Swiss National Center of Competence in Research

# Newsletter 05 / 2016

NCCR TransCure
Excellence in Membrane Transport Research

**Dear readers and colleagues,**

We are pleased to update you on the activities of the National Center of Competence in Research (NCCR) TransCure, supported by the Swiss National Science Foundation (SNSF). We are currently in the middle of phase II (2014-2018) and year 6 is in full swing.

At the beginning of phase II, we welcomed the group of Murielle Bochud (CHUV Lausanne), who brought her expertise in the genetics of membrane transporters, which is of interest to most of the ongoing NCCR TransCure projects. Afterwards, the network expanded further with the involvement of the associated groups of Sven Rottenberg and Christoph von Ballmoos, both at the University of Bern, adding expertise in cancer biology and membrane protein biochemistry. This summer, Christine Peinelt from Saarland University (Homburg, DE) will start as a new NCCR TransCure professor at the IBMM. Christine studies the biology of ion channels, in particular TRPM4. You can learn more about her expertise and the planned integration of her studies into the NCCR TransCure projects in this issue's lead article on pages 2-3.

A further welcome goes to a new member of the NCCR TransCure management office, Jolanda Paganoni, who joined the team in February 2016 as an administrative coordinator. Jolanda has a background in tourism science and experience in the administration and marketing branches. From June 2016, she will work in a job sharing arrangement with Johanna Portmann, who will be back in the team.

Year 5 saw a significant expansion of our network activities and in our relation to other NCCRs. Examples include the organization of a course on scientific presentation skills together with the NCCR Kidney.CH and the NCCR RNA & Disease, and our participation in the SwissCompanyMaker pre-seed workshop together with four other NCCRs. The challenges and opportunities of collaborating with different NCCRs are discussed further on pages 4-5 of this issue in an interview with two NCCR directors.

The NCCR TransCure aims to produce high-quality science and to educate the next generation of biomedical research scientists. The network has seen its first generation of PhD students graduate and leave the network, and a series of new fellows join various research groups. Three of our current NCCR research fellows and one of our alumni are featured on page 6. A snapshot of our publication output is also provided, with two selected publication highlights, as well as a list of the NCCR TransCure events planned for this year. These include our yearly retreat in Baden (19-20 May), a one-day symposium on drug design (16 Sep) and the 3rd edition of the Endocannabinoid Pharmacology Meeting (14-15 Oct). Details of these and other events, as well as the rich calendar of TransCure Lectures for this year, are available on our website (www.nccr-transcure.ch). The website will be relaunched with a fresh and modern design in summer 2016. We hope you will like the new design and welcome your feedback. Do not forget that you can also follow the NCCR TransCure on Twitter: @NCCR_TransCure.

We wish you a good and productive summer!

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

# STIM/Orai and TRPM4 ion channels: Potential players in the pathophysiology of prostate cancer

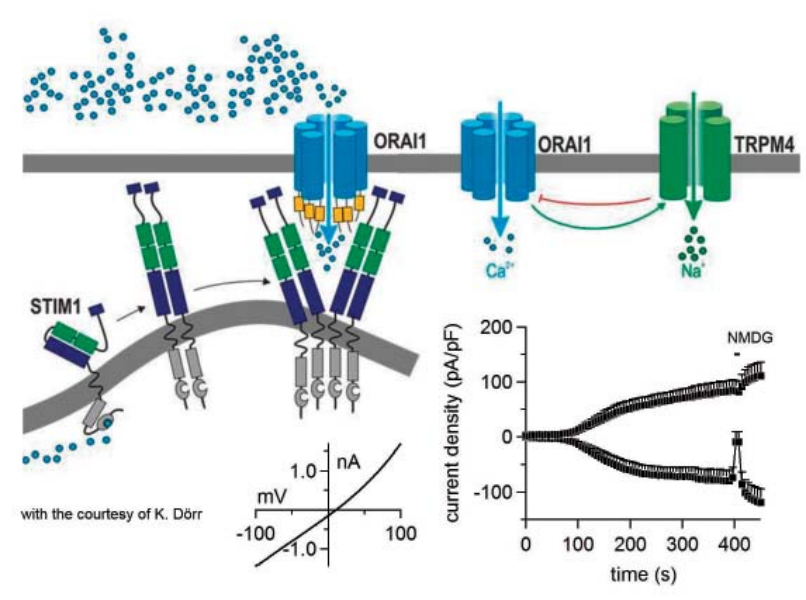
**Christine Peinelt, who joins the NCCR TransCure as a new PI in July 2016, presents her research focus and perspectives.**

