SWISS NATIONAL CENTRE OF COMPETENCE IN RESEARCH

KIDNEY
CONTROL OF HOMEOSTASIS

NEWSLETTER ⁘ NO. 12 ⁘ JUNE 2016

DOPING FOR THE SICK KIDNEY

While doping in sport can be harmful for athletes, drugs like Epo can help patients who suffer from chronic kidney disease.

Patients with chronic kidney disease may profit from novel drugs which are also being used illegally to dope athletes. Especially enzyme blockers that induce the production of the hormone Epo (erythropoietin) look promising.

Although doping in sport seems to enable extraordinary achievements, it has in the long run many negative consequences for everyone involved. Not only does it cause a lot of distrust towards every new record in endurance sports, but it holds tremendous health risks for the athletes. Especially endurance athletes – such as cyclists, marathon runners and cross-country skiers – dope with the hormone Epo (erythropoietin). Tests for Epo are only of limited reliability since athletes know all too well how to hide their criminal act. Furthermore, it is very difficult to distinguish injected Epo from the mainly kidney-derived endogenous Epo. The hormone is very essential for a sound body since it induces the formation of new red blood cells in the bone marrow. An increased red blood cell concentration in the blood enhances the athletes' oxygen supply to their tissues, mainly to their exquisitely trained muscles which can then perform even better.

ATHLETES ARE TAKING HIGH RISKS

But Epo is not the only performance booster used by athletes as an unusual occurrence proved. In April 2015 French olympic race walker Bertrand Moulinet admitted on his Facebook site that he had doped with a novel compound known as FG-4592 or "roxadustat".

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

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Murielle Bochud is an MD-PhD, full professor of epidemiology and public health at the Institute for Social and Preventive Medicine at Lausanne University Hospital (CHUV). She is a collaborative member of the NCCR Kidney.CH and is responsible for the genome-wide association studies platform.

Understanding renal dysfunction

As a public health specialist, I want to better understand the mechanisms involved in the early stages of renal dysfunction to be able to apply preventive measures to slow down age-related decline in renal function or to decelerate the progression of chronic kidney disease.

The NCCR Kidney.CH hosts a unique interdisciplinary network of researchers interested in how the kidney works and how disturbances may lead to human diseases. Their efforts accelerate translation by bridging genetic epidemiology and clinical research with fundamental research. Genome-wide association studies (GWAS) in population-based cohorts allow generating novel hypotheses to be further explored to get better insight into kidney physiology and pathophysiology.

The NCCR provides an ideal network to further decipher the functional mechanisms underlying the observed genetic associations and to lead to clinically useful findings. And I enjoy having fruitful exchanges with scientists spanning major domains of kidney physiology.

Compared to doping with Epo, the compound is much cheaper and can be applied orally. No need for an expensive recombinant hormone drug, no injections, and maybe the testing lab of the World Anti-Doping Agency (WADA) may not know about it either... The fact that there are tremendous risks with non-approved medicine is largely ignored in this milieu.

So, what does this have to do with Epo? Compounds such as roxadustat induce the endogenous Epo production mainly by the kidney and to some extent also by the liver. According to the motto "what-is-not-on-the-list-is-allowed", Bertrand hence circumvented the illegal use of recombinant Epo. And there are many more of these compounds on the chemistry market!

DOPING AGENTS ONLINE FOR SALE

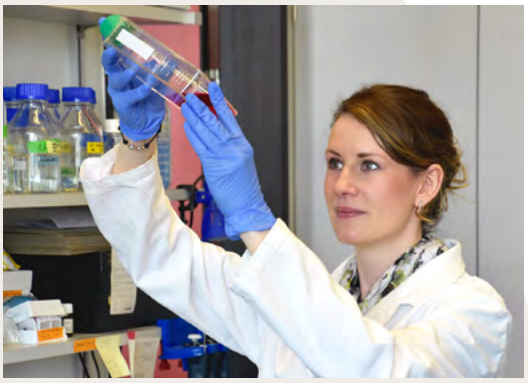
In the meantime, several cyclists were found guilty of doping with similar agents, of which up to seven different derivatives can currently be purchased online via the internet; numbers rising. All of these drugs mimic α-ketoglutarate, a very common metabolite of our body. Some of the α-ketoglutarate molecules are used by a class of enzymes called "PHDs" (prolyl-4-hydroxylase domain proteins) in a complicated reaction together with oxygen, iron and some vitamin C to modify and inhibit the regulators of Epo production, called "HIFs" (hypoxia-inducible factors). When one of these factors is missing, e.g. in a low-oxygen environment (hypoxia), HIFs cannot be modified anymore and induce Epo production. Roxadustat and other PHD inhibitors (PHDis) block the PHDs' interaction with α-ketoglutarate, thereby simulating hypoxia and inducing Epo.

