

TransCure

TRANSLATIONS

SWISS NATIONAL CENTER OF COMPETENCE IN RESEARCH

NEWSLETTER NO.1, APRIL 2012

A MESSAGE FROM THE DIRECTOR



The goal of the NCCR TransCure is to apply excellence in membrane transporter research to the treatment of human diseases. The initial approach is to generate unique knowledge in order to understand mechanisms underlying common human diseases such as diabetes, hypertension, cardiovascular diseases, cancer, preeclampsia and neurodegenerative diseases. The molecular mechanisms and structures of pharmaceutically important transporters and ion channels will then be determined to facilitate the development of innovative therapeutic strategies for the treatment of such diseases.

Welcome!

TransCure was funded in November 2010 by the Swiss National Science Foundation (SNSF). A network of 20 research laboratories across Switzerland focuses on research and drug development in the field of transport biology, addressing a variety of important diseases. I am pleased to release the first in a series of TransCure newsletters, called "TransCure Translations". It will provide you with a glimpse into the recent work we have done during the first one and a half years of TransCure funding. In this and future editions, we will also profile our researchers and their projects as well as keep you advised on upcoming TransCure activities and publications. I hope you will enjoy reading these updates and that you will follow our progress. Transport biology has had a long history in Switzerland. Many world renowned research groups have developed and prospered here in terms of uncovering scientific breakthroughs as well as training young scientists. At TransCure, we are anxious to continue this tradition through interdisciplinary research, specific educational efforts, as well as the promotion of women in science.

What makes us perhaps different when looking to the future is that we have a direct link between the academic science and its application. TransCure brings together researchers from academia and applied sciences as a key step

towards improving human health. We recognize the importance of different scientific disciplines working together in a common vision. Our strategy utilizes skills from structural biology, medicine and chemistry, working together in our so-called "TransCure Trias".

TransCure utilizes expertise across many institutions throughout Switzerland and the approach is designed to facilitate collaboration and coordination of activities with an entrepreneurial spirit. Projects and teams are already working across the network to realize this vision. I will support and encourage every member of the TransCure network to deliver high quality basic research and breakthroughs in the treatment of human diseases.

It is my intent to keep all of our stakeholders and interested parties up to date through the use of our website, newsletters and other means. These formats will be used to announce upcoming opportunities to interact with us, provide updates on scientific projects and highlight the latest breakthroughs of the TransCure network. As we move forward with our activities, we encourage you to become actively involved. Whether you are inquiring about scientific, business or personal interests, please feel free to contact me directly.

Thank you for your interest in TransCure!

Matthias A. Hediger, TransCure Director

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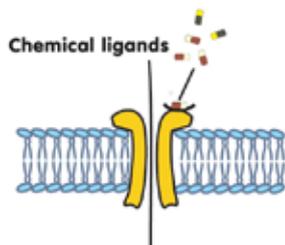
**UNIVERSITÄT
BERN**



SWISS NATIONAL SCIENCE FOUNDATION

WHAT IS TransCure ABOUT?

To apply excellence in membrane transporter research to the treatment of human diseases



Numerous human diseases result from malfunctions of membrane transporters and ion channels. These are integral membrane proteins that move important substances (chemical ligands) such as amino acids, sugars, vitamins, trace minerals, drugs and other small molecules across membranes. Because they are gatekeepers, controlling access of small molecules inside cells and organelles, they are of fundamental significance for the development of therapeutic drugs.

Transporters and channels can be used as drug targets themselves, as drug delivery systems, as modulators of the cell's sensitivity towards drugs and/or as modulators of the metabolism of drugs.

What is the NCCR TransCure?

The NCCR TransCure brings together an interdisciplinary network consisting of 20 Swiss laboratories, located in Bern, Zurich, Lausanne and Basel.

The leading house is the Institute of Biochemistry and Molecular Medicine at the University of Bern with Matthias A. Hediger as the director and Jean-Louis Reymond (Department of Chemistry and Biochemistry, University of Bern) as the deputy director.

The National Center of Competence in Research (NCCR) TransCure aims at fostering high quality basic science research in membrane biology and developing therapeutic measures. Specifically, the goal is to correct the dysfunction of transporter proteins or to utilize transport proteins for drug delivery, in order to contribute to the cure of the associated diseases.