The research focus of my group is the investigation of ion channels (STIM/Orai and transient receptor potential melastatin 4 channel; TRPM4) in the pathophysiology of cancer and immune disease. In prostate cancer cells, imbalances in intracellular $Ca^{2+}$ contribute to several cancer hallmark functions, such as unlimited proliferation, an inability to induce apoptosis, and increased migration. We recently reported on a shift in Orai1/Orai3 $Ca^{2+}$ channel subunits in prostate cancer, with consequences for the pharmacology of $Ca^{2+}$ signals in prostate cancer cells [1, 2]. Orai1/Orai3-dependent $Ca^{2+}$ entry activates the $Ca^{2+}$-dependent TRPM4 channels. TRPM4-mediated $Na^{+}$ influx can depolarize the membrane potential, decreasing the driving force for $Ca^{2+}$ and reducing $Ca^{2+}$ signals as a feedback mechanism (upper panel in the figure on page 3). In prostate cancer, TRPM4 is elevated and knockdown of TRPM4 by siRNA reduces migration of prostate cancer cells [3].

Building on these findings, summarized in [4], our project within the NCCR TransCure will investigate the physiological and pathophysiological consequences of Orai1/Orai3 and TRPM4 impairments in prostate cancer cells. Making use of the excellent NCCR TransCure research environment, we plan to test several TRPM4 blockers (commercially available as well as novel blockers made available to us by Prof. Reymond) and Orai channel blockers (made available to us by Novartis, Basel and Prof. Mikoshiba, Institute for Protein Research, Osaka University, Japan) for their ability to alter cancer hallmark functions of prostate cancer cells. The culturing of primary human prostate epithelial cells from healthy tissue is well established in my current lab. In order to strengthen the translational aspect of our research, we will collaborate with Prof. Thalmann (Department of Urology, Inselspital, Bern University Hospital) to establish this cell culture in Bern. These cells will serve as a control for the effects of TRPM4 blockers and their cytotoxicity in healthy cells. Future investigations of small molecules targeting $Ca^{2+}$ signaling (Orai1/Orai3 and TRPM4) in prostate cancer cells will be performed in cooperation with the NCCR TransCure Screening Facility (Prof. Gertsch). One of the main techniques we use to detect Orai1/Orai3- and TRPM4-mediated currents in prostate cancer cells is electrophysiology (lower panel in the figure on page 3). In addition, we plan to investigate the contribution of TRPM4 in wildtype and TRPM4-knockout mice in order to identify a possible role of TRPM4 in the development of prostate cancer (collaboration with Prof. Abriel).

In order to overcome the limitations of 2D cell culture, one long-term goal of our project will be the cultivation of different 3D human spherical prostate cancer model systems (tumorspheres, tissue-derived tumor spheres and organotypic multicellular spheroids). Cellular functions will be investigated with 3D light sheet microscopy. Following the implementation of this 3D technology, we aim to test the potential of Orai1/Orai3 and TRPM4 blockers to affect cancer cell migration, proliferation and apoptosis under more physiological conditions.

In addition to its quest for scientific excellence, the NCCR TransCure also aims to ensure equal opportunities for men and women, and the sustainable education of early career researchers. Forward-looking measures have been taken by the directorate to enable equal opportunities. My personal commitment to increasing the number of women in leadership positions will include, among others,




mentoring of young female academics within the Mentoring for Women Program (M4W). I hope that many talented women will accept my offer of personal mentoring.

