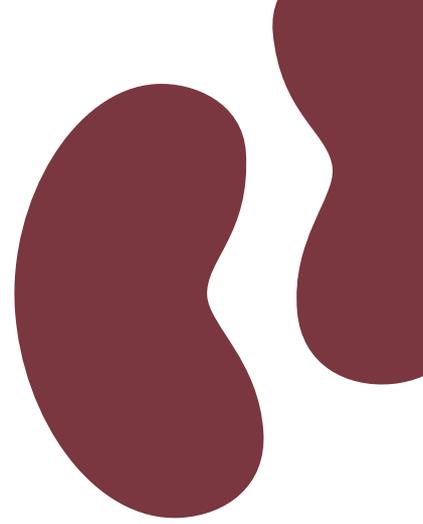


KIDNEY

CONTROL OF HOMEOSTASIS



NEWSLETTER ■ NO. 20 ■ JUNE 2020

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 Bern, Fribourg, Geneva, Lausanne, and Zurich, and corresponding university hospitals.

ALKALINE THERAPY – TRUTH OR MYTH?



Alkaline therapy has been touted online as a cure-all, and recent studies suggest that it can slow the progression of chronic kidney disease. But what do we really know about alkaline therapy, and how does it relate to renal disease?

One of the well-known complications of chronic kidney disease (CKD) is metabolic acidosis, which is defined by low blood pH (<7.35) and low blood bicarbonate levels (<24 mmol/l). This condition is associated with a variety of complications such as uremic bone disease, protein-energy wasting, chronic inflammation, insulin resistance, and importantly with increased mortality in both dialysis patients and patients with non-dialysis-dependent CKD. In that light,

it is reasonable to expect that correcting metabolic acidosis would be helpful for patients with kidney disease – or wouldn't it? Recent research has been investigating exactly this question among human patients and animal models.

The correction of acidosis by an alkalinizing agent has different names, such as alkaline therapy (also called alkali therapy), bicarbonate or citrate supplementation, and others depending on which agents are used. There are pharmacological and dietary interventions that work to correct low blood pH and bicarbonate. Recent studies have shown that alkaline therapy is associated with a significantly lower risk of CKD progression and development of end-stage renal disease (ESRD).



Juliet Manning

Hello! For those of you I haven't met yet, my name is Juliet, I'm the new scientific officer at the NCCR Kidney.CH.

I was lucky enough to join the NCCR Kidney.CH in February 2020, just in time to meet some of our team members at the University of Zurich before Covid-19 hit and changed the world as we know it. I am honoured to be part of this incredible national network of scientists and clinicians, whose resilience and tenacity over the past few months has been nothing short of amazing. The pandemic has presented a challenge for many of our colleagues, as labs and research groups have had to react quickly to comply with social distancing measures. Clinicians are working overtime, while other research activities have been suspended or reduced temporarily. But these strange times have also highlighted to me the ingenuity of NCCR members as they invent new approaches and workarounds. The vision of the network, to advance knowledge and understanding of renal mechanisms in health and disease, clearly remains unfazed. As it rounds off its 10th year, the NCCR Kidney.CH already has so much to be proud of. I can't wait to see where the next years take us.

Juliet Manning
Scientific Officer,
NCCR Kidney.CH

ALKALINE WATER VS ALKALINE SUPPLEMENTATION THERAPY

The Internet is full of blogs and videos promoting do-it-yourself alkaline diets and home remedies. One of the most popular of these is "alkaline water"—water with a high pH—which proponents claim can improve overall health by acting as an alkalinizing and antioxidant agent. Among the typical promised benefits are anti-aging effects, protection against chronic diseases, and cancer prevention.

Alkaline water can be purchased online or produced at home, but without any regulation, consumers usually have no way of knowing its exact pH level or mineral content. Depending on its composition, alkaline water could be anything from glorified tap water to an alkalotic challenge which could lead to undesired side effects.

On top of this lack of quality control, there is a major difference between alkaline water and the alkaline therapies conducted in healthcare institutes. Alkaline therapy is only administered to correct a demonstrated acid-base imbalance, and not to alkalinize a patient's blood above physiological range or to load the organism with extra alkali. For non-renal conditions and diseases, there's little evidence for benefits from any alkalinizing strategy. Controlled clinical trials are needed in order to understand the impact of this therapy and its potential benefits.

