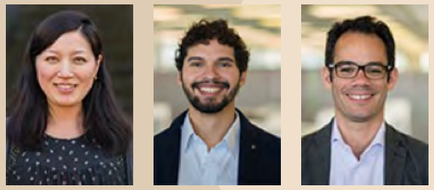
CAS/DAS IN TRANSLATIONAL NEPHROLOGY: MODULES 3 & 4

This programme provides relevant insights into 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 18, 2018, module 3—'Calcium and phosphate homeostasis'—had its return session at the University of Bern. More than 20 young scientists from all over Switzerland presented their work in front of a panel of experts from the NCCR Kidney.CH. As a final task, the students worked on a clinical case and completed the associated assignments both individually and in small groups. All participants passed the exams with good to excellent results, with grades ranging from 4.8 to 5.4. The day after, on October 19, 2017, the fourth module—'Oxygen homeostasis'—started with a kick-off meeting. The participants listened to the presentations of Prof. Roland Wenger (University of Zurich), who talked about 'Oxygen regulation of Epo production', and Prof. Vartan Kurtcuoglu (University of Zurich), who focused on the 'Physics of gases and oxygen distribution in the kidney'. The return session with the final assessment of module 4 will take place on April 4, 2019.
Info & registration for the CAS/DAS in Translational Nephrology: http://www.nephrologie.unibe.ch

FAREWELL SYMPOSIUM FOR FRANÇOIS VERREY: THE KIDNEY & TRANSPORT

In honour of François Verrey, who will retire in July 2019, the NCCR Kidney.CH is organizing a farewell symposium. The topic will be epithelial transport and the kidney. Please do already save the date: June 21, 2019; University Hospital Zurich, large lecture hall OST, HOER B 10.

JUNIOR GRANTS 2018



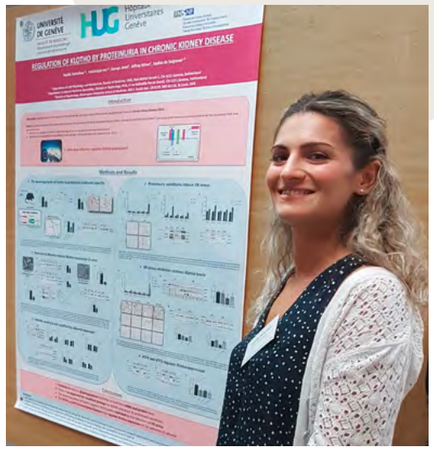
From left to right: Natsuko Tokonami, Pedro Imenez Silva and David Penton Ribas.

The NCCR Kidney.CH this year awarded three Junior Grants. Each is for the sum of CHF 60,000 per year for a maximum of three years and is intended to help increase the awardees' professional independence and to promote their projects.
The new Junior principle investigators (PIs) are Natsuko Tokonami, Pedro Imenez Silva and David Penton Ribas. Natsuko is a postdoc at the Institute of Physiology in the lab of Olivier Devuyst at the University of Zurich (UZH). Her primary research focus is on the paracrine regulation of renal tubular water transport. Pedro is also member of the Institute of Physiology (UZH) and comes from the Wagner lab. He is exploring the role of proton-sensing receptors in renal inflammation and fibrosis. David is a postdoc in the lab of Johannes Loffing from the Institute of Anatomy (UZH). He is interested in the role of protein phosphatases in K^+-stimulated adrenal aldosterone production.

NCCR KIDNEY.CH & TRENAL SUMMER SCHOOL 2018: FROM RENAL PHYSIOLOGY TO KIDNEY DISEASE

Together with the German/British research network TRENAL, the NCCR Kidney.CH organised its first international summer school September 9–12, 2018.
The main organisers were Prof. Carsten Wagner from the University of Zurich and Prof. Felix Knauf from the Charité Berlin.

This event, hosted at the Irchel campus of the University of Zurich, brought over 20 European experts in kidney research and diseases together with more than 40 young scientists. Numerous lectures, a poster session and case discussions about kidney functions and their relevance for kidney disease were held and excited the participants.
Vasiliki Delitsikou won the poster award, convincing the jury with her Poster "Regulation of Klotho by proteinuria in Chronic Kidney Disease".



EVENTS

9TH NCCR KIDNEY.CH RETREAT 2019
January 31 – Febuary 1, 2019
Murten, Switzerland

LS2 ANNUAL MEETING 2019
February 14–15, 2019
UZH, Zurich, Switzerland

CAS/DAS IN TRANSLATIONAL NEPHROLOGY: KICK-OFF MEETING MODULE 5 "NUTRIENT & METABOLISM"
April 5, 2019
University of Bern, Switzerland

56TH ERA-EDTA CONGRESS
June 13–16, 2019
Budapest, Hungary

FAREWELL SYMPOSIUM FRANÇOIS VERREY: KIDNEY & TRANSPORT
June 21, 2019
Zürich (USZ), Switzerland

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KIDNEY
CONTROL OF HOMEOSTASIS

NEWSLETTER ::: NO. 17 ::: DECEMBER 2018

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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IS PHOSPHATE TOXIC?

