3RD JOINT NCCR WORKSHOP: CAREER DEVELOPMENT AND APPLICATION TRAINING

Seminar hotel Urs & Victor, Bettlach

Knowing how to identify job opportunities and to prepare for the selection process is very important. Therefore the two NCCRs RNA & Disease and Kidney.CH invited young scientists from October 4—6, 2017, to a joint workshop on career planning to the seminar hotel Urs & Victor, in Bettlach (Solothurn). This was the third collaboration of the two NCCRs.
A key step in the career of a scientist is to undergo job interview and application processes. However, young scientists find themselves on their own when it comes to deciding on their next career step or to developing skills for their future career. These aspects are traditionally not part of the academic training.
The workshop was designed to help young scientists to explore their personal motivation and to prepare them for their professional decision making process.
Two international coaches from hfp-consulting introduced 15 doctoral students and postdocs to different tools for their career development. The feedback from the participating scientists was very positive.

3RD KIDNEY STONE SYMPOSIUM 2018: JANUARY 25, 2018

The 3rd International Kidney Stone Symposium in Switzerland focuses on the pathophysiology of kidney stones and the challenges of their therapies. Scientists from the Swiss Kidney Stone Cohort like Prof. Olivier Bonny from the CHUV, Dr. Nilufar Mohebbi from University Spital of Zurich and Prof. Daniel Fuster from the Inselspital Bern, will get together with international colleagues such as Prof. Naim Maaluf from Dallas (USA), Prof. Gary Churhan from Boston (USA), Prof. Thomas Knoll from Sindelfingen (D), Prof. Pietro Manuel Ferraro and Prof. Giovanni Gamaro both from Rome (I) and Prof. Robert Unwin from London (GB). The Symposium will take place place in the Auditorium Ettore Rossi at the Inselspital Bern on January 25, 2018.

CAS/DAS TRANSLATIONAL NEPHROLOGY: MODULE 1 & 2

This CAS/DAS programme provides relevant insights into the basics of nephrology by studying the physiological and pathophysiological bases of kidney function in health and disease. The NCCR Kidney.CH offers this e-learning programme in collaboration with the Health Science eTraining Foundation (HSeT).
On October 19, 2017, module 1 with the topic “Salt and Water Transport” ended and had its return session at the University of Bern. About 25 young scientists from all over Switzerland presented their work in front of a panel of experts from the NCCR Kidney.CH. To prepare for their presentation they had studied annotated articles on mechanism, regulation and diseases of renal sodium and water handling.
One day after the presentations, the second module on “Acid-base homeostasis” started. The participants listened during the kick-off meeting to the presentations of Prof. Carsten Wagner (University of Zurich), who talked about “acid-base homeostasis” and Dr. Nilufar Mohebbi (University Hospital Zurich) who focused on “Clinical aspects of acid-base disorders”. The return session with the final assessment of module 2 takes place on April 5, 2018. Module 3 with the topic ”Tubular handling of divalent cations and disorders of biomineralization” will start on April 6, 2018. You can register at: www.nephrologie.unibe.ch

JUNIOR GRANTS 2017

Diane de Zélicourt

Johan Lorenzen

Diane de Zélicourt and Johan Lorenzen received this year’s NCCR Kidney.CH Junior Grant. Diane de Zélicourt is a Postdoc at the Institute of Physiology and part of the Interface Group in the lab of Vartan Kurtcuoglu at the University of Zurich. Her primary research focus is on experimental and computational methods in biomechanics, and their application to understand disease mechanisms and improve device designs/ surgical procedures.
Johan Lorenzen is doing his research at the lab of Ruedi Wüthrich at the Institute of Physiology, University of Zurich, but also at the University Hospital Zurich. Johan is exploring the role of non-coding RNAs in kidney injury (see “Portrait” in this newsletter).
The grant money of CHF 60’000 per year for a maximum of three years is intended to help increase the candidates’ professional independence and to promote their projects.

