SWISS NATIONAL CENTRE OF COMPETENCE IN RESEARCH

KIDNEY
CONTROL OF HOMEOSTASIS

NEWSLETTER ⁘ NO. 13 ⁘ NOVEMBER 2016

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.

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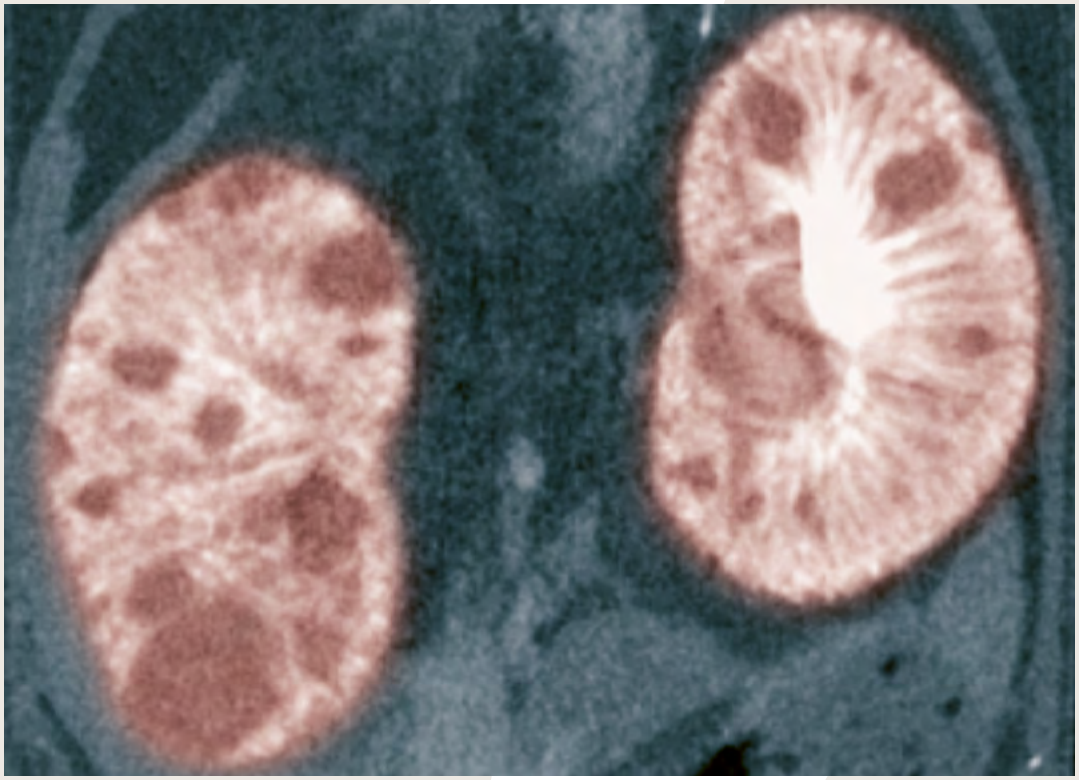
PIECING THE PARTS TOGETHER



Micro-computed tomography image of clear cell renal cell carcinomas in the kidneys of a mouse.

Clear cell renal cell carcinoma is the most frequent form of kidney cancer. One out of 65 people will develop this disease. To determine which gene mutations are responsible, an NCCR Kidney.CH research group has been testing numerous gene combinations in mice. After years of research they have managed to successfully recreate the cancer, thus laying the foundations for developing new therapies.

Cancers result from the perturbation of normal physiological processes. The study of cancer is therefore inseparable from the study of physiology. The major focus of the research carried out in my laboratory over the last seven years, during the period of my Assistant Professorship in the Zurich Integrative Human Physiology network, has been to develop an understanding of the molecular and cellular causes of the most frequent form of human kidney cancer, clear cell renal cell carcinoma (ccRCC). One person in about 65 will develop this disease within their lifetime and many of these patients will die from the disease because currently available therapies are effective in only some cases.

