Swiss National Centre of Competence in Research

Newsletter No. 4

NCCR TransCure

Excellence in Membrane Transport Research

Dear readers and colleagues,

We are glad to inform you about the latest news of the National Centre of Competence in Research (NCCR) TransCure, supported by the Swiss National Science Foundation. Our NCCR is currently in its second phase (2014-2018) and has just started its sixth year of activity. The NCCR TransCure is devoted to research in the field of membrane transporters and ion channels.

By leafing through the next pages, you will gain insights into our ongoing projects. In this issue, we feature the "VGLUTs/VMAT2" project. Short portraits of fellows and some notes on genetically engineered mice then put the spotlight on daily life in TransCure labs. We also illustrate the new Knowledge and Technology Transfer (KTT) Committee and its strategy within TransCure.

In addition, we would like to inform you about changes in the NCCR TransCure management team. After five years, Dr. Martin Weisstanner has left his position as Scientific Officer. We warmly thank Martin for his excellent work and wish him all the best for his career. Dr. Valentina Rossetti, an evolutionary biologist with further education in research management and scientific journalism, has taken over the position. Our Administrative Coordinator, Johanna Portmann, will reduce her workload due to family reasons, and an additional Administrative Coordinator, Jolanda Paganoni, will join the team in February 2016.

TransCure events are great occasions to meet the fellows and the new team members. Please take a look at the list of up-coming events on the last page of this newsletter or visit our website: www.nccr-transcure.ch
You can also follow us on Twitter: @NCCR_TransCure

We are always happy to hear from you, so please feel free to contact us if you have any questions.

The NCCR TransCure wishes you a joyful festive season and a brilliant new year!

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

How it works: Genetically engineered mice

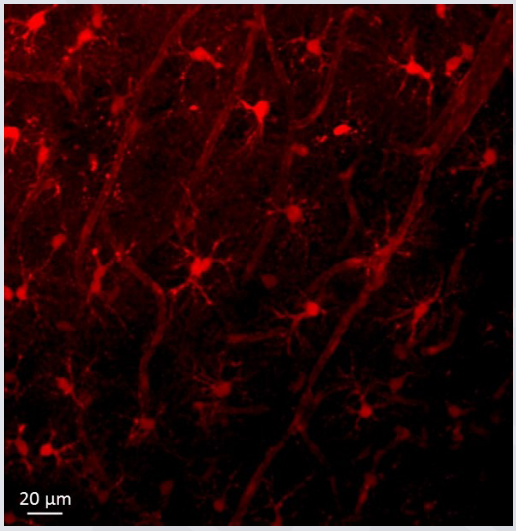
In the early 80s, progress in molecular biology allowed the generation of permanent modifications in the mouse genome, resulting in animals that were given the generic name “transgenic mice”. At that time, a gene could be inserted into the nucleus of a fertilised embryo, resulting in its expression in the mouse that was born following re-implantation of the egg. With the development of new techniques in genetic engineering, more complex sequences could be inserted into mice genomes. Today, we have advanced models in which functional genes can be replaced by mutant genes in specific organs in adult mice upon injection of a synthetic hormone. These systems allow us to mimic single mutations similar to those in patients, providing the chance to study the origins of a genetic disease, for example in cancer. In addition, these refined models allow us to test innovative therapies before clinical application, avoiding giving patients inefficient or even toxic treatments.

R.-P. Charles
NCCR TransCure PI

Cell-specific targeting: VGLUTs and VMAT2

An emerging view in neuroscience is that astroglial cells are not only housekeepers of the central nervous system (CNS) but also support CNS development and promote synaptogenesis. Moreover, they provide for CNS homeostasis and form multiple lines of neural tissue defence. Astroglia contribute to cognitive functions through multi-directional communication with cells residing in the brain. This heterotypic cell-to-cell communication between astrocytes, neurons and other glia is mediated, to a large extent, through the release of signalling molecules. Astroglial release of neuroactive substances apparently occurs through several distinct pathways that include translocation by transporters, flux via ion channels, and regulated exocytosis of secretory organelles expressing vesicular neurotransmitter transporters (VNTs), including vesicular glutamate transporters 1, 2 and 3 (VGLUT1-3) and vesicular monoamine transporter 2 (VMAT2).