Our approach is to determine the molecular architecture, function and regulation of transporters of therapeutic interest, to unravel their dysfunction in human diseases and to develop novel medicines.

The NCCR TransCure is one of the current 27 national scientific networks funded by the Swiss National Science Foundation (SNSF).

NCCRs promote long-term research projects in areas of vital strategic importance that benefit Swiss economy, society and/or public health.

Major human diseases such as diabetes, hypertension, cardiovascular diseases, cancer, osteoporosis, neurodegenerative and psychiatric disorders have a wide-ranging impact on modern society and cause immeasurable costs. Many of these diseases are related to or are based on the dysfunction of integral membrane transporters and channels.

Research Paradigm

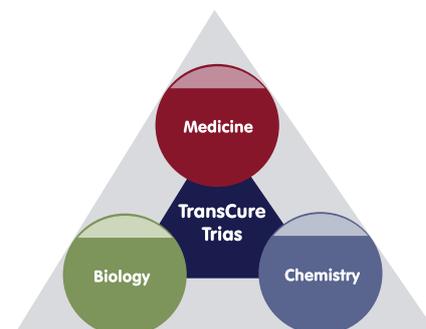
To make our vision become reality, a tight collaboration among clinicians, structural biologists and chemists (referred to as "TransCure Trias") is of utmost importance. The NCCR TransCure brings together the necessary expertise to promote high-quality basic science and translational research, and to facilitate a successful transition "from gene to drug".

Education

An important part of the NCCR TransCure activities is an interdisciplinary educational training program for PhD students and postdoctoral fellows to train "next-generation biomedical scientists" capable of understanding the whole process from genes to drugs.

Women Promotion

Special emphasis will be placed on supporting the advancement of women in the field of translational research.



The "TransCure Trias" brings together three major disciplines: Medicine (including physiology and pathology), biology (including structural biology) and chemistry.



LC-MS EQUIPMENT FOR PROTEOMICS AT TransCure

For the NCCR TransCure, a highly capable LC-MS platform at the University of Bern is of crucial importance, since the success of many projects at least partially depends on evaluating proteins and ligands for many of the ongoing transporter related research projects, including the mapping of the ligand-binding sites of transporters and

channels as well as the study of protein-protein interactions. To increase the ability of this critical facility and to facilitate a wide variety of ongoing programs, the team of Manfred Heller is planning to acquire two additional instruments. In collaboration with the NCCR TransCure, an application for partial funding was submitted and approved

by the Swiss National Science Foundation (SNSF) together with the Board of Directors at the University of Bern. Additional fundraising activities are underway to close the remaining gap required to complete these purchases.

PRINCIPAL INVESTIGATOR PROFILE

Dimitrios Fotiadis

Membrane proteins fulfill innumerable key functions in all living cells and account for about 30 percent of most proteomes. A substantial number of drugs on the market target membrane proteins, thus highlighting their critical importance in human health. In spite of their importance, less than a dozen atomic structures of human polytopic membrane proteins are reported. Clearly, there is an immense need for more structural information on membrane proteins such as transporters and channels, to understand their function and molecular mechanisms.

The Fotiadis laboratory focuses on the function, structure and supramolecular organization of membrane proteins. To this aim, biochemical and biophysical approaches as well as high-resolution microscopy and crystallography techniques are used.

Recently, a strong focus has been put on the structure and organization of membrane proteins in their native environment, the lipid bilayer. This is studied best by electron and atomic force microscopy of proteoliposomes, 2D crystals and the use of native membranes. Finally, high-resolution structures are determined by X-ray crystallography of 3D crystals of detergent-solubilized membrane proteins. The subject and title of Dimitrios Fotiadis' Ph.D. thesis was "Biochemical and structural analyses of membrane proteins in plants and animals" (2000, University of Basel).

