

## Dear readers and colleagues,

You are reading the first newsletter of the second phase (2014-2018) of the National Centre of Competence in Research (NCCR) TransCure, which is funded by the Swiss National Science Foundation.

The main goal of the NCCR TransCure is to generate new knowledge related to membrane transporters and ion channels that are important in treating human diseases. The key achievements of the first phase include solving the structures of an iron transporter (DMT1)<sup>1</sup> and an amino acid transporter (LAT2)<sup>2</sup>, the elucidation of the role of the sodium/hydrogen exchanger NHA2 in insulin secretion<sup>3</sup>, and the discovery of a new class of small molecule regulators of endocannabinoid transport that exert cognitive effects in vivo.<sup>4</sup>

In this second phase, a new project entitled “Genetics of Membrane Transporters” has been added to the TransCure network. The project, headed by Murielle Bochud from the University of Lausanne will apply modern genomic approaches to tackle the role of NCCR TransCure transporters, using cohorts from the Swiss population.

Furthermore, two additional research groups will be affiliated with NCCR TransCure: Sven Rottenberg (Bern) is interested in the role of transporters in cancer treatment, and Christoph von Ballmoos (Bern) focusses on the mechanisms of antibiotic resistance.

The new project on transporter genetics is featured in one of the articles in this newsletter. In addition, you will read about an important issue for the NCCR, i.e., how we support equal opportunity for female scientists. We also feature three young NCCR TransCure Fellows. Finally, there is a list of up-coming events within our network. For more details about these events and other interesting topics, please have a look at our website ([www.nccr-transcure.ch](http://www.nccr-transcure.ch)).

More about the activities of the NCCR TransCure will be published in the autumn 2015 newsletter. In the meantime, please contact us if you have any questions about the network and enjoy your reading.

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

1 I.A. Ehrnstorfer, et al., “Crystal structure of a SLC11 (NRAMP) transporter reveals the basis for transition-metal ion transport”, *Nat. Struct. Mol. Biol.* **21**(11), 990 (2014).  
2 A. Rosell, et al., “Structural bases for the interaction and stabilization of the human amino acid transporter LAT2 with its ancillary protein 4F2hc”, *Proc. Natl. Acad. Sci. U.S.A.* **111**(8), 2966 (2014).

3 C. Deisl, et al., “Sodium/hydrogen exchanger NHA2 is critical for insulin secretion in beta-cells”, *Proc. Natl. Acad. Sci. U.S.A.* **110**(24), 10004 (2013).

4 S. Nicolussi, et al., “Correlating FAAH and anandamide cellular uptake inhibition using N-alkylcarbamate inhibitors: from ultrapotent to hyperpotent”, *Biochem. Pharmacol.* **92**(4), 669 (2014).

## How it works: Transmission electron microscope

The transmission electron microscope (TEM) works in a similar way to the light microscope but uses an electron source for imaging instead of a light source. It produces 2D images (projections) of 3D objects. Because wavelengths of electrons are much shorter than wavelengths of visible light, TEMs are able to visualise very small objects of several microns ( $10^{-6}$  m) to angstroms ( $10^{-10}$  m) in size. Samples have to be imaged in a high vacuum to enable electrons to travel in a straight line and to avoid collision with gas molecules. TEMs are valuable tools in the physical, biological and medical sciences. The German physicist Ernst Ruska was honoured with the Nobel Prize in Physics in 1986 for his fundamental work in electron optics and for the design of the first electron microscope.

D. Fotiadis  
NCCR TransCure PI

## NCCR TransCure aims for added translational potential by teaming up with clinical researchers

Human studies are an essential step in membrane transporter research aiming to discover new therapeutic and preventive measures for human diseases. The CoLaus-PsyCoLaus studies (Cohort Lausannoise, PIs: Peter Vollenweider, Martin Preisig, Gérard Waeber) and SKIPOGH (Swiss Kidney Project on Genes in Hypertension, PI: Murielle Bochud) are Swiss population-based cohorts funded by the Swiss National Science Foundation. Whereas CoLaus is monocentric (city of Lausanne) and includes unrelated participants, SKIPOGH is multicentric (Bern, Geneva and Vaud) and has a nuclear family design.