Recent studies have shown that even moderate changes in vesicular neurotransmitter levels can have a major impact on brain function, with pathophysiological consequences. Indeed, by regulating the (re)filling of organelles in neurons and astrocytes, VNTs can strongly influence synaptic transmission and, hence, play an essential role in the chemical transmission of information in the brain. The reported expression of VGLUTs and VMAT2 in astrocytes, the neuromodulatory role of astrocyte-released glutamate and dopamine, and the potential contribution of their alteration to pathologies, strongly suggest that astrocyte-restricted VGLUT and VMAT targeting may be a promising new therapeutic strategy. Indeed, high-affinity VGLUT and VMAT inhibitors exist but their therapeutic use in pathologies with glutamatergic or dopaminergic hyperfunction (such as epilepsy and manic disorders, respectively) is not recommended as it would suppress neuronal transmission ubiquitously. The discovery of agents that display strong tropism for astrocytes in vivo (most likely via a group of specific organic transporters) provides a concrete means to transport VGLUT and VMAT inhibitors selectively to astrocytes.



In vivo injection of a fluorescent dye that targets astrocytes

By integrating physiology, structural biology and chemistry, the NCCR TransCure offers unique opportunities to collaborate in developing new therapeutic strategies for treating the most important diseases. During the first phase of the NCCR, interactions between complementary groups in the “TransCure Trias” led, among others, to the synthesis of a series of derivatives with appropriate linkers to bind VGLUT and VMAT inhibitors, as well as the development of a set of in vitro and in vivo assays to test the inhibitory potency of the astrocytic conjugates. These collaborations included two neurobiologists, Andrea Volterra and Paola Bezzi (Lausanne), a chemist, Jean-Louis Reymond (Bern), a structural biologist, Raimund Dutzler (Zurich), and experts in drug transporters, Bruno Stieger (Zurich), and bioassay development, Jürg Gertsch (Bern).

In the second phase of the NCCR, the team will focus on testing the capability of lead derivatives to cross the blood-brain barrier after peripheral administration and to distribute selectively to astrocytes in vivo, as well as the effect of astrocyte-specific VGLUT and VMAT inhibitors in animal models of CNS pathologies. The goal is to achieve proof of principle that targeting astrocyte VNTs inhibition is therapeutically relevant in those pathologies.

P. Bezzi and A. Volterra
NCCR TransCure PIs

Meet the NCCR TransCure Fellows

Xiao Huang

After finishing my PhD studies in August 2015, I am continuing my research as a postdoctoral fellow in Prof. Christiane Albrecht's group (Bern). I am interested in deciphering the mechanisms underlying gestational diseases. Specifically, our research centres on nutrient transport at the materno-fetal interface in human placenta. Utilising bioinformatic analyses and molecular approaches, we have demonstrated that the amino acid transporter SLC7A5 (LAT1) and iron transporter SLC11A2 (DMT1) may contribute to pregnancy disorders such as pre-eclampsia, intrauterine growth restriction and gestational diabetes mellitus. In collaborations within the NCCR TransCure research network, we further aim to elucidate the trans-placental transport kinetics of amino acid and iron in cell- and tissue-based models, and to evaluate the prospect of potential regulators in repairing the nutrient deficiency in gestational diseases.

Luca Pucci

I did my PhD in pharmacology in Milan, Italy and started as a post-doctoral fellow in Prof. Paola Bezzi's lab (Lausanne) in October 2011. Our lab focuses on vesicular monoamine transporter 2 (VMAT2) in astrocytes. VMAT2 is specifically expressed in astroglia of the prefrontal cortex and is directly related to the levels of dopamine in this brain region. Neuromodulation of neuronal circuits by dopamine influences synaptic plasticity and high-level executive functions, as well as playing a critical role in neurological and psychiatric disorders. Sulforhodamine B is a red dye that is able to cross the blood-brain barrier and displays a cell-specific tropism for astrocytes. Based on these characteristics, we are testing if sulforhodamine B can be expoited to transport potential therapeutics in astrocytes such as reserpine and tetrabenazine, two different inhibitors of VMAT2.