During his postdoctoral fellowship in the group

of Prof. Andreas Engel at the Biozentrum of the University of Basel, Dimitrios revised the dogma that the light receptor protein rhodopsin functions as a monomer in the retina by direct visualization of rhodopsin dimers and higher oligomers in native disk membranes using electron and atomic force microscopy (Fotiadis et al. *Nature* (2003), 421, 127-128 and Fotiadis et al. *Nature* (2003), 426, 31). This discovery led to a reconsideration of the first steps in vision (Fotiadis et al. *Curr. Opin. Struct. Biol.* (2006), 252-259). Furthermore, the results from electron and atomic force microscopy on the oligomeric state of rhodopsin were corroborated by biochemical and biophysical methods in Basel and during Dimitrios Fotiadis' scientific stay in Kris Palczewski's laboratory (University of Washington, Seattle, USA). Importantly, rhodopsin is just one example of a G-protein-coupled receptor (GPCR) of which more than a thousand exist in the human body.

It now seems likely that most of these GPCR receptors also function as paired molecules. This has implications for our health and for the development and screening for new drugs (Fotiadis et al. *Curr. Opin. Struct. Biol.* (2006), 252-259).

In 2004 Dimitrios became involved in the 'European Genomics Initiative on Disorders of Plasma Membrane Amino Acid Transporters (EUGIN-DAT)' a Specific Targeted Research Project of the 6th European Community Framework Program. Since then his laboratory focuses on the function and structure of channel and transport proteins.



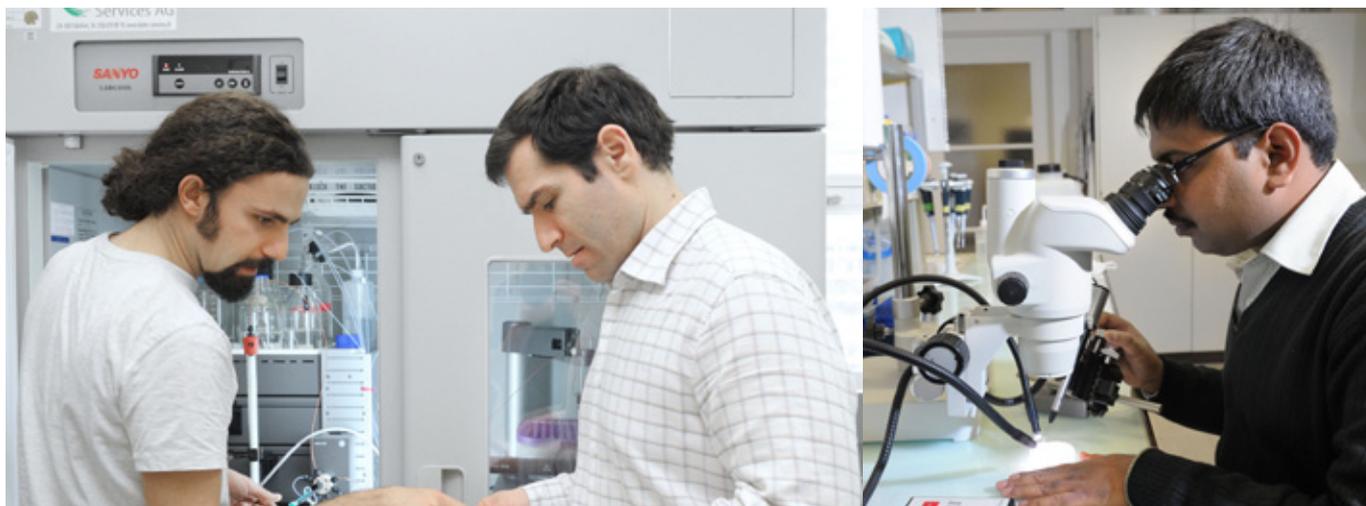
Dimitrios Fotiadis
Since 2008 Tenure-Track Assistant Professor at the University of Bern

Education

- PD (Habilitation) in Biophysics at the University of Basel
- Ph.D. in Biochemistry at the University of Basel
- M.Sc. in Molecular Biology at the University of Basel

Selected memberships

- Associate faculty member of 'Faculty of 1000 Biology'
- Swiss Society for Optics and Microscopy
- Member of the Bernese Biochemistry Association



MINISYMPOSIUM AND WORKSHOP

“Excellence in Women’s Science”



*Christiane Albrecht
Delegate for Women's promotion*



On Feb 8, 2012, the NCCR TransCure held the first symposium and workshop focused on the Advancement of Women in Science and Gender Equality

During this one-day event, a panel of four internationally renowned female scientists who are experts in the field of membrane research and drug discovery presented selected topics of their scientific work. The speakers covered scientific areas that were particularly relevant for TransCure scientists, but also gave presentations that were of interest for a broader audience interested in structural biology, medicine, physiology or immunology. This was also reflected by the fact that 67 participants registered and attended the meeting.