Apparently, PHDis induce Epo quite specifically if applied at the correct concentration. This was unexpected because all cells of our body contain PHDs and HIFs and hence should react to these compounds by HIF activation. This may be explained by the kidneys' outstanding sensitivity to even the slightest changes in blood oxygen concentration, at least in those areas where the renal Epo-producing (REP) cells are located. However, it is certainly too early to give green lights for the prescription of PHDis as specific Epo-inducing drugs!

NCCR KIDNEY.CH WORK PACKAGE 'OXYGEN'

Intriguingly, patients with chronic kidney disease (CKD), who produce insufficient Epo, showed increased circulating Epo after swallowing PHDis. Although some of this Epo is derived from the liver, the majority still comes from the kidney. While it has generally been assumed that in CKD patients the REP cells convert into fibrotic cells incapable of EPO production, these data show that PHDis either "heal" these converted cells and/or there are enough normal REP cells left but in an over-oxygenated environment that is "reversed" by the PHDis. Since nobody could culture REP cells so far, this is still an open question and one of the research goals of the NCCR Kidney.CH work package "Oxygen".

Epo for the treatment of CKD patients and its use by some athletes for doping may seem to be of minor relevance. But this is far from the truth! Despite the fact that the original drug went off-patent, Epo is still one of the most lucrative recombinant drugs in the world, with annual sales rates of far over 10 billion dollars. No wonder that basically all big pharmaceutical companies seem to run PHDis programs.



Karen Nolan focuses on investigating the regulation of the hypoxia responsive renal erythropoietin producing cells in both health and disease.

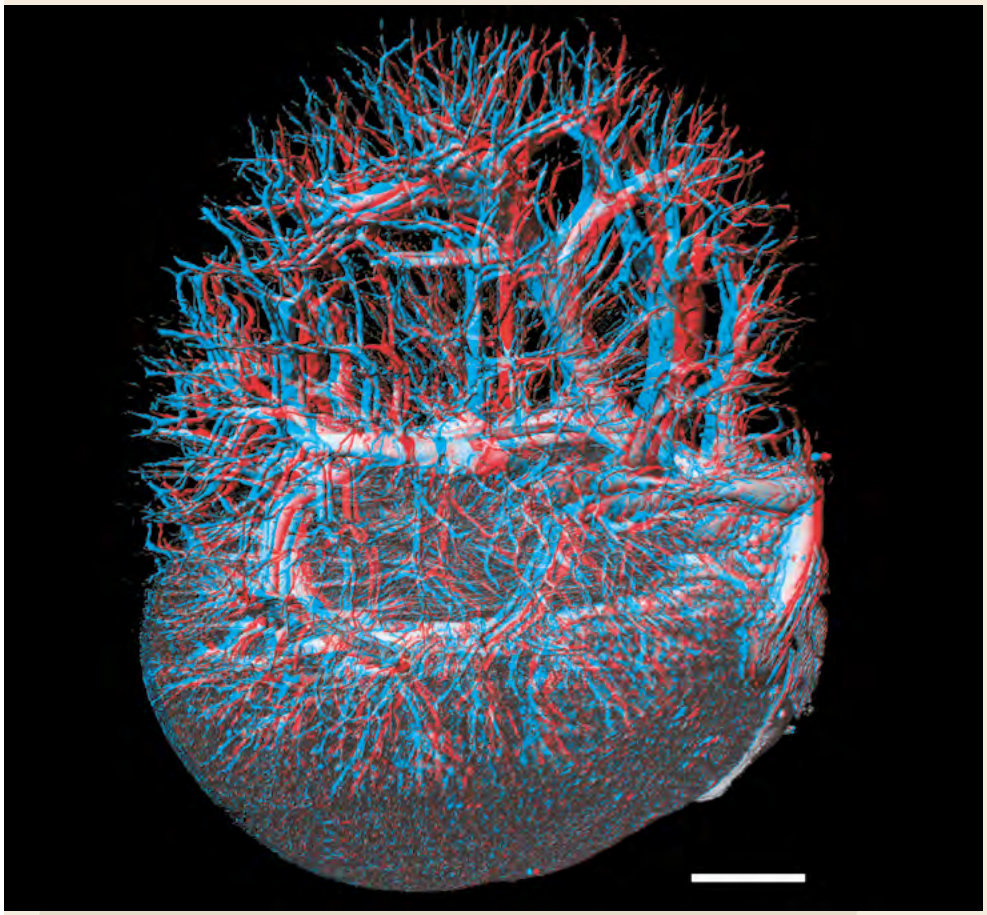
DETOURS TO THE MEDICAL TARGET

The most advanced of these compounds is roxadustat with several thousands of CKD patients in clinical phase III trials. Ironically, Fibrogen, the company producing roxadustat, originally developed these compounds to treat fibrotic diseases, because the collagen fibres must be modified by a similar reaction as the HIFs. The collagen prolyl-hydroxylase inhibitors, however, never reached the market and the whole programme was a disaster. So, CKD patients (and unavoidably endurance athletes) became the focus, and the PHDis may indeed have anti-fibrotic activities, although in a completely different context than originally anticipated. Time will show whether organ doping with PHDis will make the life of CKD patients a bit easier.

