evotec

DDup

DRUG DISCOVERY UPDATES #3

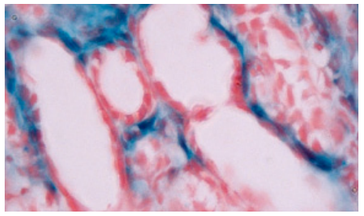
KIDNEY DISEASES

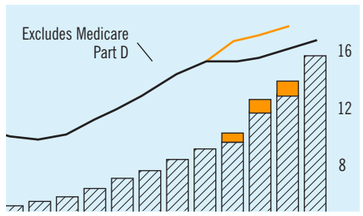
TREMENDOUS MEDICAL NEED WITH LIMITED TREATMENT OPTIONS

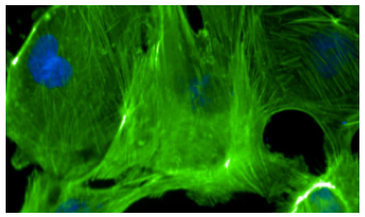
Chronic Kidney Disease, End Stage Renal Disease, Acute Kidney Injury:

- *No cures or disease modifying drugs*
- *Huge economic burden*
- *New therapies urgently needed*

CONTENT & CONTACT







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Dr Werner Lanthaler, CEO

WELCOME TO DDUP!

DEAR FRIENDS OF EVOTEC,

Welcome to the third issue of DDup, an Evotec instrument for providing you more insights into the company. This edition is especially dedicated to our second collaboration with Harvard University regarding kidney diseases.

COMPLEX SITUATIONS REQUIRE CLEAR VISIONS AND CLEAR STRATEGIES

With Cure*Nephron* we have established the world leading initiative to address the causes of one of the most complex unmet medical needs of our times. The kidney is clearly one of the most demanding organs in our body, so finding the right strategies and entry points to tackle situations like Chronic kidney disease (CDK) and other related diseases is the challenge that Harvard University and Evotec have taken up. We feel that as partners we are perfectly positioned to combine the scientific state of the art with the best-in-class drug discovery infrastructures in order to accelerate the search for novel drug targets. We have started to build a systematic unbiased and comprehensive infrastructure that looks at the problem with a holistic view — we look for biomarkers just as well as for novel pathways, mechanisms and drug targets.

Thank you for reading this DDup, thank you for your thoughts, input and hopefully also the cooperation in this field with us. Cure*Nephron* will be an open innovation process and dialogue with the community. The topic is large and important enough that it justifies the strategic attention of academia and pharma, as this is a field where research has not delivered satisfactory treatments yet and where there is no more time to lose.

We want to thank especially our cooperation partners at Harvard who together with Evotec formed the Cure*Nephron* team to take on this very important task. We see this as a long-term commitment following our mission to understand and treat the causes and not only the symptoms of diseases.

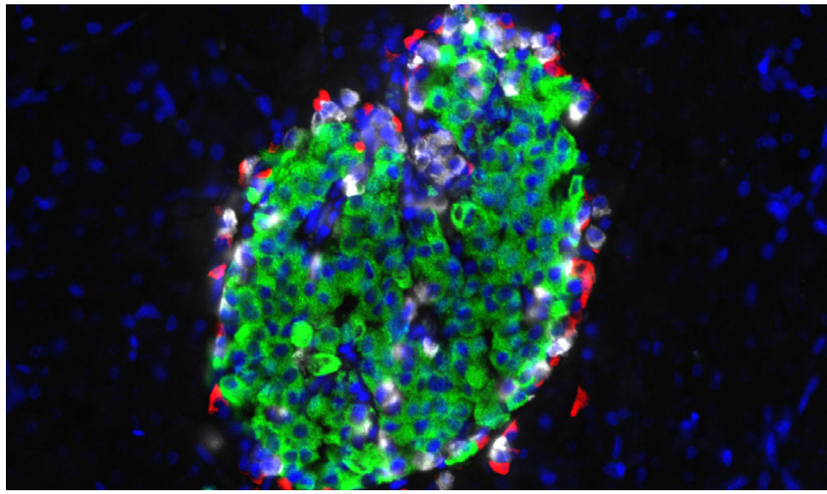
Read and enjoy and let us know if we can further help you.

Yours sincerely
Werner Lanthaler
on behalf of the management team

EVOTEC — HARVARD

TRUE ACCELERATION AND EFFICIENCY OF EARLY STAGE DRUG DISCOVERY

Two highly successful alliances designed to discover disease modifying therapies



Section of porcine pancreas with islet of Langerhans. Endocrine hormones stained by immunofluorescence: Insulin (green), Glucagon (white), Somatostatin (red). Cell nuclei are stained blue.