I am excited about the warm and welcoming environment of the NCCR TransCure and look forward to working in this supportive atmosphere and synergistic research setting.

[1] Holzmann C, Kilch T, Kappel S, Armbruster A, Jung V, Stockle M, Bogeski I, Schwarz EC and Peinelt C. ICRAC controls the rapid androgen response in human primary prostate epithelial cells and is altered in prostate cancer. Oncotarget. 2013; 11: 2096-2107
[2] Holzmann C, Kilch T, Kappel S, Dorr K, Jung V, Stockle M, Bogeski I and Peinelt C. Differential Redox Regulation of Ca(2+) Signaling and Viability in Normal and Malignant Prostate Cells. Biophys.J. 2015; 7: 1410-1419
[3] Holzmann C, Kappel S, Kilch T, Jochum MM, Urban SK, Jung V, Stockle M, Rother K, Greiner M and Peinelt C. Transient receptor potential melastatin 4 channel contributes to migration of androgen-insensitive prostate cancer cells. Oncotarget. 2015; 39: 41783-93
[4] Kilch T, Kappel S and Peinelt C. Regulation of $Ca^{2+}$ signaling in prostate cancer cells. Channels (Austin). 2016 Jan 8:1-2.

# How it works: The role of membrane transporters in drug disposition

Drug disposition includes intestinal absorption and distribution in the body, often followed by metabolism, and then ultimately excretion from the body. Organs are separated by barriers from the circulation and/or from outside and substances cannot cross cell membranes without transporters. Hence, these have a major impact on drug disposition, e.g., by mediating drug uptake in the intestine. Enterocytes, the intestinal absorptive cells, are also equipped with ABC transporters, which prevent drug entry. ABC transporters, in particular MDR1, may be induced by drugs, which then lowers drug absorption. Not only in the intestine, but in the whole body, transporters mediate uptake of drugs into the individual organs. MDR1 is also a major efflux system in organ barriers, where it protects, e.g., the brain from drugs. Transporters may be inhibited by drugs or several drugs may also compete for one transporter, resulting in drug-drug interactions (DDI). DDI lead to altered concentration and efficacy of drugs and/or side effects. Therefore, both American (FDA) and European (EMA) health agencies require in vitro studies with transporters for the approval of a drug.

Bruno Stieger,
NCCR TransCure PI

# NCCRs: A challenge of synergies

**NCCRs are complex networks that play a relevant role in shaping the current and future scenarios in many scientific areas. François Verrey and Hugues Abriel, directors of the NCCR Kidney.CH and the NCCR TransCure respectively, explain how collaborations within and between NCCRs can have an impact on this process.**

**Your NCCRs are now in their sixth year. How did the scientific collaboration within your network evolve during these six years?**

Verrey: This is a broad question because fostering collaboration within the Swiss kidney research scene is a major aim of our NCCR. There were pre-existing collaborations in the context of Swiss nephrology and nephrological research, but they were often hampered by issues of competition between centers. A very positive effect of the NCCR Kidney.CH is that our scientists strengthen their collaborations, so that in many instances local competition has decreased as people work towards a common goal. They have realized that they are stronger when working together than working apart, and this is important. Practical examples of success are the numerous collaborative studies that have already led to publications and the ongoing clinical projects and genome-wide association studies involving research groups from different locations. Another important collaborative success is the Swiss Kidney Stone cohort, in which all five nephrology clinics of the Swiss university hospitals are participating. The evolution of the collaboration is hence very positive, but it must be mentioned that the financial support provided by the NCCR represents a strong incentive to do common work.
Abriel: In the NCCR TransCure, the situation is different because we do not have the common 'umbrella' of the kidney that the NCCR Kidney.CH has. Our NCCR is much more multidisciplinary. The challenge is to bring together scientists who are all interested in transporters, but have expertise in physiology, pathophysiology, structural biology, and chemistry. These are different types of scientists with different working methods. Our collaborative effort in the NCCR TransCure has matured quite a lot during the past years. An important decision has been to have project meetings on a regular basis—at least three times a year—in order to bring people from the different disciplines together so that they can interact with their colleagues. As an example, in the project on the cation channel TRPM4, we as physiologists are collaborating very closely with chemists. Thus, our students need to understand what the chemists are doing, and vice versa. It is really interesting to follow how this is developing.