METABOLIC ACIDOSIS IN CHRONIC KIDNEY DISEASE

Systemic metabolic acidosis is a common feature of advanced chronic kidney disease. However, there is evidence that some tissues, including kidney tissue, accumulate acid from the early stages of CKD onward. According to published studies, acidification leads to the synthesis of hormones that accelerate kidney function deterioration, such as aldosterone, endothelin, and angiotensin-II. It has also been proposed that ammonium accumulation in the kidney interstitium could drive inflammation via a component of the immune system, called the "alternative complement pathway". Interestingly, inflammation is an additional source of local acidification. This suggests that alkaline therapy not only has the capacity to correct systemic metabolic acidosis in CKD but could also adjust tissue pH locally. On the other hand, local acidification has not been investigated across kidney diseases of different origins (e.g. diabetic nephropathy, crystallopathies, polycystic kidney diseases, etc.), and the validity of currently proposed alkaline therapy mechanisms has not been demonstrated in these cases. An ongoing NCCR Kidney.CH junior grant project, led by Pedro H. Imenez Silva, aims to address this topic and to identify potential new mechanisms linking acid-base status to the progression of renal diseases. Among other strategies, we intend to characterize the pathology of multiple models of kidney disease under bicarbonate supplementation, from transcriptomic data to renal function. As a proof of concept, we will compare data from animal models with data from patients receiving alkaline therapy, such as kidney transplant recipients.

METABOLIC ACIDOSIS AFTER KIDNEY TRANSPLANTATION

Metabolic acidosis is very common among kidney transplant recipients. A few recent retrospective studies, including our own data, have demonstrated that metabolic acidosis is also negatively associated with graft function, as has been shown for CKD patients. Given the high demand for organs, any therapy that could help to preserve long-term graft function would be momentous. So far, however, no interventional studies have investigated the impact of alkaline therapy on graft function. In 2016, we started an investigator-initiated clinical trial to address this topic (preserve-transplant-study.ch), and to test whether alkaline treatment preserves renal function and curbs the progression of the kidney disease among stable kidney transplant patients. This study is funded by Swiss National Science Foundation (SNSF) and will be finished in 2021, with results expected in 2022.

In summary, through combined efforts using studies with animal models and chronic kidney disease patients, we expect to better understand the potential of alkaline therapies in humans. Given that altering pH levels can have a wide range of effects on the body, alkaline therapy could potentially lead into a labyrinth of positive and negative impacts on renal and extrarenal health. The complexity of this reality clashes with the simple solutions promised by proponents of home remedies like alkaline water. Now that the debate on alkalizing therapies has crossed academic and clinical barriers, we hope to contribute concrete evidence to this lively discussion of public health.



Nilufar Mohebbi is a nephrologist with a longstanding research and clinical interest in renal acid-base disorders and kidney stone disease. Initially, she joined the NCCR Kidney.CH as the Principal Investigator of the SKSC. Currently, together with Prof. R. P. Wüthrich (Head of the Division of Nephrology of the University Hospital), she is conducting the Preserve-Transplant Study, which has been funded as an Investigator Initiated Clinical Trial by the SNSF since 2016.



Pedro Henrique Imenez Silva is a biologist and renal physiologist, who dedicates his time to researching and teaching at the University of Zurich. He became a junior principal investigator at the NCCR Kidney.CH in 2018, and since 2020 his work has been co-funded by the Hartman Müller Foundation. Passionate about research and teaching, his favorite research topics are acid-base physiology and chronic kidney disease, but he also enjoys reading and discussing nature, politics, sports, and science in general.

CARVING A NICHE IN KIDNEY REPAIR



Anna Rinaldi recently received a Junior Grant from the NCCR Kidney.CH for her research in kidney repair mechanisms.

Anna Rinaldi is one of the newest Junior Grant recipients at the NCCR Kidney.CH, having recently joined the lab of Pietro Cippà, an affiliate of the NCCR at the University of Lugano. She earned her PhD at the University of Zurich and conducted research there before moving to the Institute of Oncology in southern Switzerland, where she engineered cell culture and in vivo models to determine drug responses in individual cancer patients. We asked Anna Rinaldi about her current research and the plans for her Junior Grant project.

CONGRATULATIONS ON RECEIVING A JUNIOR GRANT! WHAT LED YOU TO APPLY?

The NCCR Junior Grant was a timely and ideal opportunity to develop our project and support my professional growth. I joined the Cippà Lab in May 2019 with the goal of investigating various aspects of kidney repair using cutting-edge technologies. In the months that followed, we designed an interesting project that happened to fit the NCCR Junior Grant requirements, and with encouragement from Dr. Pietro Cippà, I decided to apply.

YOU HAVE A BACKGROUND IN CANCER RESEARCH—WHAT SPARKED YOUR INTEREST IN THE KIDNEY?