EVENTS

3RD SWISS KIDNEY STONE SYMPOSIUM
January 25, 2018
Inselspital Bern, Switzerland

8TH NCCR KIDNEY.CH RETREAT 2018
February 1—2, 2018
Murten/Muntelier, Switzerland

LS2 ANNUAL MEETING 2018
February 12—13, 2018
Amphipôle/Amphimax,
University of Lausanne,
Switzerland

CAS/DAS TRANSLATIONAL NEPHROLOGY
Kick-Off Meeting for module 3
April 6, 2018
University of Bern,
Switzerland

KEYSTONE SYMPOSIA: THERAPEUTIC TARGETING OF HYPOXIA-SENSITIVE PATHWAYS
April 10—14, 2018
University of Oxford
Mathematical Institute,
Oxford, UK

55TH ERA-EDTA CONGRESS
May 24—27, 2018
Copenhagen, Denmark

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KIDNEY
CONTROL OF HOMEOSTASIS
SWISS NATIONAL CENTRE OF COMPETENCE IN RESEARCH

University of Zurich[UZH]

SWISS NATIONAL SCIENCE FOUNDATION

SWISS NATIONAL CENTRE OF COMPETENCE IN RESEARCH

KIDNEY
CONTROL OF HOMEOSTASIS

NEWSLETTER ::: NO. 15 ::: DECEMBER 2017

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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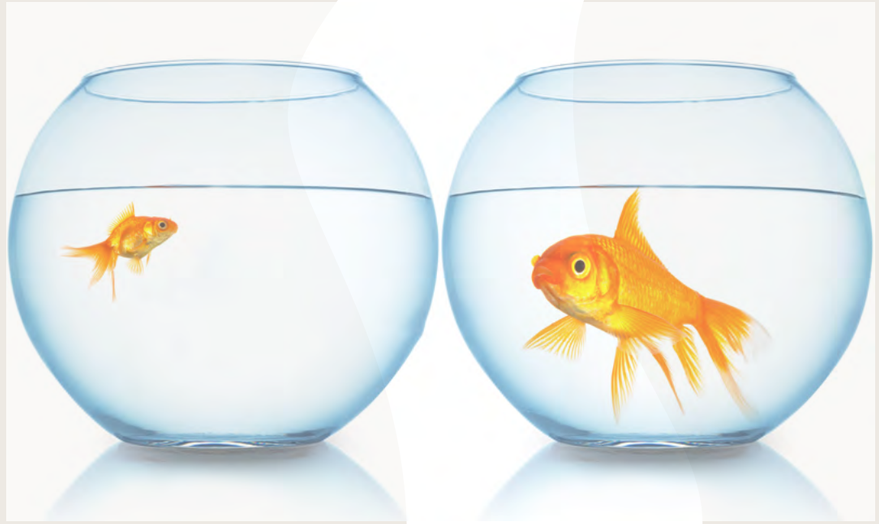
ONE SIZE DOES NOT FIT ALL



Since everyone is different, it is important to develop optimal treatments for individual patients.

Precision medicine aims to identify and develop treatments for certain groups of patients, based on genes, environment and lifestyle. Having applied this approach to cancer and rare diseases, scientists are now trying to find cures for common disorders such as hypertension, diabetes or chronic kidney disease (CKD).

For centuries, doctors have recognized the need to tailor therapeutic modalities to each individual case. In his writings, Avicenna (980 to 1037 AD) specified that the effectiveness of medications is related to the ‘temperament’ of a person and his or her organs, which themselves are altered by the environment. In the seventeenth century, Francis Bacon promised that an understanding of the true mechanisms of disease would enable us to extend life almost indefinitely. The words of Sir William Osler (1903)—‘The good physician treats the disease; the great physician treats the patient who has the disease’—resound today, as we enter the era of precision medicine.