Harvard University is a world-leading academic institution not only when it comes to science and innovation but also in translating new scientific insights into tangible products that benefit patients and society in general. In line with its enormous scientific prowess and leadership in innovation, Harvard has always been at the forefront of defining and exploring new ways to efficiently translate innovative science into products. In March 2011, Harvard and Evotec defined a new model of collaboration between academia and the biotech industry with the sole vision to truly accelerate new biological insights in beta cell biology into potentially paradigm changing therapies for diabetes. Accelerating and significantly increasing efficiency in the translational process from breakthrough science to clinical assessment is a key objective of the entire pharmaceutical industry. The Harvard Evotec model may be a step in the right direction.

Cure*Beta* — HARVARD/ EVOTEC/JANSSEN PHARMACEUTICALS

Cure*Beta* is very much focused on diabetes and potentially disease modifying approaches targeting beta cell mass and function. The extent of beta cell failure ultimately determines when patients are diagnosed with overt diabetes mellitus. Restoring beta cell function in patients with diabetes represents a promising approach to not only change the progression of the disease but potentially revert or even cure diabetes.

Unfortunately, credible beta cell regeneration targets are exceedingly rare despite the fact that physiological mechanisms are known to regulate beta cell mass and function. Harvard Professor Doug Melton and Evotec set out to systematically and comprehensively identify the underlying molecular mechanism and pathways involved in these processes and to subsequently identify high potential targets that can be therapeutically exploited to restore beta cell mass and function in diabetic patients.

There were three important premises which formed the basis of this collaboration.

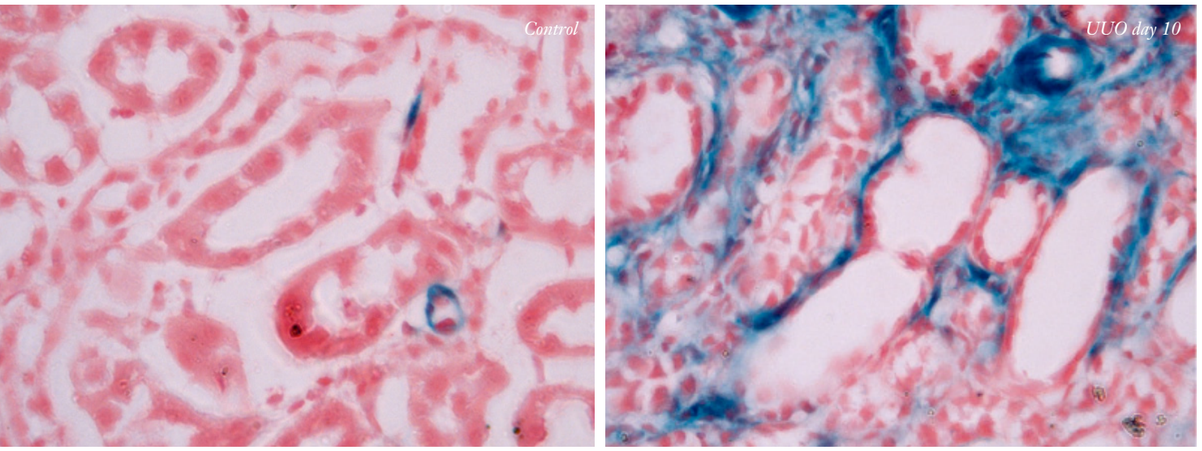
(i) First of all we committed to effectively use the individual strengths of each partner with Harvard contributing new biological insights and a great understanding of beta cell biology as well as potential assays, targets and compounds. Evotec contributed an industry leading beta cell platform and drug discovery infrastructure that transfers exploratory findings into industry standard processes and robust results that become the foundation of individual drug discovery projects based on individual targets and compounds.

(ii) In order to achieve true acceleration we agreed that the necessary resources would be provided by both partners without having to raise additional capital to finance projects. In many early stage ventures having to raise money is usually a huge distraction from the science as it requires people with different skill sets and inevitably results in significant delays as well as potential conflicts of interest. This initial commitment was further reinforced by mechanisms that would encourage continued funding.

(iii) Finally, an important objective was to secure early on a strategic partner who would share the vision and further complement our efforts in terms of required capabilities, resources and expertise in particular when it comes to formal pre-clinical and clinical development.

The initial Harvard-Evotec Cure*Beta* agreement was signed in March 2011. Just slightly more than one year later, we achieved our first strategic goal with Janssen Pharmaceuticals joining the Cure*Beta* partnership and thereby completing the value chain now reaching from world-leading academic science over innovative pre-clinical drug discovery to proven development and marketing capabilities. Janssen Pharmaceuticals convinced us that they were the perfect partner for Cure*Beta* based on their strategic commitment to the field, their outstanding biologics capabilities and fielding a highly enthusiastic, top-class team that embraced ensuing opportunities as well as challenges.