Patricia Schenker

I have been working in Prof. Jürg Gertsch's group (Bern) since July 2015. Our lab focuses on the endocannabinoid system, especially its molecular pharmacology. We are investigating endogenous and potentially therapeutic agents of endocannabinoid membrane transport modifiers, focusing on drug discovery. Additionally, with these novel modifiers, we aim to shed light on the bidirectional endocannabinoid transport across the membrane. Currently, I am continuing some of the work of Simone Nicolussi and Mark Rau, including the screening of promising compounds that inhibit anandamide uptake. This work involves collaborations with the groups of Prof. Altmann (Zurich) and Prof. Reymond (Bern) and with industry (F. Hoffmann-La Roche AG and Dr. August Wolff GmbH/ Mercachem), focusing on different scaffolds and analogues to increase potency and selectivity of the respective compounds.

Knowledge and Technology Transfer: Where are we?

Knowledge and technology transfer (KTT) encompasses a broad range of activities that support mutually beneficial collaborations between universities, industry and the public sector. On the one hand, this involves scientific exchange through publications, posters and talks at meetings. In 2015, TransCure supported the 9th International BioMedical Transporters Conference and the 2nd Endocannabinoid Pharmacology Meeting, offering interactive platforms for academia and industry. On the other hand, KTT involves the transfer of knowledge and technologies through precompetitive or competitive research collaborations with industry. The latter are driven by economic interests and aim to translate scientific knowledge and technologies into a concrete solution for a given need. KTT is also linked to education—as soon as researchers join the job market, they bring new knowledge to the private and public sector, fostering exchange between academia and industry.

Recently, TransCure took measures to make KTT even more tangible. The KTT Management Board now includes two industry representatives, Anja König (Novartis Venture Fund) and Guido Koch (Synthesis Novartis). We also plan to help our PIs develop a KTT plan if requested and to strengthen our industry interactions.

TransCure Novartis internship

TransCure will offer an exciting new programme with Novartis Basel in which selected PhD students and postdocs can spend a few months at Novartis working on their own projects, benefiting from Novartis' resources and environment. First, this will be related to screening of small molecules. One immediate common goal is to generate better tool compounds for basic transporter research. Academic PIs and industry partners will also get the chance to define potential common interests.

Validated assays can generate funding and knowledge transfer

Excellence in research also implies competitiveness. As an example, TransCure was able to sell our ample knowledge on endocannabinoid cellular uptake assays to different companies. This led to supplementary funding for TransCure and a collaboration between the Gertsch group and Dr. August Wolff GmbH, Germany. As a result, in 2016 the very first anandamide uptake inhibitor for atopic dermatitis will enter phase 1 clinical trials in Germany. Currently, we are screening compounds from F. Hoffmann-La Roche AG at the NCCR TransCure screening facility.

First patent applications filed

TransCure filed the first European patent applications on a novel class of anandamide uptake inhibitors to treat neuropsychiatric diseases. This IP will be published in late 2015 and is owned by the University of Bern (inventors: S. Nicolussi, J.-L. Reymond, and J. Gertsch). There is an ongoing formal collaboration with F. Hoffmann-La Roche AG on CNS-active endocannabinoid uptake inhibitors (Roche EIN grant to J. Gertsch).

J. Gertsch, NCCR TransCure PI and TransCure Delegate for KTT

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UNIVERSITÄT BERN

SWISS NATIONAL SCIENCE FOUNDATION

Upcoming NCCR TransCure Events

TransCure lecture in biology
Raimund Dutzler (University of Zurich)
07 December 2015 - Bern

TransCure lecture in physiology
Rudi Vennekens (K. Leuven University)
14 December 2015 - Bern

TransCure lecture in physiology
Will Brackenbury (University of York)
21 March 2016 - Bern

TransCure lecture in physiology
Andrea Meredith (University of Maryland)
20 June 2016 - Bern

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International Symposium on Chemical Biology 2016
13-15 January 2016 - Geneva

6th Annual TransCure Retreat
19-20 May 2016 - Baden

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Outreach event: Course for highly talented children
30 April 2016 - Bern

For more details, please visit:
www.nccr-transcure.ch