EDITORIAL

Johannes Loffing is professor at the Institute of Anatomy of the University of Zurich and new Director of the NCCR Kidney.CH

Tempora mutantur …

Since its launch in 2010, the NCCR Kidney.CH has significantly contributed to the high visibility of Swiss kidney research. Aside from cutting-edge research and the creation of sustainable structures including a Swiss Kidney Stone Cohort, the NCCR has made it possible to train dozens of new kidney researchers and to attract and support excellent young scientists.

Now, the NCCR is entering its third 4-year phase. This is accompanied by several important changes. New colleagues (e.g. Felix Beuschlein and Soeren Lienkamp) are joining our research program, which is now focussing on three main work packages, dealing with the role of the kidney in oxygen homeostasis, with ion handling, and with the control of mineralisation. In order to strengthen translational medicine particular attention is being paid to the disease mechanism. With the upcoming retirement of François Verrey in 2019, we also have a change in the leadership of the NCCR. Together with our NCCR colleagues, we would like to take this opportunity to thank François for his excellent leadership over the last eight years, and say that we are very much looking forward to continuing the NCCR's success story and to developing it further in the coming years.

Johannes Loffing

IS PHOSPHATE TOXIC?

Phosphate is essential for many processes inside our bodies and can be absorbed very well by our system. However, too much of it appears to cause organ calcification and heart disease. Scientists want to find out when and why it becomes harmful for us.

Phosphate is an essential mineral for life on earth. Humans require it for a plethora of processes inside the body. Phosphate helps build membranes and synthetize DNA and RNA molecules. It is used for the generation of energy-rich molecules like ATP or GTP, for the transmission of signals by phosphorylation and dephosphorylation and for stabilizing bones. During evolution our food always contained small amounts of phosphate. Thus, our body has evolved to absorb phosphate very efficiently from food and to hold on to it by reabsorbing as much as needed from urine.

Phosphate, however, can be dangerous, particularly when reacting with calcium. It can form precipitates and cause aberrant organ calcification or arteriosclerosis. Again, our body has developed powerful mechanisms to prevent this. Parathyroid hormone, calcitriol and FGF23/a-klotho cooperate to regulate minerals and to prevent phosphate from exceeding its solubility product. Plasma proteins like Fetuin-a reduce the risk of forming precipitates.

This balance in our body is being increasingly challenged. Over recent decades, food composition and preferences in many regions of the world, particularly in industrialized countries, have dramatically changed. Large percentages of the population consume soft drinks and large quantities of processed food. These food items have in common a substantial amount of inorganic phosphate, mostly added during the production process.

After all, our body is very efficient at absorbing phosphate, combining high affinity phosphate transporters (mostly active during times of low phosphate availability) and a high-capacity paracellular pathway that absorbs abundant phosphate.

In theory, this excessive phosphate absorption from our diet should not pose a problem if the kidneys are excreting all unwanted phosphate. However, higher phosphate consumption elevates blood phosphate levels.

In nephrology it has been known for decades that in patients with CKD consuming a phosphate-rich diet increases phosphate plasma levels causing cardiovascular morbidity and increasing mortality due to vascular calcification and left ventricular hypertrophy. Importantly, this association with phosphate consumption has now also been detected in the general population. However, it has remained elusive how phosphate can trigger this dramatic increase in cardiovascular morbidity not only in patients with chronic kidney disease (CKD) but also in people with normal kidney function. Only recently have several lines of evidence emerged that suggest distinct pathomechanisms.

In patients with CKD, associations between Fibroblast Growth Factor 23 (FGF23), a phosphaturic hormone highly elevated in these patients, and cardiovascular disease (particularly left ventricular hypertrophy, LVH) have suggested that FGF23 may be a missing link. Animal experiments have also shown the effects of FGF23 on the heart. More recently, this concept has been challenged by the Wagner group at the University of Zurich—as well as by others, which have shown that the isolated elevation of FGF23 without kidney disease is not sufficient to trigger LVH.

Alpha-klotho, a co-receptor for FGF23, may be another link between phosphate, CKD and LVH. Both, high phosphate intake as well as CKD cause a decrease in a-klotho levels. In the heart, a-klotho deficiency may promote LVH whereas reconstitution of a-klotho levels protects the heart in experimental models of CKD and high phosphate intake.

Direct effects of phosphate on the cardiovascular system may also contribute to the elevated risk associated with high phosphate intake. Animal experiments have demonstrated that phosphate can increase sympathetic nerve tone. Phosphate also triggers vascular calcification through a variety of mechanisms involving the local production of aldosterone in vessels.

Research within the NCCR Kidney.CH points to a blood-pressure-raising effect of phosphate in healthy persons. Reto Krapf has conducted studies with healthy volunteers, who for six weeks were exposed to normal or high-phosphate diets, the latter demonstrating an increase in systolic blood pressure paralleled by evidence of a higher sympathetic tonus. Blood pressure normalized upon ending the high phosphate diet.

Similarly, experiments in mice and healthy humans that consumed diets with high or low phosphate content over a range from a few hours to five days showed increased systolic blood pressure in the high phosphate groups. Simultaneously, the activity of the renal NaCl cotransporter NCC is increased, an effect in part mediated by the sympathetic nerve system and FGF23.