DECLINING OXYGEN LEVELS INCREASE RISK

It is an unusual epithelial cancer because ccRCC is uniquely characterised in the vast majority of cases by the mutation of the von Hippel–Lindau (VHL) tumour suppressor gene. The protein that is produced by this gene, pVHL, functions in every cell in our bodies as the gatekeeper of cells' responses to changing oxygen levels. Oxygen controls the activity of pVHL with regard to two other key proteins, the hypoxia-inducible factors HIF-1α and HIF-2α. Hypoxia-inducible factors (HIFs) are transcription factors that respond

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Joachim Fandrey is Professor of Physiology at the University of Duisburg-Essen and a member of the interdisciplinary Centre of Medical Biotechnology. He is also Dean for Student Affairs at the Medical Faculty of the University of Duisburg-Essen and is a member of the NCCR's Advisory Board.

Starting point for scientific careers

The NCCR Kidney.CH has elegantly set the table with the aim of boosting research into the central role of the kidney in our bodies' homeostasis. This table stands on four legs—oxygen, ion balance, dietary impact and calcification—and six places are laid, one each for Basel, Bern, Fribourg, Geneva, Lausanne and Zurich, providing a platform for Swiss excellence in kidney research.

I have been privileged to follow the scientific discoveries made by the NCCR. This network of leading specialists in experimental and clinical nephrology provides a convincing basis for translational research—in its truest sense, from bench to bed, serving to benefit patients with renal disease.

One of the NCCR's main objectives is to promote the careers of young scientists. A good example of the success of this programme is the work of Ian Frew, which is described in this issue. Frew, a junior assistant professor, has 'built' an accurate mouse model of kidney cancer.

For me, it is a great pleasure to review the scientific progress of the NCCR Kidney.CH at each of its yearly retreats. May this platform lay the foundations for many more successful scientific careers.

Joachim Fandrey

to decreasing oxygen in the cells, so-called hypoxia. HIF-1α and HIF-2α control the expression of hundreds or even thousands of genes that help the cell to adapt in many different ways to the changing oxygen environment. Because VHL is mutated, the cells that initially form ccRCC tumours 'think' that they are permanently in a low-oxygen environment. For reasons that are still not clear, it seems that kidney tubular epithelial cells, in comparison to most other cell types in the body, are particularly sensitive to this condition, which dramatically increases the chances that they will develop into cancer cells.

IN SEARCH OF THE RIGHT GENES

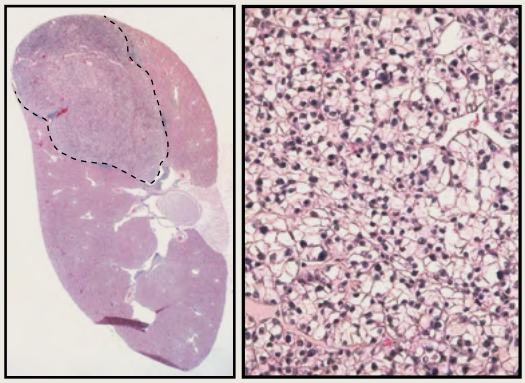
However, cancers of epithelial tissues are never caused by the mutation of just one gene, but rather by the cooperative effects of mutations in many different genes. The challenge is firstly to find out which genes are the important ones and secondly to understand how their mutation contributes to the development and spread of a tumour. This is where our research comes in: we try to recreate ccRCC by introducing different mutations into normal renal epithelial cells to see if this turns them into tumour cells.