Technological advances now allow us to explore the human genome at an unprecedented level of resolution, either by high-throughput genotyping or next-generation sequencing. CoLaus participants (N=5500), aged 35 to 75 years at baseline, have been genotyped with the Affymetrix 500K array (500,000 genetic markers) and several million other markers have been imputed on the basis of these genotyped markers. SKIPOGH participants (N=1100), aged  $\geq 18$  years at baseline, have been genotyped with the Illumina Cardio-MetaboChip (200,000 genetic markers) and 2.5 million additional genetic markers will be measured soon. CoLaus and SKIPOGH participants currently undergo a 10-year and 3-year follow-up examination, respectively. These participants have been extensively phenotyped for socio-demographic parameters, lifestyle, and cardio-metabolic and renal traits. Interactions and collaborations between the groups in these clinical projects and the other research teams involved in the second phase of the NCCR TransCure are likely to generate new knowledge on selected transporters of interest, with the potential to become clinically actionable targets.

The NCCR TransCure basic research teams have top-notch expertise in transporters such as drug, electrolyte and nutrient transporters. The population-based cohorts mentioned above have generated high-quality phenotypic data on adults randomly selected from the general population and are following them up over time, thereby collecting precious outcome data on multiple common chronic diseases such as diabetes, hypertension, cardiovascular disease, chronic kidney disease and psychiatric disorders. Both cohorts also have a valuable biobank, allowing for additional measurements to be carried out according to the research questions of interest. Additional massive human data on transcriptomics, blood and urine metabolomics, and epigenomics is either already available or about to be generated. This will allow in-depth exploration of the molecular mechanisms that are potentially involved. Although highly exploratory in nature, the genetic association analyses of these human cohorts will likely generate new hypotheses on the pathophysiology of human disorders, which will be tested experimentally by the NCCR TransCure basic research teams.

M. Bochud  
NCCR TransCure PI

## Meet the NCCR TransCure Fellows



Ines Ehrnstorfer

I am working in Prof. Raimund Dutzler's lab. We are interested in the mechanism of iron uptake and transport in health and disease. In mammals, iron is imported into cells by the membrane transport protein DMT1. In order to unravel the structural basis for its ion selectivity, we have determined the structure of a close bacterial homologue of DMT1 by X-ray crystallography. The results have allowed us to explain how transition metal ions, such as iron, are selectively transported across the membrane. They provide a basis for the development of specific inhibitors of DMT1 for the treatment of iron storage diseases.



Lijo Cherian Ozhathil

I joined Prof. Hugues Abriel's lab as a postdoctoral fellow in January 2015. Our lab focuses on channelopathies in cardiovascular diseases. One of the candidate ion channels, TRPM4, has been recently reported to contribute to lethal cardiac disorders. Within the NCCR TransCure, our goal is the biophysical characterisation of TRPM4 and the screening of potent modulators for this ion channel, working in close collaboration with chemists. Being a Marie Curie Fellow in the IFP TransCure makes a difference to my CV. Moreover, working in an active group with regular feedback and opportunities for interdisciplinary collaborations is an excellent platform for shaping my future as an independent researcher.



Clémence Delalande

I started a PhD thesis in Prof. Jean-Louis Reymond's lab in January 2015. I studied pharmacy in France, with a major in medicinal chemistry, which is why I am mostly interested in the discovery of bioactive compounds. I am currently working on two projects relating to the ion transporters TRPM4 and NHE, which have a therapeutic outlook. Several gain-of-function mutants of TRPM4 have been linked to cardiac disorders such as arrhythmias, and several mutations of two endosomal NHE (NHE6 and 9) have been linked to neurological disorders like autism. Since there are no potent modulators for these transporters, we are interested in the discovery of new modulators to see a potential corrective effect. I am very excited to join the NCCR TransCure and to have the opportunity to work on these interesting projects.