TAILOR-MADE MEDICINE

Precision medicine (or personalized, stratified medicine) is defined as ‘an approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person’ (NIH, Precision Medicine Initiative). This approach is based on identifying subgroups of individuals with distinct mechanisms of disease, primarily based on genetic analyses that can be coupled with ‘multi-omics’ profiles (e.g. epigenomics, transcriptomics, proteomics or metabolomics), biomarkers, imaging tests and electronic medical records to create a ‘systems biology’ evaluation. The goal of precision medicine is to identify and develop treatments that are effective for particular groups of patients, and to treat with a given drug only responders and patients not predisposed to toxicity.
Over the last decade, precision medicine has been developing at considerable speed in the field of cancer, using genetic changes in a patient’s tumour(s) to determine the best treatment. Examples include

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Carsten Wagner
Carsten Wagner is a professor at the Institute of Physiology at the University of Zurich and a member of the Steering Committee of the NCCR Kidney.CH

Precise knowledge for personalized medicine

The last two decades have seen a surge in the collection of very large data sets stemming from '-omics' technologies relating to many body functions, including renal function and kidney disease. Some have already provided major novel insights into fundamental processes, giving clues about which molecules/pathways may be involved in disease or be promising new diagnostic and therapeutic targets. Methods of measuring more and more data points are constantly being refined. But we often still lack precise knowledge of whether and how associations between data points (e.g. risk genes and disease) are causally linked. So new knowledge means new challenges, and new opportunities for large research consortia like the NCCR Kidney.CH, where efforts to identify novel associations go hand in hand with more mechanistic studies. Such complex and collaborative studies are essential, not only to step up our understanding of kidney function and disease, but also to prepare the ground for tailored therapies for individual patients. The NCCR Kidney.CH is well placed to take a leading role in this quest for a deeper, more precise understanding of kidney physiology and disease, and ultimately to contribute to the development of tailored therapies.

Carsten Wagner

BETWEEN THE CLINIC AND THE LAB

Johan Lorenzen, recipient of a Junior Grant from the NCCR Kidney.CH, opens up about the challenges of pursuing research in the lab while working as a physician in a hospital. The 37-year old German-born nephrologist studied Medicine at the Hanover Medical School (MHH) in Germany. After his doctorate degree, he acquired his first experiences as a group leader, at the Institute of Molecular and Translational Therapeutic Strategies in Hanover. In November 2016, he moved to Zurich, taking a position at the Nephrology division of the city's University Hospital. Shortly after, he got in touch with researchers from the NCCR Kidney.CH. In February 2017, he received the aforementioned Junior Grant, which will strengthen his research within the group of Professor Ruedi Wuethrich at the University of Zurich.

YOUR TIME IN HANOVER WAS VERY SUCCESSFUL FOR YOU. WHY DID YOU MOVE TO ZURICH?

With the completion of my residency and specialisation in Nephrology in 2016, it was time to move on and establish myself independently at another institution. I was delighted when the opportunity arose to further my career by moving to the University of Zurich.

HOW DOES YOUR TYPICAL WORK WEEK LOOK LIKE?

Professor Wuethrich, Director of the Nephrology division of the University Hospital Zurich, offers me outstanding infrastructure and protected time for research. Overall, I work in the laboratory on Mondays and Tuesdays, spending the remainder of the week at the hospital.

IS IT AN ADVANTAGE OR A DISADVANTAGE FOR A RESEARCHER TO BE PART OF THE DAILY ROUTINE OF A CLINIC?

Probably both. I myself see it as an advantage, since I also want to improve my clinical skills. In addition, if you see patients on a regular basis it's much easier to base one's research on the questions that are relevant for patient care. At the same time though, working at the hospital reduces valuable research time. Since research is very competitive, the amount of time spent on science is pivotal.

WHAT ARE YOUR RESEARCH INTERESTS?

Only few patients that need a kidney transplant will receive an organ from a donor. Kidney injury in clinical settings such as open-heart surgery, severe blood loss, or even a kidney transplant itself may result in the need for a transplant. Therapies aimed at reducing this type of injury are associated with significantly improved short- and long-term organ survival.