A COMPLEX RESEARCH TASK

A nice analogy via which to understand the challenge that we face is to imagine being asked to build a television. You are given one functioning television that contains all of the necessary parts and circuits, but the television in fact contains another 50 random parts that do absolutely nothing. This is similar to the case in tumours; we think that there are some parts (mutations) that are essential for the tumour, and other parts that have just 'come along for the ride' and don't contribute at all. You can start by cataloguing and naming all of the parts of your television but this doesn't help you much—all of them could be important. What you need in order to narrow down the search are hundreds of similar but slightly different televisions so that you can see what parts are similar or identical between them and what parts are unique to each different unit. The common ones are the ones that are probably necessary—you can then start putting them together and trying to recreate a new television. Fortunately, we can now compare the full 'parts list' or genetic makeup of hundreds of human ccRCCs. We now know which mutations are likely to be the most important in most cases of ccRCC. This gives us our list of candidate genes, which we have been altering in different combinations using genetically modified mice.

SUCCESSFULLY NARROWING DOWN THE SEARCH

Over the last 13 years, including my research as a postdoc, we have tested 23 different combinations of mutations and have learnt a lot about what does and doesn't cause ccRCC. We successfully recreated some of the early stages of ccRCC and could show that defects in primary cilia, antenna-like structures that project from the surface of epithelial cells, which are pathogenically altered in diverse renal cystic diseases, are also important contributors to the initiation of ccRCCs. We genetically proved that both HIF-1α and HIF-2α are strictly necessary for the initiation of the earliest stages of tumour formation, an important observation now that inhibitors of the activities of HIF-1α and HIF-2α are becoming clinically available. In our work in the context of Kidney.CH we identified that HIF-1α is specifically responsible for the regulation of the metabolism of tubular epithelial cells as it changes the pathways by which these cells generate energy, and also showed that HIF-1α activity in epithelial cells sends signals to neighbouring cells, recruiting new blood vessels to places where they normally should not be. This 'artificial' genetic situation has dramatic effects on the normal functioning of the kidney, but also provides a model that mimics the pathological situation in which a newly forming tumour has to establish a lifeline to the blood supply of the kidney to allow it to be nourished and grow.



Low magnification (left) and high magnification (right) views of a ccRCC tumour in a mouse kidney

EFFORTS PAY OFF: GOAL ACHIEVED

Our biggest success however is our most recent one. To return to the television analogy, we've always argued that until you can build something from scratch, you don't really know how it works. For more than two decades, the research community has tried to 'build' accurate mouse models of ccRCC, without success. By combining three different mutations in mice, we have finally achieved this goal and could show that the tumours that arise in these mice share many molecular and cellular similarities with human ccRCC, and also respond to current ccRCC therapies in similar ways. While, on one hand, this represents the achievement of a 20-year-goal, we are also very excited about it being the beginning of a new 20-year project to make more and better models of this disease, enabling us to accelerate the search for optimal therapies that can be offered to patients in the future. I am also convinced that we will learn a lot more about the normal physiology of kidney cells along the way.

Ian James Frew has been Professor at the Zurich Centre for Integrative Human Physiology (ZIHP) of the University of Zurich, and participant within the NCCR Kidney.CH. From January 2017, he will continue his research at the University Hospital of Freiburg (Germany). His new lab will be based at the Centre for Translational Cell Research (ZTZ) and he will be affiliated with the BIOSS Centre for Biological Signalling Studies and the Comprehensive Cancer Centre Freiburg (CCCF).

THE NCCR KIDNEY.CH IS EXPANDING ITS EDUCATION PROGRAMME

The NCCR Kidney.CH is adding two academic certificates to its education programme: a Certificate of Advanced Studies (CAS) and a Diploma of Advanced Studies (DAS) in Translational Nephrology. The kick-off meeting for the first of a total of five modules—a meeting that will take place at the University of Bern on March 3, 2017—will mark the start of the new programme.

High-quality research in renal physiology has a long tradition in Switzerland. With this in mind, the National Centre of Competence in Research (NCCR) Kidney.CH made it its goal to help develop a new generation of renal experts. With the introduction of its education programme in 2011 the NCCR Kidney.CH created Switzerland's first comprehensive programme that specialises in renal physiology and pathophysiology. The NCCR Kidney.CH's education programme focuses primarily on homeostatic body functions—where kidneys play a central role—which are being addressed by the NCCR's research groups.

