

KIDNEY

CONTROL OF HOMEOSTASIS

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Kidney—Control of Homeostasis

is a Swiss research initiative, headquartered at University of Zurich, which brings together leading specialists in experimental and clinical nephrology and physiology from the universities of Basel, Bern, Fribourg, Geneva, Lausanne, and Zurich, and corresponding university hospitals.

SUFFOCATING KIDNEY FIBROSIS



Hypoxia mimetics as novel therapy option.

Kidney injury can result in fibrosis, an excessive scarring of the tissue, which leads to a progressive loss of renal function. Recent research suggests that inhibition of cellular oxygen sensors is a novel therapy option for kidney fibrosis.

To this day there is no cure for kidney fibrosis. In the event of excessive formation of scar tissue (fibrosis) as a result of kidney injury current treatments can at best delay the process. Fibrosis ultimately leads to a progressive loss of renal function and can even result in kidney failure. Current research shows that inflammatory and fibrotic processes are regulated by oxygen deprivation. This regulation may be utilized to protect renal tissue against fibrosis.

OXYGEN AND FIBROSIS— A COMPLEX RELATIONSHIP

Oxygen is essential for human life, fuelling cells' energy production. If the available oxygen is decreased so that cellular energy production is affected, the condition is called hypoxia. All cells in the human body can sense decreases in oxygen levels. When hypoxia occurs, cells change their energy production, switching to an oxygen-independent, but less efficient, mechanism. The interaction between fibrosis and hypoxia is complex. On the one hand, fibrosis can cause hypoxia, as in when—for example—excessive scar tissue hinders oxygen delivery to the injured site. Fibrotic tissue is in fact often hypoxic. On the other hand, hypoxia can regulate fibrosis, but the details of



Jens Selige is Scientific Project Manager of the NCCR Kidney.CH

**„Sag zum Abschied leise; Servus“
(When leaving just say “see you”)**

For more than 5 years now, I was part of the NCCR Kidney.CH as Scientific Project Manager. During this time, I had witnessed the end of the 1st funding phase, accompanied the entire 2nd phase and was able to help shaping its 3rd phase. The NCCR Kidney.CH has become the flagship of Swiss kidney research. Numerous interdisciplinary experts from basic sciences and clinical research have formed a unique network around the topic of homeostasis of the kidney and its disease mechanisms. The NCCR has become an ideal environment that has inspired many junior researchers to study kidney disease (e.g. Junior Grant awardee Carsten Scholz; see the cover story!). Numerous cooperation and projects with the USA, Germany, France, Great Britain, Italy, etc. have made the NCCR and thus the Swiss renal research, internationally visible across the national borders and thus also strengthened Switzerland as a research location in general. It was a pleasure for me to be part of the Managing Team. I would like to thank all PIs with their groups but especially the Managing Team (Johannes Loffing, Carsten Wagner, Katharina Thomas and also François Verrey) for the very good and friendly cooperation! 3 years are still ahead of us. Keep it up! All the best!
Jens Selige



this regulation are still largely unclear. Both acceleration and dampening of fibrosis by hypoxia have been reported. This likely depends on the context of the underlying disease or tissue injury. However, the hypoxia–fibrosis interplay is thought to play an important role in the development of chronic kidney disease (CKD) after acute renal injury.

A BREATH OF FRESH AIR FOR RENAL FIBROSIS TREATMENT

Cellular oxygen sensors, called PHDs and FIH, are the main proteins responsible for the adaptation of cells to hypoxia. Given the described detrimental role of hypoxia following renal injury, it may seem unreasonable to target cellular oxygen sensors as a treatment option for renal fibrosis. However, many previous investigations have demonstrated that the exposure of tissue/organs to hypoxia or to chemicals that mimic hypoxia has tissue-protective effects. Hence, inhibiting cellular oxygen sensors is protective. The mechanisms behind this effect are not very well understood, but there are likely several different ones. For example, using a chemical inhibitor will target all cells within the kidney. This may render healthy tissue areas more inert to a possible subsequent fibrotic impact and prevent the spreading of the hypoxic scar tissue. Furthermore, chemical inhibitors will lead to a strong or even complete inhibition of cellular oxygen sensors, while in contrast the distribution of oxygen in the diseased kidney will follow a gradient (the closer to blood vessels the higher the levels) and lead to a highly variable inhibition within fibrotic tissue.