Our group is interested in the mechanisms of kidney injury and how these events are mediated by non-coding RNAs. Only 1–2 per cent of the human genome is transcribed into messenger RNA. The remaining majority of RNA transcripts are so called non-coding RNAs (ncRNAs), which are separated into long ncRNAs (lncRNAs; ≥200 nucleotides) and small ncRNAs (≤200 nucleotides). We want to identify novel non-coding RNAs in different mouse models of kidney injury. We aim to modulate pathological non-coding RNA expression by RNA therapeutics, which enables specific targeting of non-coding RNAs and thus modulation of pathological signalling pathways in vivo. In addition, non-coding RNAs are released into the blood and urine in patients. Thus, circulating non-coding RNAs may serve as a non-invasive tool with which to detect and monitor disease activity.

HOW WOULD YOU EXPLAIN YOUR JUNIOR GRANT RESEARCH PROJECT TO A POTENTIAL PATIENT?

In my Junior Grant, we are investigating a certain non-coding RNA that does not lead to the formation of a protein. Normally, this RNA is highly present during the development of kidneys, but almost absent during adult life. We discovered that this particular RNA is reactivated in the context of acute kidney injury in mice. It is known that several embryonic signalling pathways, which are highly important during the development of the kidneys, are reactivated during kidney injury. They most likely repair the organ. We aim to elucidate the distinct role of this non-coding RNA and also to modulate its expression in vivo, so that it may aid in the repair of ischemic kidneys.

WHAT KIND OF SUPPORT DO YOU RECEIVE AND HOW IMPORTANT IS THE JUNIOR GRANT FROM THE NCCR KIDNEY.CH FOR YOUR WORK?

We have three grants running in the laboratory. I received the Else Kröner-Fresenius Memorial scholarship in Germany in 2015, which I was able to transfer to Zurich. Malte Kölling, a postdoctoral fellow in the laboratory, was recently awarded the Nephro-physician Scientist grant by the NCCR Kidney.CH. The recent Junior Grant from the NCCR was fundamentally important to me in initiating my research group at the University of Zurich. I am very grateful that I received this grant after just having moved here. It enabled me to hire a PhD student, almost immediately after my start in Zurich. And it allows me to interconnect and collaborate with other scientists interested in kidney research all over Switzerland.

melanoma and leukaemia, as well as breast, prostate, ovarian, colon and pancreatic cancer. Through the expanded use of genetic testing (next-generation sequencing (NGS)), precision medicine is also changing the landscape of rare, inherited disorders. The ability to search for variants across all genes, either using whole exome sequencing or whole genome sequencing, has already defined new genetic disorders and improved the classification of disease, yielding insights into disease manifestations and mechanisms and guiding treatment. For instance, the treatment of monogenic kidney diseases such as Gitelman syndrome, Gordon syndrome (pseudohypoaldosteronism type II) or Liddle syndrome is now directly based on the mechanisms involved. It should be pointed out, however, that there is a need to develop specific skills to analyse the vast amount of sequence data involved, to explain the genetic results (expected or not) to the patient and to his or her physician, and to use the information gathered in a clinically sound way.

PRECISION MEDICINE FOR COMMON DISORDERS

Applying the principles of precision medicine to common disorders such as hypertension, diabetes or chronic kidney disease (CKD) is much more difficult than applying it to rare diseases. This difficulty reflects the fact that the genetic architecture of most common diseases is complex, based on a large number of relatively frequent genetic variations, each having a small effect size. These genetic factors are balanced with a usually strong environmental component (diet, physical activity, pathogens, etc.).

Since 2007, genome-wide association studies (GWAS) have established themselves as the most powerful tool for detecting new genetic variants associated with common diseases. The GWAS concept is simple and unbiased: it consists of running an association test millions of times over the entire genome, using models that are fitted for the same outcome on one single nucleotide polymorphism (SNP) at a time. SNPs represent common genetic variations between human subjects and are measured using commercial genotyping arrays. Following the direct genotyping, the number of SNPs can be expanded via genetic imputation based on reference genomes, such as those of the 1000 Genomes Consortium. The hits along the genome are presented as a Manhattan plot, with P values of ≤10−8 normally considered to an indication of genome-wide significance. Using this technique, thousands of loci have been associated with several biomarkers and complex disorders.