TRAINING FUTURE RENAL EXPERTS

Before the creation of this education programme students pursuing a PhD in the life sciences learned very little about renal pathophysiology. During their Bachelor studies medical students or medical biology students were introduced to renal physiology as part of general physiology courses. Only when studying for their master's in medicine were they given lectures in renal pathophysiology and clinical nephrology. To close this knowledge gap the NCCR Kidney.CH introduced a Swiss-wide training programme in integrative kidney physiology and pathophysiology (IKPP), with a translational approach.

E-LEARNING COURSES FOR CAS/DAS

At the core of the new CAS/DAS in Translational Nephrology lie the e-learning courses developed by specialists from the NCCR Kidney.CH in collaboration with the Health Sciences eTraining Foundation (HSeT). These two programmes have been accredited by the University of Bern, acollaboration agreement with the other participating Swiss universities is pending.

To obtain the CAS and DAS, students must complete five e-learning modules, including the corresponding face-to-face sessions, and perform successfully in performance audits at the end of each module. Each module will be accredited with 3 ECTS (European Credit Transfer and Accumlation System) credits.

To obtain the CAS participants need to complete all modules (15 ECTS). The DAS (35 ECTS) requires—on top of the successful completion of all modules—documented scientific achievements (e.g. publication in a peer-reviewed journal) and active participation at conferences, retreats or relevant workshops.

INSIGHTS INTO NEPHROLOGY

The programme will provide extensive insights into the basics of nephrology by studying the physiological and pathophysiological role of kidney function in health and disease. Starting with key articles and with clinical cases illustrating the translational aspects, the topic will be further explored by a blended-learning approach—including face-to-face sessions with module leaders and tutors, access to annotated online resources, self-guided learning, presentations, and assessments.

The CAS/DAS programme is intended for national and international graduates, with a natural- and medical-science background, interested in basic and clinical renal research. The programme will be endorsed by the Swiss Society of Nephrology, which accredits each single module for Continuing Medical Education (CME) with 28 credits for all physicians and medical scientists.

COSTS, GRANTS AND FELLOWSHIPS

The fee for the CAS study programme is CHF 3,000 (including final exam and certificate). Single modules can be attended (completed) for CHF 500 each. The DAS study programme will cost CHF 4,000. The NCCR Kidney.CH is granting a limited number of fellowships. In addition, travel grants are available for participants domiciled outside Switzerland. To apply for these travel grants, send an e-mail to: jens.selige@nccr.kidney.ch

More information and registration at:
www.nephrologie.unibe.ch
www.nccr-kidney.ch

For questions about the programme "CAS/DAS in Translational Nephrology" please contact:

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2ND JOINT NCCR WORKSHOP: LEARNING TO WORK TOGETHER

Scientists often face very complex problems, which is why collaboration with other researchers is particularly important. To build a fruitful collaboration despite differences in approach, interpersonal skills are essential.
With this in mind, two NCCRs — RNA & Disease and Kidney.CH — invited a group of young scientists to attend the two centres' second joint workshop on improving communication skills. The workshop took place November 24–26, 2016 at Schloss Muenchenwiler in the Canton of Bern. Two international coaches from hfp-consulting taught 16 PhD students and postdocs the basics of collaboration. To begin with, the participants were given several exercises to improve their communication skills; skills which were later needed to tackle topics such as conflict management and team development. Additional exercises in the field of process management aimed at increasing the participants' competence profiles.
In addition to teaching new skills, the workshop also provided an excellent opportunity for scientific exchange between the two NCCRs — as all participants confirmed in their feedback.

RESULTS OF THE 4TH HCP CALL

On October 31, 2016 the NCCR Kidney.CH's Steering Committee approved five proposals for human/clinical and translational cooperative projects (HCP).

