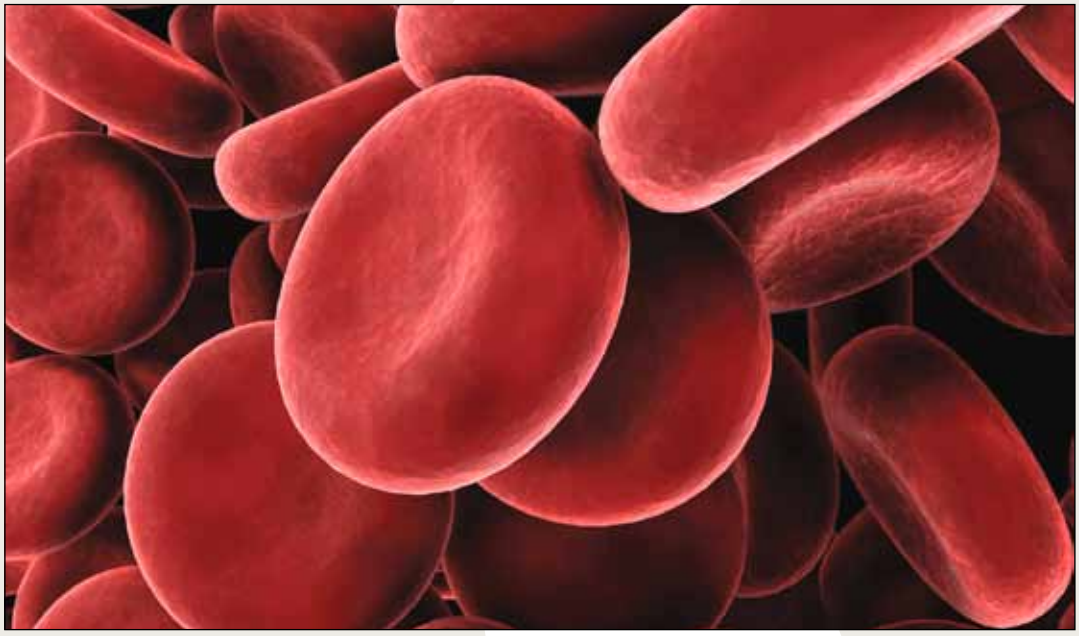
SWISS NATIONAL CENTRE OF COMPETENCE IN RESEARCH

KIDNEY
CONTROL OF HOMEOSTASIS

NEWSLETTER ⁝ NO. 3 ⁝ DECEMBER 2011

LOVE, LIFE, OXYGEN



The British rock band The Sweet entered the charts 33 years ago singing "Love is like oxygen,... not enough and you're gonna die". At least with regard to oxygen (O_2) it was not always like this. Just 2.5 billion years earlier we had only little oxygen on earth. Oxygen rose in the atmosphere when organisms started to use photosynthesis as energy source. The by-product of this elegant way to make use of solar energy, oxygen, increased in the atmosphere over time and after another billion years allowed organisms with mitochondria to use oxygen for glucose metabolism and then later oxidative phosphorylation, an even more efficient means of generating cellular energy.

Since then the words of The Sweet apply perfectly. Humans – who entered the stage not before 0.0002 billion years ago – die when they face too low oxygen, which was finally discovered 0.0000002 billion years ago. Unfortunately, as often in life, too much of a good thing is also not advantageous and several acute as well as chronic diseases are linked to excess oxygen with production of reactive O_2 species, inflammation and tissue damage.

KIDNEYS SENSE OXYGEN

The dependency on oxygen and the importance of regulation of oxygen levels demand a sophisticated control system for O_2 uptake, transport, and metabolism in the body. Here the kidneys play a key role.

Oxygen is transported from the lungs bound to haemoglobin, a metalloprotein in red blood cells, to all organs of the body where it is released again and used for energy metabolism. The production of these red blood cells in the bone marrow is tightly regulated by erythropoietin, a hormone specifically produced by a unique cell type in the kidney. This fact becomes evident when patients suffering from renal failure develop severe anaemia, i.e. deficiency of red blood cells and haemoglobin due to inadequate erythropoietin levels. The introduction of recombinant erythropoietin as treatment for such renal anaemias represented a tremendous progress in clinical nephrology and changed the quality of life in these patients dramatically.

But why is erythropoietin specifically produced in the kidney? The healthy kidney shows a unique oxygen gradient with low partial pressure of O_2 (pO_2) in the inner part, the renal medulla. At the corticomedullary

KIDNEY
CONTROL OF HOMEOSTASIS
SWISS NATIONAL CENTRE OF COMPETENCE IN RESEARCH

University of Zurich[UZH]

FNSNF
Swiss National Science Foundation

EDITORIAL

Heini Murer is professor emeritus at the Dept. of Physiology and former vice-president of the University of Zurich. He is a member of the Kidney.CH advisory board.