Karen Nolan is postdoc in the lab of Roland Wenger at the University of Zurich since August 2014. She completed her PhD in the Diabetes Complications Research Centre at the Conway Institute, University College Dublin in 2013. During her PhD, Karen became interested in the role of hypoxia signalling pathways in kidney fibrosis.

Roland Wenger is Professor at the Institute of Physiology of the University of Zurich, member of the Zurich Center for Integrative Human Physiology (ZIHP), and participant within the NCCR Kidney.CH.

COMPUTERS SHED LIGHT ON HOMEOSTATIC PROCESSES



Anaglyphic three dimensional rendering of a mouse kidney vasculature acquired with X-ray micro-computed tomography. The top part shows only larger blood vessels and vasa recta bundles, while in the bottom part capillaries are displayed as well. Scale bar: 1 mm. Use red-cyan glasses for viewing.

Computational modelling is a powerful tool for renal research, generating data that cannot be gathered using traditional experimental methods. The NCCR Kidney.CH is using computers to develop a model that will predict the oxygen distribution in the kidney

Engineers and scientists working in technical fields have long embraced computers as invaluable tools to assist them in their endeavours. NASA's Apollo 11 lunar landing in 1969 would not have been possible without the spacecraft's computer navigation and control system, even though it was far less powerful than today's smartphones. The recent confirmation—at CERN—of the existence of the Higgs boson relied heavily on computational models that allowed experimental physicists to narrow their search. And in the field of chemistry, computational modelling has also made its mark, with the 2013 Nobel Prize being awarded for research into how the behaviour of molecules can be predicted across multiple length scales.

As the complexity of the system being investigated increases, the challenges of using computational tools escalate too. While Newtonian mechanics (used to predict a spacecraft's trajectory) or even quantum mechanics (used to describe particle behaviour) can be expressed mathematically, translating organ function into a form suitable for computational modelling may seem impossible at first glance. But history teaches us not to underestimate the rate of progress made in computer technology.

Until IBM's Deep Blue defeated the reigning human chess world champion in 1997, many had dismissed the idea of computers beating humans at the game. Critics were quick to point out that chess, with its limited rules and possible moves, was a poor basis for comparison. Attention shifted to Go, the much more complex traditional Chinese board game. And this year, Google's AlphaGo beat one of the world's best players. It won't be long before computers are playing in Go leagues of their own, just like they do today with chess.

COMPUTATIONAL MODELLING IN KIDNEY RESEARCH

Within the NCCR Kidney.CH, we embrace computational modelling as a powerful tool, used together with traditional experimental methods, for renal research. Through the Computational Modelling Reference Center, we offer NCCR members support in the evaluation and application of computational tools for the modelling of physiological and homeostatic processes. In addition, we provide consulting services, help to arrange access to both in-house and external experts, and broker computational resources.

Currently, our largest application of computational modelling is embedded in Work Package 1 (WP1). With WP1 we aim to elucidate the mechanisms involved in renal oxygen sensing and that sensing's consequences for metabolism and the regulation of erythropoietin production. Since it is impossible to measure oxygen distribution in the kidney with high spatial resolution, we are developing a computational model that will predict it instead. To this end, we rely on anatomically accurate representations of the mouse's renal vasculature and tubular systems. These are acquired using synchrotron propagation-based phase-contrast X-ray micro computed tomography. Each of the resulting data sets can occupy up to a terabyte of data, which necessitates pre-processing on super computers before we can begin with the modelling.

While it may take longer than turning the worlds of chess and Go upside down, numerical modelling will, sooner or later, fundamentally change the way biomedical research is conducted. The NCCR Kidney.CH has already embraced this change with its Computational Modelling Reference Center.

Willy Kuo is a PhD student in the lab of Vartan Kurtcuoglu at the University of Zurich since June 2014. He completed his Master's in Interdisciplinary Natural Sciences at ETH Zurich in 2013. In his PhD, Willy works on high resolution 3D imaging using X-ray micro-computed tomography and light microscopy.

Vartan Kurtcuoglu is a professor at the University of Zurich and head of the Interface Group at the university's Institute of Physiology. He received his PhD in Biomedical Engineering from ETH Zurich in 2006 with a thesis on the computational modelling of the cerebral ventricular cerebrospinal fluid system. His particular interest is the convergence of engineering, biological, and medical research to address clinical needs.