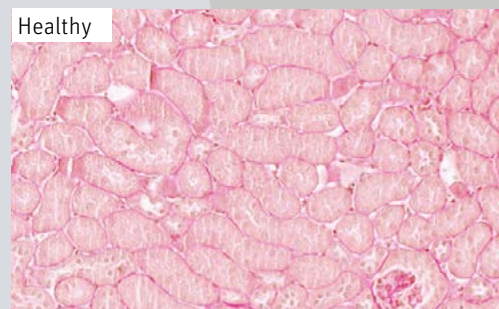
JUNIOR GRANT ENABLES RESEARCH

While chemical inhibition of cellular oxygen sensors may be a promising and novel treatment option for preventing fibrotic remodelling during CKD, a more detailed understanding of the underlying mechanisms leading to the protective effect is necessary before such inhibitors may be used on patients. A Junior Grant from Kidney.CH is enabling me to

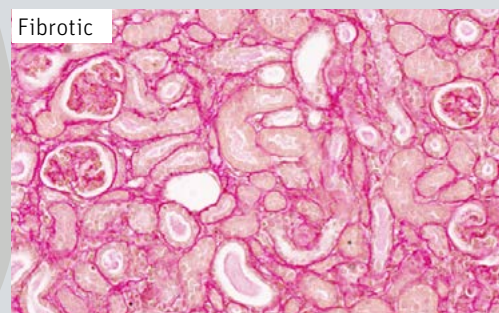
investigate a possible mechanism contributing to this protective effect. It furthermore allows me to supervise my own PhD student and to prove myself as an independent scientist. The transition from a researcher working for a supervisor to supervising someone yourself is difficult, and a bottleneck in academic research. The Junior Grant offers a great opportunity to efficiently bridge this transition. If the Junior Grant period is successful, I will be able to compete for larger funding, which is often otherwise a limiting factor in the development of an independent research career. In addition, the network of the Kidney.CH provides a unique basis for collaboration, which in turn contributes to a successful Junior Grant period. It enabled me (working in Zurich), for example, to establish a collaboration with CKD experts at the University of Geneva. Therefore, Kidney.CH and its Junior Grants offer an exceptional framework and opportunity for young scientists to drive their ideas independently, while benefitting from this large network of leading Swiss kidney experts.



Carsten Scholz, senior associate scientist at the Institute of Physiology of the University of Zurich, is a Junior Grant Awardee of the NCCR Kidney.CH. Before coming to Zurich, he completed his PhD in Translational Medicine at the Conway Institute of University College Dublin in Ireland and worked as a postdoc at Systems Biology Ireland. His research focuses on oxygen-dependent regulations in physiology and disease.



Healthy



Fibrotic

WHAT IS FIBROSIS?

When tissues and organs are injured, a highly coordinated healing process is set in place to achieve functional recovery. This process involves the removal of damaged tissue, the expansion of cells to replace missing or non-functional tissue, and the guidance of expanded cells into the correct place, as well as keeping the cells in the necessary position. Each of these steps has to be properly controlled and stopped in time. If this fails, an excessive “tissue repair” ensues, leading to uncontrolled scar formation and further tissue destruction, which ultimately could destroy the entire organ. This excessive tissue repair is called fibrosis. Renal fibrosis can eventually lead to kidney failure.

Visualization of components of the tissue scaffold (dark red colour) in a healthy mouse kidney and during fibrosis.

THE RIGHT MIX OF RESEARCH AND TEACHING: IDEAL FOR FOSTERING THE SPIRIT OF COOPERATION



Christian Stockmann is an assistant professor at the Institute of Anatomy of the University of Zurich and joined the NCCR Kidney.CH as affiliate in 2018.

Christian Stockmann has been Assistant Professor for Molecular Medicine at the Institute of Anatomy at the University of Zurich since 2017. With his research group, the 41-year-old German aims to decipher how immune-cell-driven angiogenesis influences organ remodelling during tissue hypoxia. Funding sources for his research projects include the Swiss National Science Foundation, the Swiss Cancer League, and the Swiss Cancer Research Foundation. Within the NCCR Kidney.CH he leads a human/clinical and cooperative project (HCP) on the role of macrophages in adrenal gland homeostasis and blood pressure control, with Vartan Kurtcuoglu, Felix Beuschlein and Jan Loffing.