During the morning session, the speakers gave insights into structural biology (Christine Ziegler, Max-Planck-Institute of Biophysics, Frankfurt, Germany), the physiological roles of membrane proteins in diverse organisms and clinically relevant diseases (Catherine Williamson, Imperial College London, UK) and the role of membrane transporters in nutrition and drug metabolism (Hannelore Daniel, Technical University Munich, Germany). Furthermore, immunological phenomena were presented that occur at the blood brain barrier and are important for drug delivery to the brain (Britta Engelhardt, Theodor Kocher Institute, University of Bern, Switzerland). The four excellent presentations attracted a great deal of interest from the audience and were intensively discussed not only during the scientific sessions but also in the coffee and lunch breaks.

After further networking opportunities during lunch, all attendees were invited to join a workshop that specifically addressed measures for promoting the advancement of women in science. Our guest speakers formed a panel for discussions concerning various aspects of equal career opportunities and shared their experiences regarding the balances of leading a scientific career with family responsibilities. In particular, concerns of the attendees regarding the possibility to reconcile scientific work with a family life, and measures to support balanced

gender distribution at all academic levels were discussed. Sabine Höfler, a delegate of the Gender Equality Section of the University of Bern “Abteilung für Gleichstellung” (AfG) presented data on the actual situation of gender equality issues at Swiss universities and presented the areas of activity of the AfG in this context.

During the plenary discussion, the invited speakers shared their passion for science with the workshop participants and pointed out which hallmarks were critical for their scientific career. The main topics discussed included:

- Opportunities for part time working or job sharing in research
- The importance and possibilities for scientific networking
- The establishment of mentoring groups

The ideas and potential initiatives that came up during the afternoon session are currently discussed within the management team of the NCCR TransCure, and even resulted already in concise actions. Thus, in March 2012, it was decided that TransCure will actively support the establishment of a mentoring network at the Medical Faculty of the University of Bern.

Due to the success of this meeting it is planned to organize a similar session in near future to optimize individual measures for promoting young female researchers.



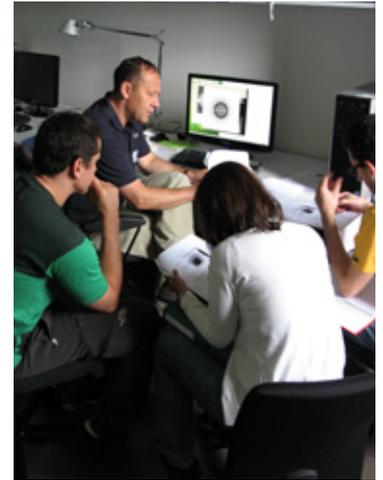
THE EDUCATION PROGRAM HAS BEGUN

Training the next generation of scientists in advanced fields to further the translational research in the area of membrane transport is of utmost importance. In early July, the first advanced training course entitled "Expression, Purification, Crystallization and Structure Determination of Membrane Proteins" was held by Kaspar Locher (ETH Zurich) and Raimund Dutzler (Univ. of Zurich).

The course received an "excellent" evaluation from students and was composed of a diverse program of lectures and hands-on training including an introduction to 3D-crystallization of membrane proteins. The course had 16 participants from seven institutions across Switzerland. Susanne Bentz, Postdoctoral fellow (Univ. Bern) commented "the first TransCure course was a very well done and I really learned a lot". Another PhD student, S. Nicolussi, from the University of Bern also commented "the idea

to implement a training program representing the outstanding features of the NCCR TransCure has helped me to improve my scientific skills in translational research". Dutzler also expressed his thoughts by saying "the students did a very good job and I enjoyed seeing them discussing and interacting during the course. The Advanced Training courses will certainly become an important platform for exchange between our students".