In contrast to previous collaboration models between academia and the biotech and pharmaceutical industry, this three-pronged partnership creates a new dynamic which primarily focuses on the science as it keeps academic inventors involved without limiting their freedom to conduct basic research and incorporates biotech's spirit and penchant for innovation while at the same time benefiting from enormous pharma experience.



Pericytes are myofibroblast progenitors in adult kidney fibrosis

Cure*Nephron* — HARVARD / EVOTEC

As novel models of academia-industry collaborations were needed and the fact that Cure*Beta* was on a good path triggered a second partnership between Harvard and Evotec.

This second partnership, Cure*Nephron*, was started in January 2012 and focuses on kidney disease. The key scientists involved in this collaboration are Dr Andrew McMahon and Dr Benjamin Humphreys. Both of them have been working as a team at the Harvard University to establish animal models that would allow high resolution expression profiling of specific cell types in kidney during disease progression and recovery. These models combined with Ben's and Andy's expertise in kidney development, biology and disease made a perfect match with Evotec's internal initiatives. Together these efforts constitute a formidable basis for a highly systematic, unbiased and comprehensive approach to identify and develop novel approaches to kidney disease targeting mechanisms that have the potential to become disease modifying therapies.

Cure*Nephron* has made tremendous progress since it was started and is generating candidate targets and compounds. We have recently started a process to identify a strategic pharma partner that will complement the team and complete the value chain.

ASSETS

The recently established collaboration by Harvard/USC (University of Southern California), Brigham and Women's Hospital and Evotec was, just like the Cure*Beta* program, based on the vision to combine academic and industrial excellence and expertise in the field of diabetic complications, in particular kidney disease.

ASSETS CONTRIBUTED BY HARVARD/USC, BRIGHAM AND WOMEN'S HOSPITAL INCLUDE:

- **Relevant *in vivo* models of chronic and acute kidney injury**
- **Transgenic mice allowing high resolution expression analysis of different disease stages**
- **Biobank for chronic and acute kidney injury animal models**
- **Growing human kidney biobank**
- **Specific tools and assays for target identification**
- **Extensive experience and clinical expertise in kidney biology and pathology**
- **Target lists from high resolution analysis of kidneys**
- **Extensive expertise in genetic modeling approaches**

ASSETS CONTRIBUTED BY EVOTEC INCLUDE:

- **Regenerative approach to identify protective factors or factors that lead to differentiation of key cells in the kidney**
- **Comprehensive bioinformatics capabilities for the assessment and in silico validation of kidney disease targets**
- **Broad range of *in vitro* and *in vivo* models to assess relevant mechanisms of kidney disease in key cell types**
- **State-of-the-art animal models for diabetic nephropathy including glomeruli preparation and culture of different species**
- **High content screening (HCS) format for relevant kidney cells, like podocytes and pericytes**
- **Extensive experience and expertise in selecting high-value drug targets for further development in the regenerative medicine field**

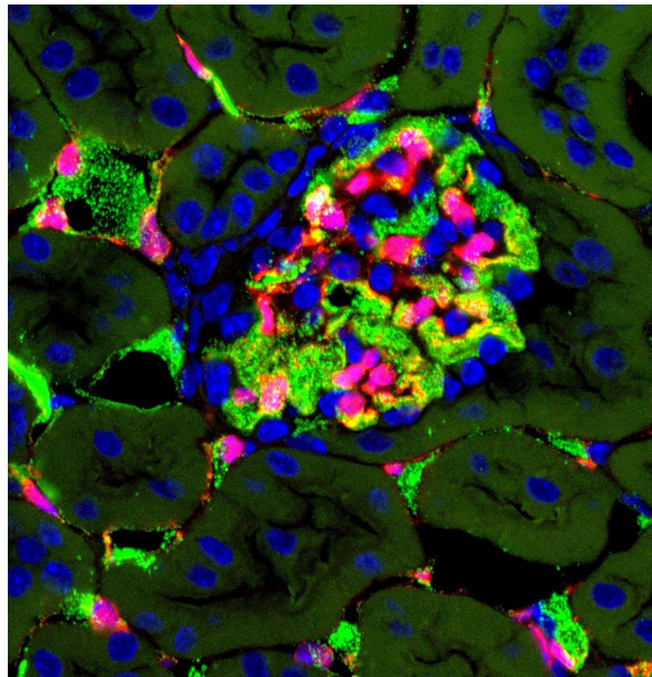
Together we intend to conduct a comprehensive search for target candidates that have the potential to slow, halt or even reverse kidney injury. Our target ID and target validation approaches will cover both acute and chronic kidney disease with a focus on diabetic nephropathy.

The product pipeline currently includes small molecules as well as biologics (secreted factors) with *in vitro* activity and proven relevance for targets in certain kidney disease *in vivo* models. In addition, long lists of target candidates have been generated.

Both HCS and high throughput screens (HTS) have been designed and will be conducted to identify additional target candidates that can be fed into our proven target selection cascade.