NCCR KIDNEY.CH RETREAT 2016

On the evening of February 25 almost all the members of the NCCR Kidney.CH met just like last year at the SBB Loewenberg Centre in Murten for the 6th retreat. The more than 80 participants enjoyed networking and exchanging research results. Hugues Abriel from the University of Bern presented the NCCR TransCure and Robert Unwin from the University College London held a talk about "The Pharmaceutical Industry: What is it good for?! A Future for Drug Discovery in Nephrology?".

Group Picture from the RETREAT 2016 (more pictures at www.nccr-kidney.ch)

POSTER AWARD 2016

46 posters were presented in two posters sessions. The best three posters were selected by a jury consisting of eleven members from the NCCR steering committee and its advisory board. The 1st prize was awarded to Eric Olinger (postdoc in the Devuyst lab, UZH), the 2nd prize went to Willy Kuo (PhD-student in the Kurtcuoglu-lab, UZH) and Jan Czogalla (postdoc in the Loffing-lab, UZH) received the 3rd prize.

INTERNATIONAL SYMPOSIUM "PUMPING, CHANNELLING AND EXCHANGING"

This symposium is organized in honour of the internationally renowned scientists Kaethi Geering and Jean-Daniel Horisberger who greatly contributed to the physiological and molecular understanding of the sodium pump and FXYD proteins. It will take place at the CHUV (Auditorium Tissot) in Lausanne on June 24, 2016. Programme and registration at www.unil.ch/sodiumpump

NEW NCCR KIDNEY.CH BROCHURE

A new and updated version of the NCCR Kidney.CH info brochure is now out.
Digital version at www.nccr-kidney.ch
(download at the right column)

FOURTH E-LEARNING MODULE COMPLETED

19 young scientists from the NCCR Kidney.CH network participated in the e-learning module 4 on oxygen homeostasis. Module 4 started in autumn 2015 and ended with the return session on March 17, 2016 in Bern.
During the course the participants had to review the online resources and to complete four different questionnaires. In addition, they individually studied six annotated articles and completed several group assignments. As final task the students worked on a clinical case and completed the associated assignments both individually as well as in small groups. All participants passed the exams with good to excellent results with grades ranging from 4.9 to 5.5.
E-learning module 5 is already under construction and will focus on Metabolism and Chronic Kidney Disease. The kick-off meeting will be held on October 13, 2016 at the University in Bern.

MORE THAN 100 SCIENTISTS GATHER AT 1ST SWISS KIDNEY STONE SYMPOSIUM

More than a 100 guests attended the 1st Swiss Kidney Stone Symposium at the Inselspital in Bern on February 25th which hosted a number of renowned speakers. Among them were Gary Curhan, an epidemiologist from Boston, Naim Maalouf, an endocrinologist from Dallas, Robert Unwin, a nephrologist from London, Felix Knauf, a nephrologist from Erlangen, Thomas Knoll, a urologist from Sindelfingen and Daniel Fuster, a nephrologist from the Inselspital Bern. The event attracted scientists from different fields; 46% nephrologists, 27% basic renal scientists, 19% urologists and 8% general practitioners. The Symposium provided not only interesting scientific insights but also increased the Swiss Kidney Stone Cohort's visibility among Swiss nephrologists and urologists.

JOINT NCCR WORKSHOP ON INTERDISCIPLINARY COLLABORATION

From November 24-26, 2016 the three NCCRs RNA & Disease, TransCure and Kidney.CH will organise a joint workshop for young scientists. Following the positive feedback of the first joint workshop, this one will also be conducted by international coaches from hfp consulting and will focus on collaboration in science. Participants will learn how to establish and maintain collaboration and how to integrate and strengthen their complementary skills. Resolving conflicts in a team will also be addressed. The interactive workshop will foster the exchange among the participants and strengthen the network within the NCCR communities.
The number of participants is limited. Registration for the workshop starts in September 2016.

EVENTS

8. JAHRESTAGUNG DER DEUTSCHEN GESELLSCHAFT FÜR NEPHROLOGIE (DGFN)
September 10–13, 2016
Berlin, Germany

ASN KIDNEY WEEK 2016
November 15–20, 2016
Chicago, IL, USA

SWISS SOCIETY OF TOXICOLOGY: ANNUAL MEETING 2016
November 17–18, 2016
Basel, Switzerland

48TH ANNUAL MEETING OF THE SWISS SOCIETY OF NEPHROLOGY
December 8–9, 2016
Interlaken, Switzerland

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

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

Imprint
Editor: Jens Selige and Inken De Wit
Design: bigfish.ch
Print: SuterKeller Druck AG

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