## Equal Opportunity – Where are we?

Apart from its scientific mission to apply excellence in membrane transporter research to the treatment of human diseases, the NCCR TransCure is taking active measures in the areas of knowledge transfer, education and equal opportunity. Since the start of the first phase, TransCure has offered several actions dedicated to equal opportunity (previously called “advancement of women”).

### Mentoring

The “Mentoring4Women” programme is run by the NCCR TransCure in cooperation with the Faculty of Medicine at the University of Bern. This programme, starting at PhD level, is designed for young and motivated women who have a strong commitment to an academic career. Over two years, they are accompanied by a mentor who provides support in planning and pursuing an academic career, raising funding, publishing in high-impact journals and building a professional network. This programme is free of charge. Interested mentees can start whenever it best fits their career plans.

### Courses

During the first phase, the NCCR TransCure offered several courses tailored to the demands of female scientists, such as communication skills, self-confidence or time management. The participants learned and practised the techniques of giving oral presentations and were given advice on how to define professional and personal goals, and how to become more professionally productive. The next course organised by TransCure will be in autumn 2015.

### Symposia

Meeting with role models is essential in order to increase the motivation of young students for an academic career. During the first phase, the NCCR TransCure held two mini-

symposia for the advancement of women, which were very well received by the participants. Besides presentations from excellent female scientists, there was a podium discussion where the speakers shared their personal experiences about how to successfully combine academic work and family. Starting with the second phase of the NCCR TransCure, these symposia will be held annually. The next “women in science” symposia with Frances Ashcroft (University of Oxford) as a keynote speaker will focus on ion channels. It will take place on 4 September 2015 in Bern. In addition, there will be a podium discussion about cultural aspects in the careers of women at the 9th international BioMedical Transporters Conference from 9-13 August 2015 in Lugano.

J. Botthof, Administrative Coordinator  
and C. Albrecht, NCCR TransCure PI

For an overview of the current opportunities and events, please visit [www.nccr-transcure.ch](http://www.nccr-transcure.ch).

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SWISS NATIONAL SCIENCE FOUNDATION

## Upcoming NCCR TransCure Events

### TransCure lecture in biology

David Drew (Stockholm University)  
03 June 2015 - Zurich

### TransCure lecture in biology

Jana Kusch (University Hospital Jena)  
04 June 2015 - Bern

### 5th Annual TransCure Retreat

11-12 June 2015 - Baden

### TransCure lecture in biology

Henriette Meyer zu Schwabedissen  
(University of Basel)  
18 June 2015 - Bern

### TransCure training course: Structural studies of membrane proteins using X-ray crystallography

18-20 June 2015 - Zurich

### 8th European Placenta Perfusion Workshop

23-24 June 2015 - Bern

### TransCure lecture in biology

Maria-Clemencia Hernandez  
(F. Hoffmann-La Roche Ltd)  
24 August 2015 - Bern

### Ion Channel Woman Scientists Symposium

04 September 2015 - Bern

### TransCure lecture in physiology

Andrea Brüggemann  
(Nanon Technologies GmbH)  
14 September 2015 - Bern

### TransCure lecture in physiology

Nicole Schmitt (University of Copenhagen)  
28 September 2015 - Bern

### TransCure lecture in physiology

Rudi Vennekens (KU Leuven)  
12 October 2015 - Bern

### TransCure training course:

#### Electrophysiology

29-30 October 2015 - Bern

### TransCure lecture in drug design

Cristina Nevado (University of Zurich)  
11 November 2015 - Bern

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For more details, please visit:  
[www.nccr-transcure.ch](http://www.nccr-transcure.ch)