A fortunate stroke of serendipity! I was finishing my postdoc in the Theurillat Lab at the Institute of Oncology Research in Bellinzona when I learned of an open position in the Cippà Lab. After my first interview there, I became fascinated by the biological processes regulating kidney injury and repair – and importantly, their clinical relevance.

WHAT DOES YOUR CURRENT RESEARCH FOCUS ON?

In a nutshell, my research focuses on how the kidney repairs itself. In response to injury, the renal tissue activates an orchestrated process to replace damaged cells and restore functional structures. The repair process involves different cell types, including damaged cells and cell states unique to the injury response. These all interact closely inside a reparative compartment called the tubule repair niche. This process is critical for the early response to injury, but it can also affect renal pathophysiology in cases of chronic kidney disease. In my

research, I will use single-cell RNA sequencing in a mouse model of Acute Kidney Injury (AKI) to take a closer look at cellular composition and changes in renal cell identity after a kidney injury. I will also look into the role that senescent cells play in the tubule repair niche, and how they affect the outcome of an injury.

WHAT DO YOU FIND MOST INTERESTING ABOUT THIS TOPIC?

I'm excited about the opportunity to better understand the tubule repair niche and to investigate factors that could have clinical relevance. Understanding transcriptional changes in single-cell types during kidney repair might offer unique insights into disease pathogenesis and could even lead to new therapeutic strategies.

YOUR APPROACH IS VERY INNOVATIVE—CAN YOU TELL US MORE ABOUT YOUR TECHNIQUES?

The beauty of my approach is the use of single-cell technology to study the kidney repair process in a transgenic mouse model, which will enable me to both identify and exploit the function of certain cell types in clinically relevant settings. Single-cell RNA sequencing has already allowed gene expression to be studied in unprecedented detail by various groups, bringing our understanding of kidney biology to a new level. For example, it has been used to discover new cell types and characterize changes in cell states during development or under pathological conditions. However, major current challenges related to single cell RNA sequencing still need to be considered, such as technical aspects of tissue dissociation, elevated costs and lack of standard pipelines for data analysis and datasets integration. Validation

of potential therapeutic targets derived by this innovative approach is fundamental. Future studies will likely help identify novel disease mechanisms and therapeutic targets as well as diagnostic and prognostic biomarkers.

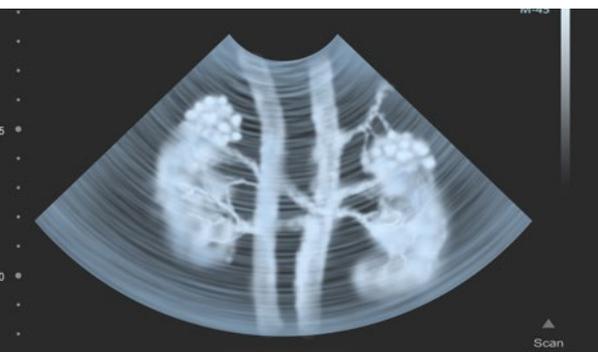
WHAT OUTCOME ARE YOU HOPING TO HAVE BY THE END OF THE GRANT PERIOD?

This project will provide extensive and detailed data on fundamental biological processes that affect how kidney diseases develop. The data generated by this project will also be available for other NCCR-affiliated groups to use, hopefully leading to further analysis from different perspectives. From a translational perspective, the characterization of the tubule repair niche will be instrumental to refine the selection of new compounds for targeted interventions to modulate the repair process and prevent irreversible renal damage after tubular injury. My work on senescent cells could also define a new line of research, focusing on discovering whether removal of senescent cells after AKI can improve clinical outcomes.

WHAT ARE YOU PLANNING TO DO AFTERWARDS?

The NCCR Junior grant will allow me to set up my first independent project and gain expertise and skills to progress my academic career in the field of nephrology and renal diseases. The University of Lugano is creating a new Biomedical Faculty in 2020 and an Institute of Biomedical Research in 2021, which will offer the ideal setting to continue my multidisciplinary research, combining academic science and clinical applications—something I find very important.

NCCR KIDNEY.CH MINISYMPOSIUM IN INTERLAKEN



Renal scan (Image: Shutterstock)

A mini symposium was held at the 2019 Swiss Society of Nephrology Annual meeting to showcase the work of the NCCR. Two NCCR PIs each gave a presentation on the theme of “Kidney imaging in the 21st century: Between science and art”. Prof. Vartan Kurtcuoglu (Institute of Physiology, Zurich) discussed how whole organ imaging with micro-CT scanning and novel contrast agents allows visualization of the entire kidney vasculature in 3-D, in unprecedented detail. Meanwhile, Prof. Andrew Hall (Institute of Anatomy, Zurich) explained how intravital microscopy of calcium signals enables single cell activity to be mapped to the structure of the kidney tubule. Both presenters emphasized the increasingly important role of computational analysis in extracting quantitative data from images. The symposium was very well attended and stimulated a lot of interest in the future of kidney imaging and the cutting-edge research of the NCCR.