The use of a high resolution genetic approach in combination with relevant kidney disease *in vivo* models as well as cellular screening on key cells of the kidney will lead to a highly systematic and comprehensive search for relevant kidney disease targets. This approach will generate both potential drug candidates and very likely novel biomarkers for diagnosis of kidney injury. Most promising drug candidates will be fed into our target validation and drug discovery pipeline.

The glomerulus forms a primary filtrate from the blood. Here, the fine capillaries in the glomerulus are filled with a fluorescent green tracer and glomerular endothelial cells labeled in red



TRULY WORLD-CLASS SCIENTISTS DEDICATED TO KIDNEY DISEASES

Dr Andrew McMahon

Dr Benjamin Humphreys

Dr McMahon received a B.A. in Zoology from St. Peter's College, Oxford University and a Ph.D. from University College in London.

He served as Adjunct Professor in the Department of Genetics and Biological Sciences at Columbia University and as a Full Member of the Department of Cell and Developmental Biology at the Roche Institute of Molecular Biology before he became Professor of Molecular and Cellular Biology at Harvard University in 1993 and Chairman of the Department in 2001.

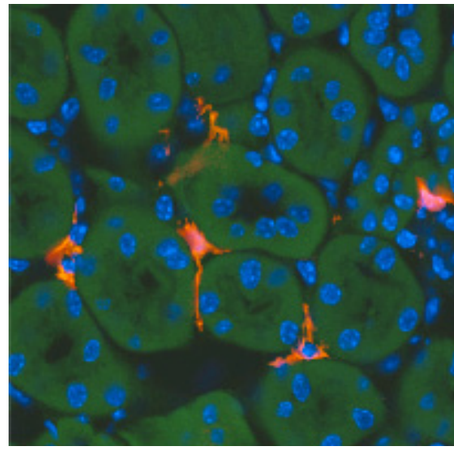
Dr McMahon is a co-discoverer of the vertebrate Hedgehog, and his developmental genetic studies on Wnt and Hedgehog signaling have led to many key insights into the roles of these signals in a wide range of developmental processes.

In 2007 he was elected fellow of the Royal Society. Amongst others he is Javits and Merit Award winner from the NIH. In July 2012, Dr McMahon was elected Chairman of Department of Stem Cell Biology and Regenerative Medicine at USC.

Dr Humphreys is an Assistant Professor of Medicine at Harvard Medical School and Principal Faculty Member of the Harvard Stem Cell Institute and Co-Director of the Harvard Stem Cell Institute Kidney Program.

He received a bachelor's degree from Harvard College and MD and PhD degrees from Case Western Reserve University. He completed a residency in Internal Medicine at Massachusetts General Hospital and a fellowship in Nephrology at Brigham and Women's Hospital in Boston. He is the recipient of a Harvard Stem Cell Institute Seed Grant, the National Kidney Foundation Young Investigator Award and the American Society of Nephrology Gottschalk Research Scholar Award.

Dr Humphreys investigates kidney repair in order to translate this knowledge into therapies for patients with kidney disease.



Kidney pericytes (red)

5 MINUTES
WITH ANDREW MCMAHON AND BENJAMIN HUMPHREYS ON KIDNEY DISEASE

CD: Andy and Ben, you are highly accomplished scientists in the kidney field and decided to team up in order to investigate novel, innovative approaches for chronic kidney disease (CKD) and acute kidney injury (AKI). Before we discuss your ideas and current focus in these areas could you summarize some of your thoughts on what is the biggest unmet medical need in kidney disease and what are the most promising current approaches?

BH: There are substantial unmet medical needs in the treatment of both CKD and AKI. In the CKD field, we control blood pressure and block the angiotensin system, but these only slow but do not halt, much less reverse kidney disease. In the AKI field, we provide supportive care but there are no therapies proven to alter the natural history of the disease. It is now clear that AKI leads to CKD and end stage renal disease, but there are not nearly enough kidneys for all the transplants that are needed in patients with kidney failure. So clearly we need new strategies for prevention and effective therapies for treatment. One area where there has been some success recently is in biomarker development. One of the possible reasons we lack more CKD and AKI therapies is that clinical trials enroll patients beyond the 'golden window' where intervention will still make a difference — and this is because we lack sensitive enough biomarkers. But there has been encouraging progress on this front.

AM: Another area where we are really making progress is understanding the basic pathophysiology of acute and chronic kidney disease. The kidney is such a complex organ that until recently it was not clear which were the most important cells to focus on when designing new therapies. Is it the essential cells that exhibit the primary pathology or surrounding cells may contribute to or prevent disease? Because we have new tools to examine the roles of each individual cell type in kidney injury, we are developing a remarkably detailed molecular picture of kidney disease, and this gives us new insight about pathways that might be manipulated to treat kidney disease.

> "Clearly we need new strategies for prevention and effective therapies for treatment."