CH in the NCCR's name Kidney. CH does not only point to the main function of the kidneys, to the control of homeostasis, and is not only part of its web address, no, it also indicates a special role in renal research of our country, the Confederatio Helvetica. This role is well documented by the international recognition of Swiss research teams and also by the successful competition for this National Center of Competence in Research (NCCR), a nationwide network based on excellence of present research teams and their research projects. Renal research was and is blooming in Switzerland! This is thanks to motivated scientists and the generous support from our universities as well as from national and international grant-agencies. The funding of the NCCR Kidney. CH by the Swiss National Science Foundation, the University of Zurich as home institution and the partner Universities of Basel, Bern, Fribourg, Geneva and Lausanne offers kidney research in Switzerland a bright future which must build on continuing disciplinary strength in basic science, clinical science and translational science, and most importantly also on promoting young scientists, the future leaders in Swiss kidney research. The NCCR successfully installed one year ago is not only a unique chance, but it is also an obligation for the years to come!

Heini Murer

junction, interstitial cells produce erythropoietin in response to a drop of blood haemoglobin and decrease of tissue pO_2 (Fig. 1). The sensing of insufficient oxygen (hypoxia) is fascinating and was mainly unravelled during the last decade: In normoxia prolyl hydroxylase enzymes utilise O_2 to add a hydroxyl group (-OH) to specific transcription factors, so called hypoxia-inducible factors alpha (HIF-α). This hydroxylation makes HIF-α prone to polyubiquitination and rapid degradation by the proteasome. This means that HIF-α is constantly degraded when oxygen is sufficiently available. When pO_2 drops hydroxylation can no longer take place, HIF-α is stabilized, heterodimerizes with HIF-β, and functions as transcription factor for an array of genes, among others erythropoietin which is secreted and stimulates production of red blood cells in the bone marrow.

A PHANTOM IN CELL CULTURE

However, most of what we know about these molecular mechanisms was discovered in cultured cell types that do not produce erythropoietin in the healthy body. This is because the interstitial renal cells that normally produce erythropoietin could not be kept in cell culture for unknown reasons. The lack of a reliable cell model has a huge impact. For instance, HIF-1α,

PORTRAIT

LIFE IS NOT A PATH THAT IS FIXED AT THE VERY BEGINNING

An interview with Jean-Pierre Montani

Jean-Pierre Montani, since 1995 you are Professor and Chairman at the Dept. of Medicine, Division of Physiology in Fribourg. How did you get into science?
Well, life is not a path that is fixed at the very beginning. In my case I wanted to become a physician from a very young age even though I always loved sciences in school. However, when you wanted to become a physician in the early 60s, they said you needed to study Latin and Greek and less science. So I did and went after to medical school in Fribourg, where I did the pre-clinical years, and finished in Geneva with the clinical years. My objective was to work in internal medicine. But before, I thought it might be a good idea to do two years of physiology. I did my medical thesis in physiology, working on vasopressin. I went then to Geneva for a 3-year program in Internal Medicine in the Department of Alex F. Muller, a master of physiopathology.

So you became – as you wanted – a physician. Why didn't you continue your way as physician?
I very much planned to at the beginning. One day Alex Muller asked me about my future plans and I answered that I definitely wanted to stay working in the hospital rather than opening my own private practice. "If this is what you want, then for your career you have to first spend one or two years in the US" he answered. Therefore I organized together with my wife and our two little children to go for one year in the US, to work with the help of a SNF grant in Arthur C. Guyton's lab in Jackson, Mississippi.
From the very beginning Arthur Guyton liked the way I was interested in understanding physiology and asked me to stay longer. He promoted me as assistant professor and from the originally planned one year, we stayed 13 years, which were great. Even though I took the US exam to work as a physician, I never again worked as a physician and became a cardiovascular physiologist.