**Other NCCRs work in scientific areas closely related to yours. Do your researchers collaborate with scientists in these NCCRs as well?**

Abriel: We share a common interest in pathophysiology with the NCCR Kidney.CH and there are NCCR TransCure PIs that are also PIs in NCCR Kidney.CH. The same is true for the NCCR Chemical Biology. This is of course interesting. However, scientists typically work within their networks and at the moment there is not much collaboration at the scientific level beyond the individual NCCR boundaries.
Verrey: I would tend to agree. Since there are PIs involved in other NCCRs, there are of course overlaps of interest and possible points of contact that might increase in the future, but at the moment we have punctuated collaboration rather than cooperation on a regular basis.

**In addition to scientific excellence, NCCRs are also active in education, equal opportunities, communication and technology transfer. Does your NCCR profit from cooperation with other NCCRs in these fields?**

Verrey: There are good opportunities for cooperation in these areas because NCCRs have the same type of framework and face common expectations from the SNSF. This allows us to co-organize soft skills courses with other NCCRs, such as the one on presentation skills in which the NCCR TransCure also participated. Further possibilities exist in the context of equal opportunities and we should increase these types of cooperation because these areas are only relevant for a fraction of people within the network, and joining forces can help us to improve measures.
Abriel: I agree. A further example is the upcoming course on how to make short scientific movies, organized by the NCCR TransCure together with three additional NCCRs.

**Competition can act as an antagonist in collaborations. How do you cope with the risk that competition disrupts important network links?**

Verrey: Competition is something that exists and can also be positive. In the NCCR Kidney.CH, we have

F. Verrey and H. Abriel talk about cooperation within and between NCCR programs.

organized collaboration whereby responsibilities and authorships are pre-discussed. So far, competition has not been a problem. On the contrary, the existence of the NCCR has helped us to go beyond basic competition and to work together, since the added value gained is of more importance.
Abriel: Within the NCCR TransCure it is more difficult to observe competition, since scientists come from different fields and have different horizons. Our scientists definitely recognize the added value and the potential of collaboration.

**NCCRs are expected to produce structural changes at the institutional level. What type of collaborations do you see as a prerequisite for successful and enduring structural changes?**

Verrey: This is probably one of the most difficult issues. For as long as we are financed, we maintain our strength and have the means to enforce collaboration. However, what continues afterwards cannot only be a virtual structure; it also needs to have a concrete output, and therefore money is a central issue. So far we do not have a good solution for that. The University of Zurich would rather commit to supporting new initiatives than those that are ongoing—that is understandable. There are some NCCR Kidney.CH initiatives, such as the Swiss Kidney Stone cohort, that will continue in the future, but which will need to obtain independent funding in the long term. Also worth mentioning is the Integrative Kidney Physiology and Pathophysiology (IKPP) postdoctoral program that started within the NCCR Kidney.CH and which is supported by the EU. In this context, a blended learning program conceived and financed by the NCCR Kidney.CH has recently been accepted by the University of Bern as a CAS and DAS program. It is very important that kidney research in Switzerland continues at a high level and involves notable collaborations. We hope that what the NCCR Kidney.CH does will strongly impact the way the Swiss Society of Nephrology and the Swiss kidney research community work together to advance kidney research in the future.