Even though we still do not understand if the associations between high phosphate intake and increased cardiovascular morbidity and mortality in the general population are causative, the picture is becoming clearer. Experimental data from humans and from rodent models provide evidence for direct detrimental effects of high phosphate intake on cardiovascular risks. Many open questions remain to be addressed, including examining whether the association between dietary phosphate and cardiovascular risk includes also other ingredients typically found in phosphate-rich diets, such as high salt or high fructose, both well known risk factors for cardiovascular disease. Also, crosstalk between kidney and bone may further contribute to the overall effects of phosphate.

As clear as it is that we cannot live without phosphate, it also emerges that too much may bear considerable risks for our health.

Carsten Wagner is a professor of Physiology. His research interest is in renal physiology and particularly in aspects of acid-base balance and phosphate homeostasis.

PORTRAIT

A PASSION FOR COMPLEX PROBLEMS

In January 2019, Soeren Lienkamp will join the Institute of Anatomy at the University of Zurich (UZH). He has been appointed Assistant Professor of Molecular Medicine in Anatomy. Just this summer, the 40-year-old German was awarded an ERC Starting Grant from the European Research Council. Prior to his upcoming move to Switzerland, Lienkamp worked in the Renal Division at the University Hospital Freiburg. Since 2014, he has also headed an independent Emmy Noether research group funded by the German Research Foundation (Deutsche Forschungsgemeinschaft) and he is a member of the "NEOCYST" research network.

WHY DID YOU SPECIALIZE IN NEPHROLOGY AND DID NOT CHOOSE A DIFFERENT MEDICAL AREA?

I like people and I love to tackle complex problems. Nephrology encompasses exactly those two aspects. Kidneys control so many vital processes of the human body and on top of that patients with a renal disease are often very challenging to take care of. So, if you treat patients with renal diseases you get to know them very well, in all their complexity. Joining the Department of Nephrology in Freiburg gave me a broad and sound training in internal medicine, since it takes in patients with a wide spectrum of medical conditions, not just kidney-related problems.

WHAT ARE YOU CURRENTLY FOCUSSING ON WITH YOUR RESEARCH?

I am really interested in how the kidney forms during embryonic development. We still understand too little about how the forces that shape this intricate organ are controlled and how they go astray in genetic kidney disease. Also, we study the similarities between kidney formation in tadpoles and mammals to understand the workings of core molecular players that drive renal development.

YOU HAVE RECEIVED ONE OF THE PRESTIGIOUS ERC GRANTS; WHAT OPPORTUNITIES DOES THIS FUNDING OFFER YOU?

We recently found that only four genes sufficed to turn skin cells (fibroblasts) into a kidney-like state. This so-called direct reprogramming can teach us a lot about how renal cell identity is controlled and help us to understand kidney disease better. The 1.5 million euros from the ERC Starting Grant allow us to bring this technology closer to a tool that could benefit patients in the future. For example, we plan to simulate kidney disease in the Petri dish or test drugs on patient-derived cells.

WHY DID YOU CHOOSE TO LEAVE FREIBURG AND FURTHER PURSUE YOUR CAREER IN ZURICH?

As much as I enjoyed patient care, I felt the strong urge to focus more on research. The excellent environment in Zurich plus the unique Kidney.CH consortium offer exciting new opportunities. I admit that I dread moving my lab to a new location a little; but fortunately three members of my team will join me in Zurich and the support I am already receiving to set things up is enormous.

WHAT KIND OF OPPORTUNITIES AND SUPPORT DOES THE NCCR KIDNEY.CH OFFER TO A RESEARCHER SUCH AS YOURSELF? WHAT DO YOU APPRECIATE IN PARTICULAR?

It's mostly the exchange of ideas and intellectual input from this group of superb kidney research teams. We have already started several collaboration projects, even though I'm not yet in Zurich. What more could I ask for? So, I can't wait to start with all the new experiments I want to pursue.

WHAT ARE YOUR PROFESSIONAL GOALS FOR THE NEXT FEW YEARS?

I'm mostly focused on what I would like to do. Most of all I hope to build a great team, and to make exciting findings. I find the transition of molecular biology into quantitative science extremely fascinating. And we still don't know what a third of the human genes do! There really is so much more to explore…

WHAT DO YOU DO TO BALANCE RESEARCH AND TEACHING?

Actually, I enjoy teaching and don't consider it a burden or balancing act. I look back at the days of my medical studies with fond memories and hope to be as good a teacher as those who taught me.

IS THERE ANY TIME LEFT FOR FAMILY AND HOBBIES?

Well, a lot of exciting things have happened also on the personal side during the last couple of months. Our first child was just born four months ago, and I enjoy every minute I get to spend with my family. It's so much fun to see him grow a little from day to day. Also, we are all very excited about getting to know Switzerland and Zurich. Look for me at the zoo or near the lake when I'm not in the lab.

Soeren Lienkamp joind the NCCR Kidney.CH. He has been appointed Assistant Professor of Molecular Medicine in Anatomy at the University of Zurich.