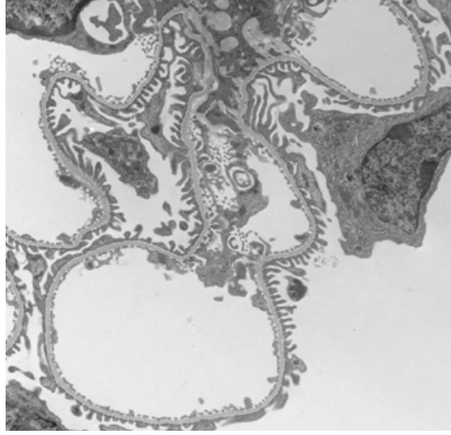
CD: Current treatment options for CKD are very limited. In your opinion, where do we stand today and what are the most promising new ideas, options and strategies?

BH: It is becoming clear that targeting one single pathway is unlikely to reverse CKD. There are multiple pathways, some are redundant, and strategies that target several of these will likely be the most successful in the future.

Additionally, it will be critical to develop new biomarkers of CKD that are more sensitive than serum creatinine, so we can better identify patients at the highest risk for progressive kidney fibrosis and track their response to therapy more accurately. This is especially true when one considers that typical CKD progresses inexorably, but slowly — so clinical trials based on serum creatinine would likely need to be so long as to be impractical.

But it is also true for AKI, where the challenge is to accurately diagnose patients as early as possible, to begin effective treatment immediately, or better still pretreat at risk patients to prevent an acute injury episode, for example patients undergoing cardiac surgery where ischemia triggers AKI. As it stands on the diagnostic front, serum creatinine rises one to two days after the injury, and this may be too late to intervene therapeutically.

> "The kidney is such a complex organ that until recently it was not clear which were the most important cells to focus on when designing new therapies."



Electron micrograph image displaying the complexity of kidney

CD: What approaches have the potential to attenuate or even reverse disease progression?

AM: Of course this is not yet clear, in part because of our sketchy knowledge of injury/repair mechanisms. It is possible that reactivating developmental pathways required during nephrogenesis may have uses therapeutically. The kidney has an impressive endogenous repair capacity but certain responses appear to be maladaptive in the long-term. One question we are interested in is whether reactivating developmental pathways can induce the kidney back into a regenerative mode.

CD: The kidney is a very complex organ containing a number of different mature cell types that are functionally linked to each other. Which cell types are of particular importance in what type of kidney disease?

BH: The adult kidney has more than thirty distinct cell types, and they all work together, and so all are important. However, within the spectrum of kidney disease there are marked differences within each of these populations. For example, in glomerular diseases, such as focal segmental glomeruloscerosis, podocytes are affected and their dysfunction causes proteinuria, ultimately leading to fibrosis and kidney failure. In AKI, the proximal tubule epithelial cells are critical, as these metabolically active cells are particularly susceptible to low oxygen and toxins. In CKD, it is less clear, but attention is focusing on interstitial pericytes: the progenitors for myofibroblast, scar-secreting cells. Macrophages and other immune cells are also important, as it is becoming increasingly clear that inflammation both accompanies and accelerates CKD.

> "The kidney has an impressive endogenous repair capacity but certain responses appear to be maladaptive in the long-term"

CD: What about stem cells? In your opinion will they play an important role in treating kidney disease in the foreseeable future?

AM: Stem cells do hold tremendous promise for regenerative medicine and the kidney is no exception. But the kidney's cellular complexity is a real challenge so stem cell based therapies may take longer to develop for the kidney relative to other diseases where a single cell type needs to be replaced, like type 1 diabetes.

BH: Still mesenchymal stem cell (MSC) therapies are already in clinical trials in humans to prevent AKI already, so this is a rapidly developing new field, possibly too rapidly given our current understanding of disease mechanisms and MSC actions.

CD: Are there common mechanisms that could potentially have an impact on both CKD and AKI?

AM: Yes. CKD can be viewed as an injury followed by repair just as

in AKI, but in CKD the insult is continuous. These ongoing cycles of injury and repair may exhaust the kidney's repair capacity ultimately. So if we can understand how to interrupt the injury, or better promote repair, then such mechanisms could be useful in both AKI and CKD. Interestingly, the kidney and several other organ systems is referring to. The bulk of kidney parenchyma is comprised of epithelial cells, but these are supported by surrounding blood vessels and all held together by mesenchymal stromal tissue. A wide range of growth factor, matrix, cell-cell and autocrine mechanisms are required to work in concert to maintain kidney function.

"If we can understand how to interrupt the injury, or better promote repair, then such mechanisms could be useful in both AKI and CKD"

can undergo conditioning where a mild injury makes the kidney resistant to a later, life-threating insult. A molecular definition of conditioning may facilitate development of preventative therapies to block damage responses. Modulating inflammation is another area where common mechanisms are likely to exist, and immunomodulatory treatments could have beneficial effects in both diseases.