**What are the key 'ingredients' for successful long-term collaborations?**

Verrey: One major ingredient is visibility. It is important to increase the awareness and visibility of kidney research, in particular as regards the progression of Chronic Kidney Disease (CKD). The aim is to strengthen the prevention of CKD, which is a major health problem in the aging population, and to support research in this field. The second ingredient is people. Currently, we have many young people working in kidney research. They will hopefully continue to work and strengthen collaborations in this field in Switzerland and worldwide. This will have an important long-term effect.
Abriel: The first ingredient for me is sustainability. We need a long-term vision of what we want to achieve. In the academic environment of an NCCR, sustainability means training good scientists and trying to find a good balance between the available funds and the support needed by the various areas in which the NCCR is active. The next two ingredients start with "trans", namely transdisciplinarity and translational science. Transdisciplinarity is very relevant to the NCCR TransCure. I am convinced that what we once knew as disciplines are concepts with moving borders. We are in fact often integrating expertise and concepts from different angles, such as system biology and bioinformatics. This can be very difficult, however it is a necessity and represents the future of biomedical research. Translational science is something I have been learning about and enjoying in the past years. It can be explained as a way of thinking, not only about science itself, but also about more general aspects such as inclusivity and diversity in science. Gender equality is a very important aspect, as is the broadening of our thinking horizons beyond national (Swiss) borders. And like François Verrey, I would also say that people play a fundamental role for long-term success.

Interview: Valentina Rossetti
Interview partners: François Verrey (NCCR Kidney.CH) and Hugues Abriel (NCCR TransCure)
NCCR Kidney.CH Annual Retreat, SBB Center Löwenberg, 26.02.2016

# Meet the NCCR TransCure Fellows

### Beatrice Bianchi

I have been doing my PhD in Prof. H. Abriel's lab since July 2014. Our lab is mainly focused on channelopathies in cardiovascular and neurological systems, and I am currently involved in two projects on the calcium-activated non-selective TRPM4 channel. The first project involves the identification of cellular and biochemical pathways linked to gain-of-function and loss-of-function TRPM4 variants found in patients with cardiac conduction disorders. New selective TRPM4 inhibitors, generated in collaboration with Prof. J.-L. Reymond's lab, are being tested for their molecular chaperone activity on loss-of-function TRPM4 variants. The second project investigates the involvement of TRPM4 in neurodegenerative diseases such as multiple sclerosis. The above-mentioned compounds are being tested as potential new drugs in a mouse model of multiple sclerosis (experimental autoimmune encephalitis). The NCCR TransCure is an exciting platform to share ideas between research labs and gives me the opportunity to work together with excellent scientists.

### Cristian Carmeli

I am a biostatistician with a PhD in applied mathematics from EPF Lausanne. My role in the NCCR TransCure is to identify targeted physiological and pathophysiological human traits associated with the genetic variants located within and around genes encoding for transporters of interest to TransCure research groups. I work under the direction of Prof. M. Bochud and with Dr. I. Guessous at IUMSP, Lausanne. Thanks to the extensive database and biobank of the Swiss multicentric cohort "SKIPOGH", we will explore molecular phenotypes spanning genomic, epigenomic, transcriptomic, and metabolomic data, as well as macroscopic phenotypes, including anthropometry, renal and cardiac function, and many others. We hope to build a bridge between the basic research performed in the NCCR TransCure and clinical research, to generate knowledge relevant to understanding, treating and preventing human diseases.

### Melanie Zechner

I joined the group of Prof. K.-H. Altmann as a PhD student in January 2015, after finishing my studies in chemistry at TU Graz and TU Munich and an internship at Novartis in Basel. My project involves the synthesis of fumitremorgin (FTC)-derived inhibitors of the ABCG2 transporter. FTC is a natural product produced by the fungus *Aspergillus fumigatus* that was first isolated in 1977 by Clardy. It is a potent and partly selective inhibitor of the ABCG2 transporter, but it also exhibits profound neurotoxicity. Ko143 is a synthetic analog of FTC that is not neurotoxic, but retains the ABCG2 inhibitory capacity of the natural product. Our work is conducted in collaboration with the group of Prof. K. Locher at ETH Zurich and aims to synthesize new Ko143 analogs for in vitro functional studies on ABCG2 and to support structural studies. So far, I have focused on modifications at positions 3 and 9 of the tricyclic scaffold and have identified several analogs with potencies similar to or potentially better than Ko143.