YOU'VE MOVED AROUND QUITE A BIT PROFESSIONALLY. FROM ESSEN TO JAPAN, TO THE UNIVERSITY OF CALIFORNIA SAN DIEGO AND LATER TO THE EUROPEAN HOSPITAL GEORGES POMPIDOU IN PARIS. WHY DID YOU CHOOSE TO COME TO ZURICH?

The University of Zurich is a leading player in European research and has a lot to offer in terms of research infrastructure and funding opportunities and, most importantly, has an outstanding network of experts who are leaders in their field. Having seen many different places, I must say that Zurich provides a unique and one of the most dynamic research environments in Europe and even beyond. It is a privilege to work here. And although I might be a bit spoiled by California and Paris, I would say that the quality of life in Switzerland and particularly in Zurich is quite high.

YOU WORK IN MOLECULAR MEDICINE WITH FOCUS ON TISSUE FIBROSIS? WHY DID YOU SPECIALIZE IN THAT?

As a postdoc I was initially researching cancer biology. Then I accidentally came across the topic 'organ fibrosis'. There are quite some similarities between malignant tumours and fibrotic organs. I discovered, however, that the pathophysiology of tissue fibrosis was not at all understood and that this topic was, and still is, not well researched despite its huge clinical relevance. Since my postdoc supervisor had given me a lot of freedom, I decided to dig into the molecular mechanisms of fibrosis rather than tackling this problem from the clinical side.

WHAT IS THE CURRENT FOCUS OF YOUR RESEARCH?

In addition to our focus on immunology and vascular biology I'm studying, with my research group, the mechanisms of fibrosis after organ damage and inflammation. We are interested in the organ-specific functions of the immune system that contribute to organ and whole-body homeostasis in the absence of severe inflammation and under steady-state, physiological conditions.

WHAT KIND OF OPPORTUNITIES AND SUPPORT DOES THE NCCR KIDNEY.CH OFFER YOU? WHAT DO YOU APPRECIATE IN PARTICULAR?

What I appreciate the most is Kidney.CH's multidisciplinary nature, the complementarity of expertise, and the spirit of cooperation. Within the NCCR I can talk with experts on kidney physiology and nephrology, in vivo imaging, or endocrinology, all of which are not really my core expertise. In exchange, I can contribute with my knowledge of immunology and vascular biology.

WHAT ARE YOUR PROFESSIONAL GOALS FOR THE NEXT FEW YEARS?

Well, as all scientists, I want to further develop our projects and make exciting findings. Besides that, one major goal, in addition to international cooperation, is to further expand the collaboration between the University and ETH Zurich. Most importantly, though, I would like to promote the careers of young researchers

in my lab. I received a lot of support from my previous supervisors and I would like to do the same for the people in my lab.

WHAT DO YOU DO TO BALANCE RESEARCH AND TEACHING?

Many researchers consider the absence of teaching as ideal, but after having worked in positions without any teaching for years, I am convinced that this is not true. It is, indeed, the mix of teaching basics to the next generation of MDs and scientists while pursuing cutting-edge research in the lab that is the vital ingredient of a successful research career. Fortunately, here at my institute—the Institute of Anatomy—we have found a pretty good balance between teaching and research.

LASTLY, TELL US SOMETHING ABOUT YOUR PERSONAL LIFE.

My partner Anna, a cell biologist, and I have a son and a daughter, 6 and 15 years old, who of course deserve, most of our spare time. Other than that, I enjoy sports, such as running, swimming or soccer, and I love to catch up with long-time friends who go back all the way to med school or even kindergarten.

NCCR KIDNEY.CH RETREAT 2019

Around 80 members of the NCCR Kidney.CH followed the invitation to the 9th retreat at the SBB Centre Loewenberg in Murten from 31 January to 1 February 2019. After a welcome apéro on the first evening, numerous presentations on oxygen, dietary ions and mineralization were on the agenda on the second day. Maria-Christina Zennaro, Professor at the Cardiovascular Research Center Paris (INSERM), had been invited as guest speaker and talked about “Recent advances on the mechanisms of primary aldosteronism”. The NCCR’s Junior Grant recipients David Penton, Pedro Imenez Silva, and Natsuko Tokonami presented their projects.