Approved HCP projects
(Main applicant / Project title)

Idris Guessous (University Hospital of Geneva):
Comparison of food intake and physical activity between a cohort of stone formers and the general population using validated food frequency questionnaires (FFQ) and physical activity frequency questionnaires (PAFQ).

Andreas Pasch (University Hospital of Bern):
Establishment and validation of a novel method for the assessment of the calcium phosphate crystallization propensity of urine.

Carsten Wagner (University of Zurich):
Contribution of specific human phosphate transporters to renal phosphate handling.

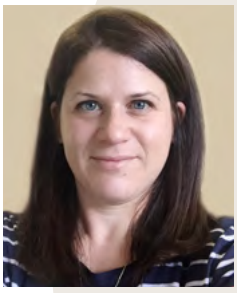
Sophie de Seigneux (University of Geneva):
Anemia in individuals with CKD—the deleterious role of arterial stiffness and blood volume-regulating hormones and correction by exercise.

Olivier Bonny (Swiss Kidney Stone Cohort and University Hospital of Lausanne):
Control cohort of subjects without stones and renal diseases, built on the SKSC protocol.

E-LEARNING MODULE 5 STARTED: METABOLISM AND CKD

On October 13, 2016 the 5th e-learning module—on Metabolism and CKD—started with a kick-off meeting in Bern. The NCCR Kidney.CH offers this e-learning programme in collaboration with the Health Science eTraining Foundation (HSeT).
About 20 young scientists from all over Switzerland listened to presentations from Prof. François Verrey (University of Zurich), who talked about amino acids, kidney size and urinary concentration, and Prof. Reto Krapf (Hirslanden Klinik St. Anna, Lucerne) who focused on the physiological effects of variations in dietary potassium intake. Prof. Jean-Pierre Montani (University of Fribourg) complemented the lecture with a talk on markers of renal function and evolution with age.
As part of the module the participants are currently studying annotated articles on oxygen homeostasis via the e-learning platform of the Integrative Kidney Physiology and Pathophysiology (IKPP) programme. In addition, tutors will provide them with questions and exercises that need to be answered and executed, respectively. On March 2, 2017 the participants will present their work to a panel of experts from the NCCR Kidney.CH.

JUNIOR GRANTS 2016


Eva Bernabeu Dizin


Carsten Scholz

Eva Bernabeu Dizin and Carsten Scholz received this year's NCCR Kidney.CH Junior Grants.

Eva is a postdoc at the Department of Cell Physiology and Metabolism in the lab of Eric Feraille at the University of Geneva. She is investigating the 'POD-ATTAC mouse', a new rodent model of nephrotic syndrome, in order to decipher sodium retention mechanisms in renal tubules.
Carsten Scholz is doing his research at the lab of Roland Wenger at the Institute of Physiology of the University of Zurich. Carsten is exploring the oxygen-dependent functions of OTUB1 (ovarian tumour (OTU) domain-containing ubiquitin aldehyde-binding protein 1) in kidney injuries and fibrosis.
Each grant — CHF 60,000 per year for a maximum of three years — is intended to help increase the candidate's professional independence and to promote their projects.

EVENTS

LS2 ANNUAL MEETING 2017
February 2—3, 2017
University of Zurich, Switzerland

2ND SWISS KIDNEY STONE SYMPOSIUM
February 9, 2017
Inselspital, Bern, Switzerland

7TH NCCR KIDNEY.CH RETREAT 2017
February 9—10, 2017
Murten/Muntelier, Switzerland

KICK-OFF MEETING FOR MODULE 1: CAS / DAS IN TRANSLATIONAL NEPHROLOGY
March 3, 2017
University of Bern, Switzerland

ADAPTATIONS TO HYPOXIA IN PHYSIOLOGY AND DISEASE
March 5—9, 2017
Whistler Conference Centre, British Columbia, Canada

DPG 96. JAHRESTAGUNG 2017
March 16—18, 2017
Greifswald, Germany

54TH ERA-EDTA CONGRESS
June 3—6, 2017
Madrid, Spain

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