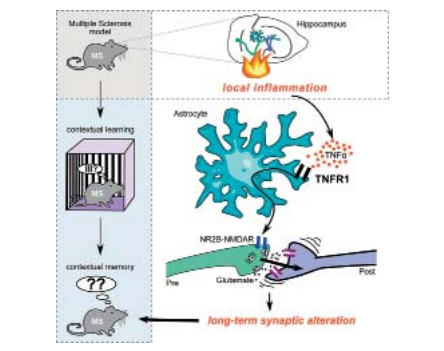
# NCCR TransCure Alumni

### Pascale Anderle

I currently have a joint appointment as a project manager at sitem-insel AG, Bern (www.sitem-insel.ch) and the Health Sciences eTraining Foundation (HSeT, www.hset.org), and as a lecturer at the University of Lausanne (UniL). I mostly work on the development of a new Master of Advanced Studies in Translational and Entrepreneurial Medicine and on a course on biostatistics. In many ways, my time as a PI at the NCCR TransCure is linked to my current activities. The interest generated by the workshops on data analysis I had organized contributed to my motivation to develop a hands-on e-learning biostatistics course for UniL using HSeT's platform. The idea behind the NCCR TransCure to identify drug candidates is in line with the main objective of sitem, which is to improve the environment for translational medicine in Switzerland by creating facilities and a Swiss school for professionals.

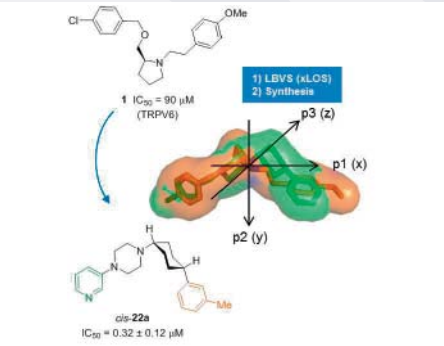
# Publication highlights

**Habbas et al, Neuroinflammatory TNFα Impairs Memory via Astrocyte Signaling, Cell 2015 Dec 17; 163(7):1730-41.**




In a mouse model of multiple sclerosis, A. Volterra and collaborators elucidated the role of the astrocyte TNFR1 in the memory impairment typically observed upon inflammation of the central nervous system. Since this correlation between CNS inflammation and cognitive disorders is found in many neurological and neuropsychiatric diseases, this discovery could be of great relevance in the understanding of their pathogenesis and in the development of treatments.

**Simonin et al, Optimization of TRPV6 Calcium Channel Inhibitors Using a 3D Ligand-Based Virtual Screening Method. Angew. Chem. 2015 Dec 1; 54(49):14748-52**




The TransCure teams of J.-L. Reymond, M. Hediger and R.-P. Charles have discovered the first potent and selective inhibitor of the calcium channel TRPV6. TRPV6 is typically overexpressed in breast and prostate cancer, and some studies indicate that the inhibition of calcium transport through this channel can control cancer cell proliferation. The discovery was possible thanks to a virtual screening method that is suitable for poorly characterized targets.

# Upcoming TransCure Events

**TransCure Lecture in Biology**
Klaas Pos
(Goethe University Frankfurt, DE)
9 May 2016 – Bern

**6th Annual NCCR TransCure Retreat**
19-20 May 2016 – Baden

**TransCure Lecture in Physiology**
Andrea Meredith
(University of Maryland, US)
20 June 2016 – Bern

**NCCR TransCure Symposium on Drug Design**
16 September 2016 - Bern

**3rd Endocannabinoid Pharmacology Meeting**
13-14 October 2016 – Bern

**TransCure Lecture in Physiology**
Jeanne Nerbonne
(Washington University, US)
21 October 2016 – Bern

**6th SNSF Site Visit**
24-25 October 2016 – Bern

**TransCure Lecture in Physiology**
Bin Qu
(Saarland University Homburg, DE)
18 November 2016 – Bern

**TransCure Lecture in Physiology**
Jutta Engel
(Saarland University Homburg, DE)
25 November 2016 – Bern

Please visit www.nccr-transcure.ch for more details.

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