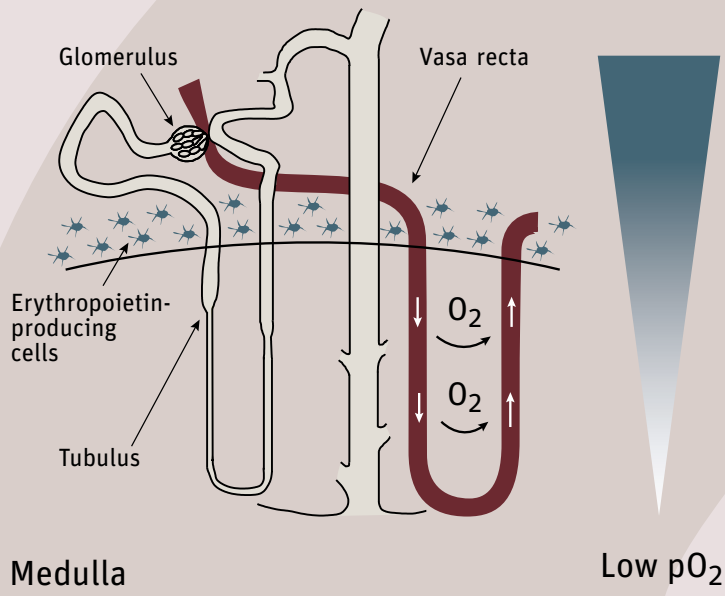
How was it, working with Arthur Guyton?
Guyton was a wonderful and extremely smart person. He had an open-door policy; anyone could enter his office at any time. He made crucial discoveries in cardiovascular physiology leading to many seminal concepts in cardiovascular regulation. His concepts of cardiac output and venous return, negative interstitial fluid pressure and regulation of tissue fluid volume and blood flow, renal-pressure natriuresis and long-term blood pressure regulation became most relevant in understanding cardiovascular disorders such as hypertension, heart failure and edema. He was also among the first to propose the kidney as a central organ in blood pressure regulation. And he is the author of the first comprehensive and up today most sold medical textbook in physiology.

And how did it happen that you went back to Fribourg?
As much as I enjoyed working with Guyton, it was always clear that I would like to go back to Switzerland one day. Even though we met lots of good people and made good friends, we had no extended family over there; it was good to go back with our meanwhile four children. I was very happy to come to Fribourg not only because I grew up and studied there, but because there was room to develop a cardiovascular program.

And what is a cardiovascular physiologist doing in Kidney.CH?
The importance of the kidney became clear to me very early from my mentors Muller and Guyton. Also as a physiologist I'm always interested in the integrative nature. Therefore I happily joined the Swiss research initiative Kidney – Control of Homeostasis, where I focus my investigations on the regulation of the energy metabolism by the kidney.

Jean-Pierre Montani is professor of physiology and chairman of the Dept. of Medicine, Division of Physiology at University of Fribourg. He acts as vice-chair of the research module Nutrients & Metabolism of the NCCR Kidney.CH.

Fig. 1: **Kidney as oxygen sensor of the body**



MODULE 1: OXYGEN

PROJECT 1.1: BASIC MECHANISMS OF RENAL OXYGEN SENSING

ROLAND WENGER
University of Zurich
Cellular regulatory mechanisms of the renal oxygen signaling pathway and visualizing renal oxygen (re)distribution

IAN FREW
University of Zurich
Effects of disrupting oxygen signalling in renal epithelia

PROJECT 1.2: OXYGEN SENSING IN KIDNEY DEVELOPMENT AND DISEASE

UYEN HUYNH-DO
University Hospital Berne
Intrauterine oxygen in renal development

CLEMENS D. COHEN
University of Zurich
Oxygen and progression of acquired nephropathies

HOLGER MOCH
Universtiy Hospital Zurich
VHL and HIF in renal tubulus cell proliferation

the first HIF characterized as hypoxia-dependent transcription factor in many cells, was assumed for many years to be the key transcription factor for the erythropoietin-encoding gene EPO. Now it is clear that HIF-2α plays this role in the naturally erythropoietin-producing renal cells and HIF-1α functions as hypoxia-inducible factor in other cells which do not transcribe EPO. One project of the NCCR Kidney.CH headed by Roland Wenger aims to better characterize these specific renal cells and decipher novel molecular factors which enable these cells to sense and respond to oxygen levels and to stop erythropoietin production at the right time before systemic haemoglobin levels become too high.

TOO HIGH OR TOO LOW, NO ONE KNOWS

Another enigma in this field is why these cells do not produce sufficient amounts of erythropoietin when the kidneys are affected by disease. It has been demonstrated by different means that these cells do not disappear in renal disease and are still capable of producing erythropoietin. One theory is that oxygen consumption by normal kidney tubule cells is low in malfunctioning kidneys and that the interstitial Erythropoietin producing cells therefore are constantly exposed to higher than normal oxygen tension. It is difficult to disprove this hypothesis but evidence accumulates that chronically diseased kidneys rather face tissue hypoxia than high pO_2. This became evident when we studied the gene expression in kidney biopsies from patients with chronic renal disease (Fig. 2). Here most of the known HIF-dependent gene transcripts were clearly induced. However, there were some notable exceptions, among others erythropoietin. This finding is in accordance with a functional dysregulation of erythropoietin expression in diseased kidneys. The elucidation of this puzzling phenomenon of inadequately low erythropoietin in kidney disease

Fig. 2: Intrarenal expression levels of hypoxia-associated gene transcripts in patients with different renal diseases.