CD: What physiological mechanisms are known to maintain kidney structure and function?

AM: The answer to this question depends on which structure one

CD: Numerous studies have been conducted looking for novel targets and markers with limited success. What are the major obstacles and how could these be addressed?

AM: One of the problems with previous efforts is the cellular complexity of the kidney. Unbiased approaches to define transcriptional changes after kidney injury integrate the cumulative signals from dozens of cell types. One promising approach is to systematically define transcriptional changes over time for all of the most important cell types in the kidney during the injury response. This is the approach we have been taking with Evotec, and the preliminary results are very encouraging.

CD: How important is fibrosis in CKD and AKI? What are the most promising mechanisms to address fibrosis?

BH: Fibrosis is essentially the primary problem in CKD. As nephrons die, they are replaced by fibrotic tissue and scar. This scar impairs the microcirculation, causing local hypoxia, which further injures adjacent nephrons, causing them to die, and so on. Strategies to limit the progression of fibrosis should allow the kidney's inherent repair capacity to function properly, increasing kidney lifespan. In AKI, it is less clear what role fibrosis plays, but it is likely a factor in why patients that develop AKI are at much higher risk of developing CKD in the future.

CD: Especially for AKI, but also for CKD, traditional blood and urine markers of kidney injury are lacking sensitivity and are nonspecific at least for the diagnosis of AKI. Will there be a kidney troponin?

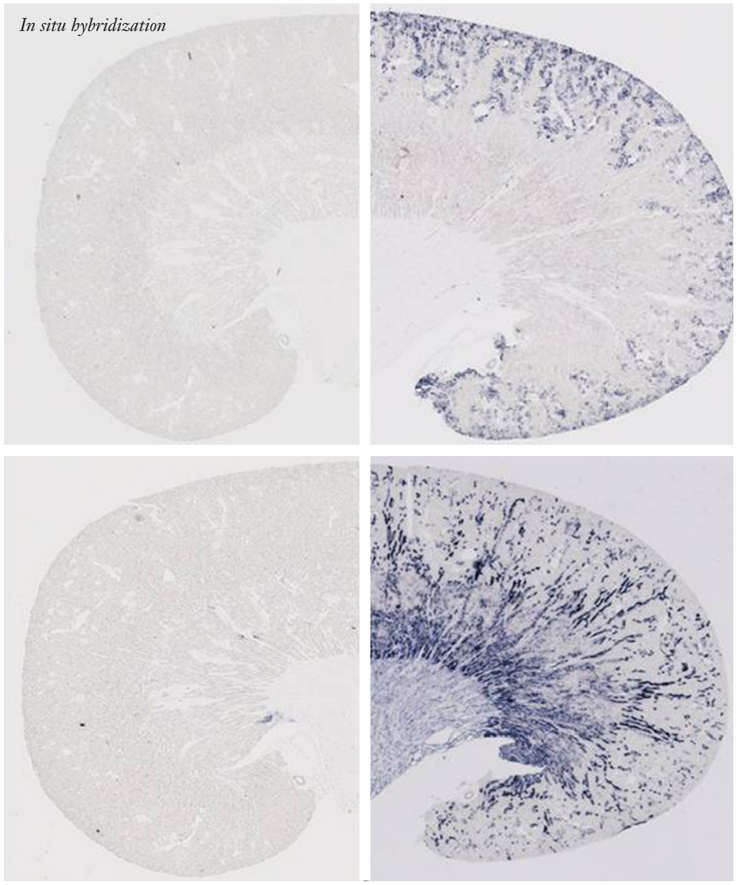
BH: As I mentioned earlier, developing new biomarkers for both AKI and CKD is critical in order to diagnose and track patient responses

"There will be no single kidney troponin for all kidney disease, but there will likely be a dozen or more markers, each specific to a different form of kidney injury and produced in different cells in the kidney"

earlier and more accurately. There will be no single kidney troponin for all kidney disease, but there will likely be a dozen or more markers, each specific to a different form of kidney injury and produced in different cells in the kidney. For example one could imagine a podocyte-specific marker that heralds glomerular disease, or a proximal tubule marker in AKI, or a myofibroblast marker for CKD, or an inflammatory marker for allergic interstitial nephritis and so on. It is not unreasonable to imagine the time when all of these markers will be available on a single strip — much like the urine dipstick we use today — for rapid point of care diagnostics.

CD: Thank you for your time.

Dr Cord Dohrmann (CD) is Chief Scientific Officer and Member of the Management Board at Evotec. Dr Dohrmann has spent over 20 years in biomedical research at leading academic institutions and in the biotech industry.



Response of two AKI activated genes (in situ analysis). Left panels normal kidney, right panels AKI.