“Human studies” has been introduced as a new module at this Retreat. Carsten Wagner and Eric Feraille held presentations about their Human Clinical/Collaborative Projects (HCP) and Olivier Bonny talked about the progress of the Swiss Kidney Stone Cohort.

The retreat concluded with a speech from Professor Thomas Jentsch (Max-Delbrück-Centrum for Molecular Medicine, Helmholtz-association Berlin) on “Properties and surprising roles of volume-regulated VRAC/LRRC8 anion channels”.

Poster Award 2019

At the Retreat 2019, a jury consisting of members of the NCCR’s Steering Committee and Advisory Board selected the best three posters among 30 posters. The first prize was awarded to Anna Faivre (MD/PhD student in the De Seigneux-lab, UniG), second prize went to Adisa Trnjanin-Hadzic (PhD student in the Loffing-lab, UZH), and third prize went to Susan Ghazi (PhD student at Hall-lab, UZH). Congratulations!

NCCR Kidney.CH Communication Award

For the first time the “Communication Award” for achievements regarding the public presentation of the NCCR was awarded during the retreat. The award went to Milica Bugarski (UZH) and Joana Delgado Martins (UZH) for setting-up and running the NCCR Twitter account.



EUKISS
European Kidney
Summer School

EUKISS – EUROPEAN KIDNEY SUMMER SCHOOL 2018

The NCCR Kidney.CH, TRENAL (Translational kidney research – from physiology to clinical application), and two Kidney-centered “Sonderforschungsgebiete” (SFB) from Regensburg (SFB 1350) and Berlin (SFB 1365), Germany, establish a joint European Summer School. It will take place at the University of Zurich from September 8–11, 2019.

This European summer school will bring together experts in kidney research and disease to discuss in a stimulating and interactive setting the basis of renal functions and their relevance for kidney disease. Small group clinical case discussions will highlight both common and rare forms of kidney disease. Participants are invited to present their research projects during a poster session.

For more information and registration will be soon available under www.eukiss.org

FAREWELL JENS, WELCOME ROMINA

We have to say good-bye to Jens Selige, who was our NCCR Kidney.CH project-manager for the last five years and who will now take over a new position at the UZH. As a trained biologist with experience in science management and as a passionate yachtsman, too, Jens helped a lot to navigate the course of the NCCR in its second phase. Jens’ organizational skills and commitment combined with just the right portions of tenacity, patience, and humor were instrumental for the management of the NCCR. We warmly thank Jens for his great job and we wish him all the best for his new position and future career. Take care, Jens!



At the same time, we warmly welcome Romina Theiler as our new project-manager. Romina studied Biology and Molecular Life Sciences in Bern. She has several years of experience in research and research management obtained at the Institutes of Molecular Pathobiology and Pathology and the Department of Neurology in Bern as well as at the WPI Immunology Frontier Research Institute in Osaka, Japan. We are very glad to have recruited, with Romina, an excellent new project-manager and we are very much looking forward to work with her within the management team and within the entire NCCR. Let’s go ahead!

EVENTS

FAREWELL SYMPOSIUM

**FRANÇOIS VERREY:
KIDNEY & TRANSPORT**
June 21, 2019

USZ, Zürich, Switzerland

SUMMER SCHOOL 2019

September 8–11, 2019

USZ, Zurich, Switzerland

4TH SWISS KIDNEY STONE SYMPOSIUM

September 26, 2019

Hörsaal Langhans

Inselspital Bern, Switzerland

11. JAHRESTAGUNG DER DEUTSCHEN GESELLSCHAFT FÜR NEPHROLOGIE

October 10–13, 2019

Düsseldorf, Deutschland

ASN KIDNEY WEEK 2019

October 20–25, 2019

Denver, Co, USA

51TH ANNUAL MEETING OF THE SWISS SOCIETY OF NEPHROLOGY

December 5–6, 2019

Congress Center Kursaal
Interlaken, Switzerland

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