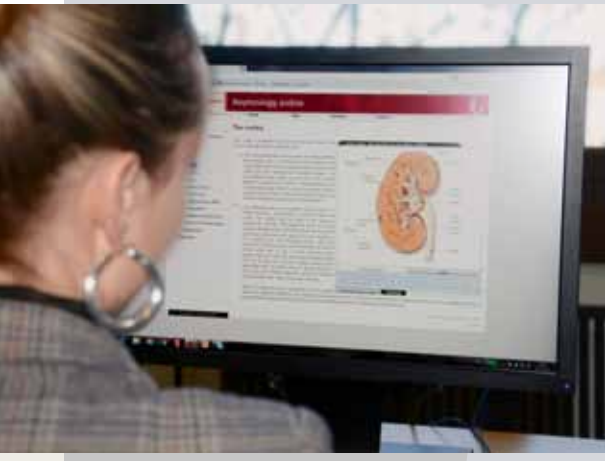
requires the joined forces of experts in molecular biology, physiology, and medicine. Therefore different groups from the NCCR cooperate to decipher the molecular mechanisms driving hypoxia-regulated gene transcription in health and in diseased kidneys.

The Sweet sang about love and oxygen in 1978, a time shortly before the gene EPO was identified and a decade before erythropoietin was approved as treatment for renal anaemia. Another hit of the year 1978 on love and the atmosphere was “Love is in the air”. Be that as it may, what we can take for granted nowadays: “Life is in oxygen” – and its body homeostasis is controlled by healthy kidneys.

Clemens D. Cohen has a translational research position as senior consultant at the Division of Nephrology, University Hospital Zurich, and senior researcher at the Institute of Physiology, University of Zurich. He acts as vice-chair of the research module Oxygen of the NCCR Kidney.CH.

E-LEARNING PILOT PROJECT FOR BASIC PRINCIPLES IN NEPHROLOGY

Kidney.CH and the Health Sciences eTraining Foundation (www.HSeT.org) have joined forces to develop a new eLearning tool for teaching basic principles in nephrology. The contract signed for the pilot project is for a 2-year-period and started during the 2nd half of 2011. HSeT is a specialist in the field of eLearning and already successfully runs a platform mainly for immunology and pharmacology online courses. The content development will be under the lead of Bernard Rossier and Jean-Pierre Kraehenbuel in collaboration with the NCCR Kidney.CH specialists.



The Main objective of the new eLearning tool is to acquire specific knowledge in nephrology towards fulfilling the educational requirements for PhD, MD or MD-PhD degrees. Starting with an article from the literature and/or with a practical problem we will review the theoretical principles necessary to understand the basis of the presented articles (article-based learning) or problems (problem-based learning).

At the end, the trainee should be able to

- describe and apply the basic physiological and patho physiological concepts of nephrology to medically relevant questions.
- acquire the basic anatomical knowledge (virtual microscope) to understand the functional anatomy of the nephron.
- critically read, analyze and present a scientific paper and to address the unsolved questions.

A first version of the eLearning tool should be available in fall 2012.

Kidney – Control of Homeostasis is a Swiss research initiative with leading house at University of Zurich bringing together leading specialists in experimental and clinical nephrology form the Universities of Basel, Berne, Fribourg, Geneva, Lausanne and Zurich and from corresponding University Hospitals.

PROGRESS REPORT APPROVED

The first project review by the Swiss National Science Foundation together with an international review panel, comprising of eight leading experts, took place over two days in June 2011. The Research Council of the Swiss National Science Foundation followed the review recommendations and approved the first progress report of the NCCR Kidney.CH and granted the funding for the 2nd year.

KIDNEY.CH SYMPOSIUM 2011

Our first international Kidney – Control of Homeostasis symposium took place on June 17 at the University Hospital Zurich. Speakers from Germany, France, England and Switzerland gave excellent insights into hypoxia related issues, EPO and iron metabolism and what role the kidney plays or might play. We warmly thank all the speakers and attendees who made this event such a great success!

EVENTS

RETREAT NCCR KIDNEY.CH
January 27 – 28, 2012
Spiez / Switzerland

WORLD KIDNEY DAY 2012
March 8, 2012
Planet Earth

2ND KIDNEY.CH STUDENT'S DAY
March 22, 2012
Berne, Switzerland

ISN FOREFRONTS SYMPOSIUM – SYSTEMS BIOLOGY AND THE KIDNEY
June 7 – 10, 2012
Ann Arbor, Michigan, USA

OUTLOOK

2ND INTERNATIONAL KIDNEY.CH SYMPOSIUM
June 14, 2012
Geneva, Switzerland

Imprint
Editor: Matthias Meier
Design: bigfish.ch
Print: Druckerei Suter AG

NCCR-Kidney.CH
Institute of Physiology
University of Zurich
Winterthurerstrasse 190
8057 Zurich | Switzerland
Tel: +41 44 635 5216
Fax: +41 44 635 6814
www.nccr-kidney.ch
info@nccr-kidney.ch