CHRONIC KIDNEY DISEASE (CKD)/END STAGE RENAL DISEASE (ESRD)/ ACUTE KIDNEY INJURY (AKI)

CKD IS A DEVASTATING DISEASE WITH LIMITED TREATMENT OPTIONS DRIVEN BY DIABETES AND HYPERTENSION

PREVALENCE OF DIABETES
26 MILLION PATIENTS IN THE USA
346 MILLION PATIENTS WORLDWIDE

MORE THAN 35% OF ADULTS WITH DIABETES SUFFER FROM CKD

PREVALENCE HYPERTENSION
68 MILLION PATIENTS IN THE USA

ACCORDING TO WHO NEARLY 40% OF ADULTS AGED 25 AND OVER HAD RAISED BLOOD PRESSURE IN 2008

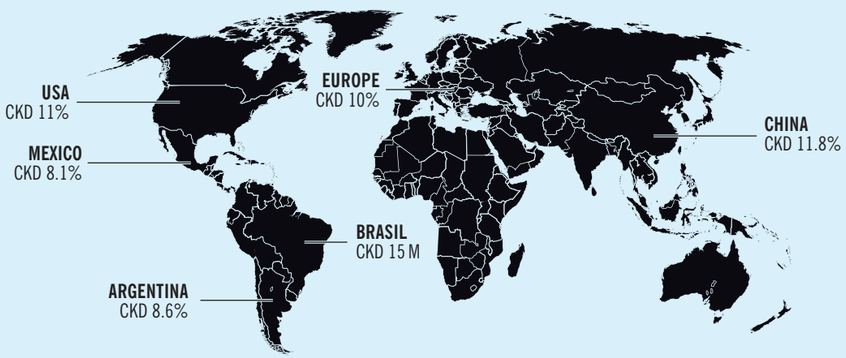
EVERY YEAR, HYPERTENSION CAUSES MORE THAN 25,000 NEW CASES OF KIDNEY FAILURE IN THE USA

Early stage CKD usually goes undiagnosed as patients do not feel any symptoms. CKD almost always develops into ESRD, which necessitates renal replacement therapy. Survival rates for ESRD are very poor, about 50% of patients starting on dialysis today will be dead by the end of 3 years!

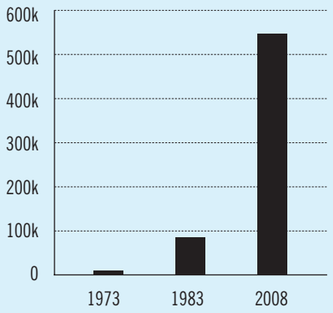
CKD/ESRD/AKI – FATAL DISEASES HAVE THREE THINGS IN COMMON:

- NO CURE OR DISEASE MODIFYING DRUGS
- HUGE ECONOMIC BURDEN
- DRUGS WHICH FIGHT THE CAUSES ARE URGENTLY NEEDED

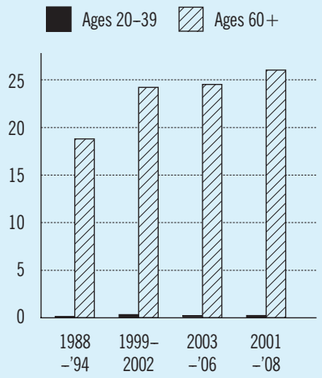
MORE THAN 500 MILLION CKD PATIENTS WORLDWIDE