The second two-day course on "Ion Channels in Physiology, Disease, and as Drug Targets" by Hugues Abriel and Jean-Sebastien Rougier took place September 1-2, 2011. The objective of the course was to give a first overview on the roles of ion channels in physiology and in pathophysiology, including ion channel pharmacology and the current challenges in this field. The course was well received by the participants.



Raimund Dutzler with students

1st ANNUAL TransCure RETREAT

The TransCure scientific network is geographically spread across Switzerland and it is important for the scientists to get together at least once a year in order to coordinate activities and share information.

The first two-day TransCure scientific event and retreat was held at the University of Bern with an overnight event being held in Magglingen at the Swiss Federal Institute of Sports in May 2011.

The program included scientific talks on the latest progress made in the field of translational research by the principal investigators, as well

as important updates on the TransCure activities.

In the evening, the TransCure scientists were invited to join a "hike & cheese" event in Maglingen. Here, scientific discussions and networking opportunities were continued during a one-hour walk to the Lothurm tower, followed by a delicious out-door cheese fondue in the beautiful scenery of the Three-Lakes Region.

The TransCure administrative team is currently organizing the next scientific retreat and event in Gruyère (May 31 and June 1, 2012).



Jean-Louis Reymond speaking at the Event

NEWS IN THE MANAGEMENT OFFICE

We are delighted to introduce Martine Reymond as the new Communications and KTT Director of the NCCR TransCure Management Team.

Martine graduated from the EPFL as a Chemical Engineer and started her career working in academic research studying peptide and protein structure as well as catalytic antibodies. During her early career, Martine was working at The Salk Institute for Biological Studies, the Scripps Research Institute in California. She also spent time at the University of Bern.

Martine then obtained an MBA from HEC Lausanne and was subsequently employed by the pharmaceutical industry for 8 years, heading a quality control laboratory as well as working on global projects, managing large cross-functional networks in various domains, such as information technology, manufacturing and human resources. In each of these roles she

brought a strong focus on operational excellence. She was engaged in many international programs that required her to develop effective communication skills across large remote teams, turning key participants into valuable and motivated business partners.

We are extremely excited to have Martine join the NCCR TransCure team, bringing both her strong academic and industrial experience in the fields of communication, knowledge and technology transfer and team development.

We look forward to working with Martine as part of our challenging mission within the NCCR TransCure network, wishing her the very best in her new role with us.

Matthias Hediger & the
TransCure Management Team



*Martine Reymond
Chem. Eng. EPFL, MBA*

RECENT PUBLICATIONS FROM TransCure

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TransCure JOINS BioParadigms

BioMedical Transporters Conferences 2011 and 2013 - www.bioparadigms.org

The 7th BioMedical Transporters Conference took place in Grindelwald, from August 7 - 11, 2011 for 5 days. 170 participants from twenty different countries and various disciplines participated in a varied program of scientific talks and poster exhibition. Several evening events and special activities provided a good environment for lively discussions and networking opportunities.

Over the one-week event, Professor Matthias Hediger, organizer and NCCR TransCure director, hosted high-ranking speakers from industry and academia to present and discuss their research projects on transporter-based drug discovery strategies, pharmacokinetics, drug delivery, drug elimination, and medically relevant transporters as potential novel therapeutic targets.

At the poster exhibition, participants gained insight into the broad spectrum of membrane transporter related research and drug discovery. During the poster session, each exhibiter had the opportunity to present and discuss the scientific work. Posters were reviewed by a committee and through a detailed examination, including a short presentation. The first BioParadigms Prize was awarded to Itziar Pinilla-Macua and

Marçal Pastor-Anglada (Universitat de Barcelona, Spain). Tim Rasmussen (University of Aberdeen, UK) won the second Prize and Atsushi Yonezawa (Kyoto Pharmaceutical hospital, Japan) received the third Prize.

A major conference highlight was the special excursion into the beautiful mountain scenery of the Grindelwald region. After taking the gondola to the top of the Männlichen the BioParadigms guests enjoyed the stunning views of the Jungfrau region which included a relaxed one-hour walk to Kleine Scheidegg. In the Restaurant Grindelwaldblick the group had a dinner and enjoyed some delicious Swiss food. The BioParadigms conference 2011 was officially closed after the traditional farewell dinner with another great Swiss meal and traditional Swiss music at Barry's Restaurant.