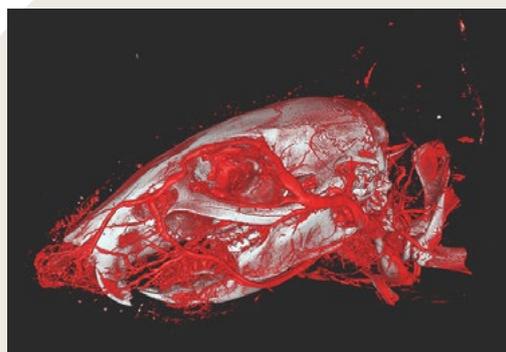
JUNIOR GRANT AWARDEES 2020



Stellor Nlandu Khodo, Anna Rinaldi and Ganesh Pathare.

Stellor Nlandu Khodo (University of Zurich), Anna Rinaldi (Ospedale Regionale di Lugano), and Ganesh Pathare (University of Zurich) have joined the NCCR Kidney.CH as the latest recipients of the popular Junior Grant. The NCCR will provide each of the three postdocs with CHF 120 000 for their research projects. The Junior Grant program aims to support these young scientists in launching successful careers by providing an opportunity for them to implement their own research projects, while simultaneously supervising the next generation of PhD students. The topics of the three newest Junior Grant projects are: “Epithelial TGF- and Cadherins in Proximal Tubule Response to Fibrosis” (Stellor Nlandu Khodo), “Characterization of the renal tubule repair niche at single-cell resolution” (Anna Rinaldi), and “Effect of Dehydration on Fibroblast Growth Factor-23 Release and Mineral Metabolism” (Ganesh Pathare).

NCCR MEMBER CO-DEVELOPS EXCITING NEW IMAGING TECHNOLOGY



3D imaging of the blood vessels of a mouse head using X-ray computer tomography and the newly developed contrast agent “XlinCA” (Image: Willy Kuo, UZH)

Researchers at the University of Zurich (UZH), the NCCR Kidney.CH and the Biomaterials Science Center of the University of Basel have developed a new X-ray contrast agent that allows for unprecedented precision in vascular imaging. NCCR member Vartan Kurtcuoglu and his colleagues Ngoc An Le, Willy Kuo, Bert Müller, and Bernhard Spingler were behind the breakthrough.

The contrast agent, dubbed “XlinCA”, is injected into blood vessels, revealing their three-dimensional structure. This is an important method for the diagnosis and treatment of cardiovascular and other diseases, as well as a useful research tool. Previously, contrast agents were added to plastic resins before being injected into the blood vessels of euthanized animals. However, it is very difficult to completely fill out the delicate capillaries in various organs with viscous resins. Water-soluble X-ray contrast agents offer an alternative, but these agents cannot solidify and thus leak through blood vessel walls into the surrounding tissue within minutes. Compared to these methods, the XlinCA contrast agent is easier to use and distributes into all blood vessels more reliably. This results in more accurate images and reduces the number of animals required in research experiments. It also allows multiple organs or even whole animals such as mice to be examined at the same time.

UZH ANATOMY & PHYSIOLOGY JUMPS TO 11TH PLACE WORLDWIDE

The Home Institution of the NCCR Kidney.CH, the University of Zurich, has risen steadily in the QS World University Rankings under the category “Anatomy and Physiology” since the category was introduced in 2017. The QS World University Rankings are calculated and published annually by Quacquarelli Symonds, and are the only international rankings to have received International Ranking Expert Group approval. Since 2017, the University of Zurich has jumped up through the 20th, 19th and 18th position, and now sits at #11 worldwide, and at #1 in continental Europe. Congratulations to both Institutes and to the University!

VIRTUAL SITE VISIT 2020

In a first for the NCCR, this year's site visit took place virtually. A panel of international experts joined us via video conferencing while the NCCR Kidney.CH researchers presented the progress of their work and answered questions.

The feedback from panellists during the visit was encouraging as the panellists noted the the quality of the research and the vision of the network. The panel is currently preparing its official comments.

EVENTS

10TH KIDNEY.CH RETREAT 2020
September 24–25, 2020
(Virtual event)

LS2 PHYSIOLOGY MEETING 2020
August 31-September 1, 2020
(Virtual event)

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