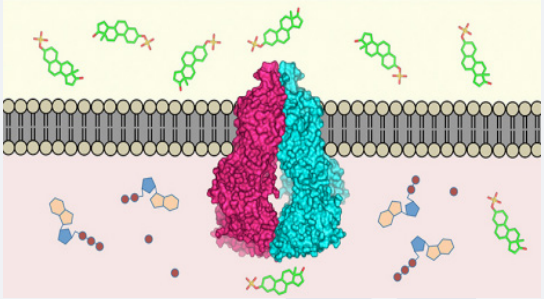
SwissCompanyMaker Pre-Seed Workshop

The NCCR TransCure will host the 2018 edition of the SwissCompanyMaker Pre-Seed Workshop **in Bern** on **17, 18 and 25 April 2018.** The workshop targets young potential entrepreneurs who want to test the marketability of their high-tech ideas and get valuable input from experts on how to move ahead. A preliminary, independent course on intellectual property will be offered on **29 January 2018** by the Swiss Federal Institute of Intellectual Property.

Boost your idea and apply today at:
https://swisscompanymaker.ch/

Publication highlights

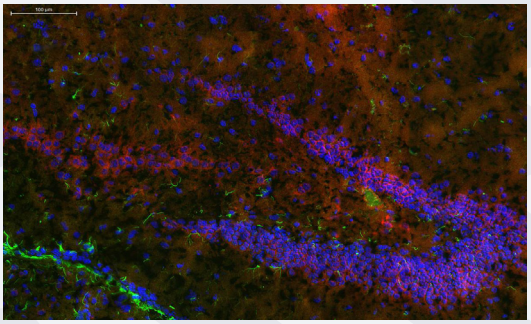
Taylor NMI, Manolaridis I, Jackson SM, Kowal J, Stahlberg H, Locher K, "Structure of the human multidrug transporter ABCG2", Nature Jun 22;546(7659):504-509 (2017)



© ETH Zürich / S.Jackson, I. Manolaridis, K.Locher

Researchers in the groups of K. Locher and H. Stahlberg determined for the first time the high-resolution, three-dimensional structure of a human multidrug transporter, the ABCG2 protein. This membrane transporter has important roles in the extrusion of endogenous and exogenous substances, and affects the pharmacokinetics of many commonly used drugs. The activity of ABCG2 also has a negative effect on the efficacy of anti-cancer drugs, which are extruded from tumour cells. This breakthrough study, which was accomplished using cutting-edge single particle cryo-electron microscopy, may in the long term allow for new approaches aimed at improving cancer therapies.

Chicca A, Nicolussi S, Bartholomäus R, Blunder M, Aparisi Rey A, Petrucci V, del Carmen Reynoso-Moreno I, Viveros-Paredes M, Dalghi Gens M, Lutz B, Schiöth HB, Soeberdt M, Abels C, Charles R-P, Altmann K-H, Gertsch J "Chemical probes to potently and selectively inhibit endocannabinoid cellular reuptake" PNAS 114:25 (2017)



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The endocannabinoid system is involved in several pathophysiological conditions in brain and peripheral tissues. J. Gertsch and collaborators recently reported the synthesis and characterisation of the first potent and selective inhibitors of endocannabinoid cellular reuptake. These inhibitors increase the levels of endocannabinoids and show a novel pharmacological modulation of the endocannabinoid system, leading to anxiolytic, anti-inflammatory and analgesic effects. Selective endocannabinoid reuptake inhibitors pave the way towards the development of new drugs that modulate endocannabinoid signalling.

Upcoming TransCure Events

TransCure Lecture in Biology
Christian Löw (EMBL Hamburg, DE)
11 December 2017 – Bern

Intellectual Property Training
Swiss Federal Institute of Intellectual Property
29 January 2018 – Bern

SwissCompanyMaker Pre-Seed Workshop
17, 18 & 25 April 2018 – Bern

8th NCCR TransCure Annual Retreat
24-25 May 2018 – Spiez

TransCure Lecture in Physiology
Lucie Delemotte (KTH Royal Institute of Technology, Solna, SE)
6 June 2018 – Bern

More on www.nccr-transcure.ch

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