The organization of the next BioMedical Transporters conference is well under way. We are pleased to announce that it will take place August 11 - 15, 2013, in St. Moritz, Switzerland.

For further details, please visit the bioparadigms.org website.



The organizer Matthias Hediger would like to thank all participants for the inspiring time and hopes they all will attend the next BioMedical Transporters Conference in St. Moritz in 2013.

TransCure PROJECTS & FACILITIES

Project 1

Ion channels of the TRP family and their implications in cancer and heart diseases.

Principal Investigators: M. A. Hediger, E. Niggli, H. Abriel, W. Hofstetter

Transporters of metal ions, sugars, vitamins, nucleobase, amino acids and peptides in major human diseases.

Principal Investigators: M. A. Hediger, W. Hofstetter

Project 2

Sodium/calcium exchangers of the SLC8/SLC24 family and the pathogenesis of heart diseases and obesity.

Principal Investigator: H. Stahlberg

Project 3

Sodium/hydrogen exchangers of the SLC9 family and their role in hypertension and diabetes mellitus.

Principal Investigator: D. Fuster

Project 4

Anoctamine channels and metal ion transporters (SLC11 family) potentially contributing the pathogenesis of cancer.

Principal Investigator: R. Dutzler

Project 5

Exploiting tumor-specific amino acid (SLC7, SLC38) and lactate transporters (SLC16) as drug targets.

Principal Investigator: P. Anderle

Project 6

Vesicular glutamate (SLC17 family) and monoamine (SLC18 family) transporters in the treatment of neurological diseases.

Principal Investigators: A. Volterra, P. Bezzi

Project 7

Transporters involved in vitamin C (SLC23) and monocarboxylate (SLC16) homeostasis and their role in cancer.

Principal Investigator: D. Fotiadis

Project 8

Glucose, myo-inositol and urate transporters of the SLC2 family: from heart metabolism and gout to mood disorders.

Principal Investigator: B. Thorens

Project 9

Placental nutrient transporters and their role in pregnancy-related disorders.

Principal Investigator: D. Surbek

Project 10A-C

In silico screening and chemical synthesis of ligands targeting transporters and channels of interest; chemical synthesis of fluorescence- and photoaffinity-labeled ligands for localization and binding studies.

Principal Investigators: J.-L. Raymond, K.-H. Altmann, M. Lochner

Project 10D

Targeting of the endocannabinoid transporter for the treatment of pain.

Principal Investigator: J. Gertsch

Project 11

Cholesterol (ABCA1) and drug (SLC47) transporters and their role in lipid metabolism disorders and extrusion of hydrophobic drugs.

Principal Investigator: K. Locher

Project 12

Role of transporters for canalicular lipid secretion in acquired forms of cholestasis.

Principal Investigator: B. Stieger

Project 13

Cholesterol transporter ABCA1 and its impact on normal placental development, maternal-fetal exchange and hypoxic gestational diseases.

Principal Investigator: C. Albrecht

Platforms & Facilities

- Compound screening and assay development facility
A. Simonin and M. A. Hediger
- Proteomics
M. Heller
- Bone and Mineral Research
W. Hofstetter
- Electron Crystallography
H. Stahlberg
- CardioMet Mouse Metabolic Evaluation
B. Thorens
- Natural Product Libraries
J. Gertsch

UPCOMING TransCure EVENTS

NCCR TransCure

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April 30 - May 2, 2012

TransCure Advanced Training Course

“Ion Channels and Transporters and Their Role in Calcium Signalling”

by Prof. Ernst Niggli, University of Bern, Switzerland

May 31 - June 1, 2012

“2nd Scientific Event and Retreat”

Gruyères, Switzerland

August 19 - 25, 2012

TransCure Advanced Training Course

“Electron Crystallography Workshop”

by Prof. Henning Stahlberg, University of Basel, Switzerland

October 15 - 16, 2012

“SNSF Site Visit”, NCCR TransCure

Institute of Biochemistry and Molecular Medicine, University of Bern, Switzerland



BioMedical Transporters 2011, Grindelwald, Switzerland