GENETIC ARCHITECTURE OF KIDNEY DISEASE

More than 20 GWAS of CKD-defining traits have been published, with more than 60 loci associated with eGFR (the most studied outcome) in various ethnic groups. Although the genetic variants uncovered through genome-wide studies are typically associated with a relatively small increase in disease risk, these studies have provided major breakthroughs in our knowledge of the genetic architecture of kidney diseases.

The *UMOD* locus, which is being investigated within the NCCR Kidney.CH, stands out among the loci associated with CKD, as it shows the largest odds ratio (OR) for CKD compared to all other loci in nearly all ethnicities. The relevance of *UMOD* for CKD is immediate, because the encoded protein, uromodulin (Tamm–Horsfall protein) is exclusively produced by the kidney tubule and has specific biochemical properties that sustain its role in the kidney and urine. Translational studies have highlighted the functional relevance of the variants, which are associated with renal damage and salt-sensitive hypertension. Based on these findings, uromodulin is increasingly considered as a biomarker for the risk of kidney disease in various populations. Furthermore, a clinical trial that recently secured funding from the British Heart Foundation will test the response of hypertensive patients to loop diuretics as a function of the *UMOD* genotype.

In summary, researchers are gearing up to develop precision medicine approaches for patients with rare and common kidney disorders. The use of genomics, and its eventual integration with multi-omics profiles, offers opportunities for medical breakthroughs and should facilitate disease stratification, early diagnosis, and improved therapeutics.

PRECISION MEDICINE IN KIDNEY.CH

Precision medicine as applied to kidney disease is actively pursued within the NCCR Kidney.CH network, including GWAS and activities in rare kidney disorders. Results from GWAS for kidney parameters, with nutrigenomics and metabolomics aspects, were obtained through collaborations between groups in Lausanne, Zurich, Geneva and Bern, and NCCR partners are involved in large meta-GWAS. In collaboration with clinical centres, NCCR groups are also using multi-omics analyses to investigate rare kidney diseases, and more common conditions such as kidney stones and CKD.

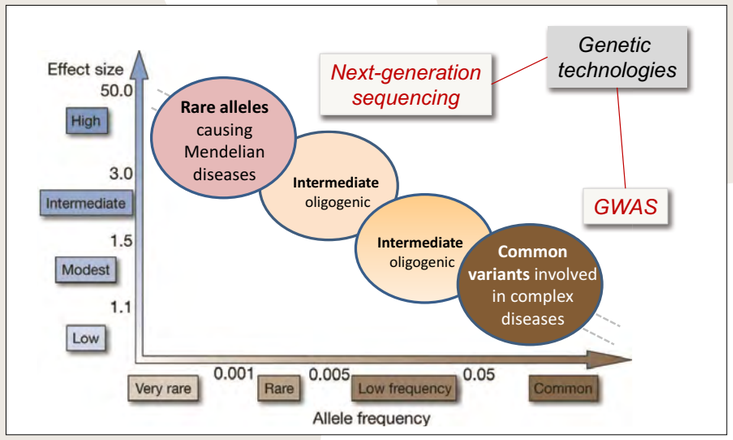

Figure. Genomics and precision medicine in kidney disease. New technologies such as next generation sequencing (NGS) and genome-wide association studies (GWAS) allow to gather genomics information which, alone or integrated with other –omics profiles, can be used to deliver precision medicine for patients with rare or more frequent kidney disorders. Modified from Manolio et al. *Nature* 461, 2009

Olivier Devuyst is a nephrologist and professor at the Institute of Physiology of the University of Zurich (UZH) and member of the steering committee of the NCCR Kidney.CH. He is also invited Professor at the Université catholique de Louvain (UCL) Medical School in Brussels, Belgium, and has a joint appointment in the Division of Nephrology of the InselSpital Bern and the Saint-Luc Academic Hospital in Brussels.