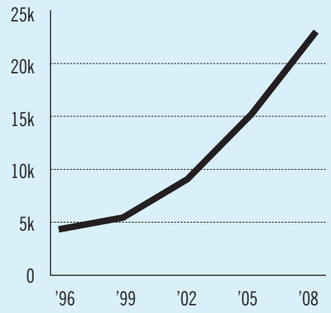
NUMBER OF PATIENTS ENROLLED IN THE USA ESRD MEDICARE FUNDED PROGRAM



PERCENT OF POPULATION IN THE USA WITH STAGE 3 CKD BY AGE GROUP



USA AKI INCIDENCE



FACTS & FIGURES

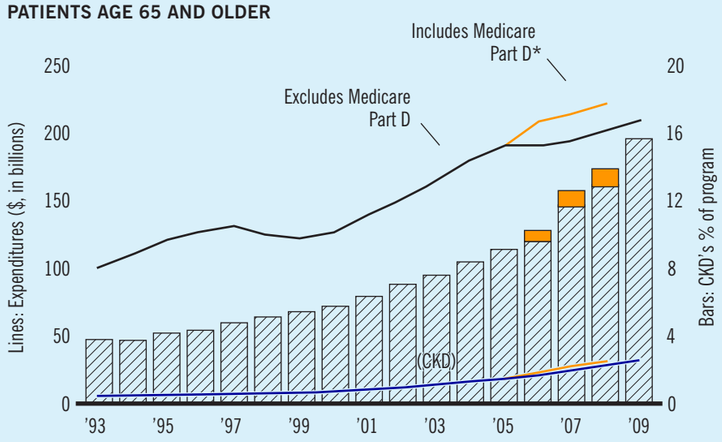
Tremendous public health burden

Mortality

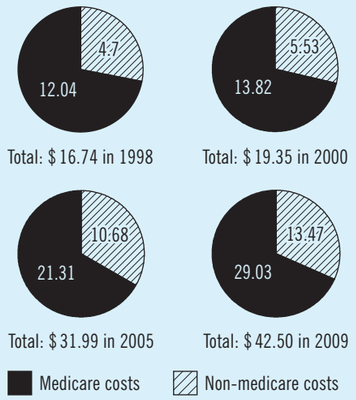
Altough mortality rates have decreased over the last decade, they still remain on a very high level. According to the United States Renal Data System, 147 per 1,000 Medicare CKD patients age 66 and older died in 2009. Only 50% of dialysis patients and 82% of those who receive a preemptive transplant are still alive three years after the start of ESRD therapy. The mortality rate in 2009 for ESRD and dialysis patients 65 and older was 274 and 313 per 1,000 respectively. The Renal Association states that patients who present with uncomplicated AKI have a mortality rate of up to 10%, in patients presenting with AKI and multiorgan failure the rate increases to over 50%, and rises further to as high as 80% if renal replacement therapy is required.

Costs

PATIENTS AGE 65 AND OLDER



USA ESRD COSTS IN BILLION



In 1993, costs for Medicare patients with CKD accounted for 3.8 % of overall Medicare expenditures. In the US, cost for Medicare patients with CKD reached $ 34 billion and accounted for nearly 16% of total Medicare dollars in 2009.

England spent £ 1.45 billion for CDK stage 3–5 patients in 2010. Annual costs for dialysis and transplantation amount to approx. € 2.5 billion in Germany.

Insufficient and very limited treatment options

Current treatment options primarily focus on the control of blood glucose levels and high blood pressure and include standard diabetes therapies, anti-hypertensive agents as well as dieting.

In end-stage kidney disease, kidney functions can be replaced only by dialysis or by kidney transplantation. The planning for dialysis and transplantation is usually started in Stage 4 of chronic kidney disease.

Treatment of AKI is focused on removing the cause of the kidney failure. If the patient's kidneys do not respond to treatment, and adequate kidney function does not return, they will need to undergo dialysis.

TECHNOLOGY OVERVIEW

What we can deliver

A BROAD RANGE OF TARGET IDENTIFICATION APPROACHES

- Acute kidney injury (ischemia-reperfusion injury model): High resolution deep sequencing
- CKD/Kidney fibrosis (unilateral ureteral obstruction (UUO) model): High resolution deep sequencing
- Kidney regeneration (embryonic vs adult kidney): Deep sequencing
- Podocyte apoptosis & (de)differentiation: Cellular screening
- Pericyte to myofribroblast transdifferentiation: Cellular screening

Primary cells / ex vivo (rat & Goettingen minipig)
- Pericytes/fibroblasts
- Tubular epithelial cells
- Glomeruli
- Whole kidney (in situ, WB, PAS, IHC, podocyte quantification)

Mouse kidney biobank (disease models)
- IRI (acute kidney injury): 0h, 4h & 24h
- UUO (chronic kidney disease/fibrosis): d0, d3, d5, d10
- BTBRobob vs wt: (diabetic nephropathy): 4/8/12/16 weeks
- Akita/FVBN vs wt: (diabetic nephropathy): 6/9/16/20 weeks

TARGET VALIDATION AND COMPOUND PROFILING IN RELEVANT *IN VITRO / EX VIVO* MODELS

Cell lines
- Human immortalized primary podocytes
  - Palmitate/high glucose-induced apoptosis
  - PAN-induced apoptosis
  - H_2O_2-induced apoptosis
  - Nephrin-reporter assay (differentiation)
- Rat pericyte-like cell line
  - Pericyte to myofibroblast transdifferentiation (HCS; α-SMA)
  - H_2O_2-induced apoptosis

TARGET VALIDATION AND COMPOUND PROFILING IN RELEVANT *IN VIVO* MODELS

Surgery mouse models (AKI & CKD)
- IRI, ischemia-reperfusion injury
- UUO, unilateral ureteral obstruction
- Unilateral nephrectomy

Genetic mouse models (diabetic nephropathy)
- Db/db
- BTBR ob/ob
- Ins2/Akita

Food/chemical-induced mouse models (diabetic nephropathy)
- STZ/Alloxan induced diabetes
- High fat diet induced diabetes

Urine analysis
- Metabolic cages for urine sampling
- Creatinine & FITC-inulin
- Albumin
- Glomerular filtration rate (GFR)
- Albumin-Creatinine-Ratio (ACR)

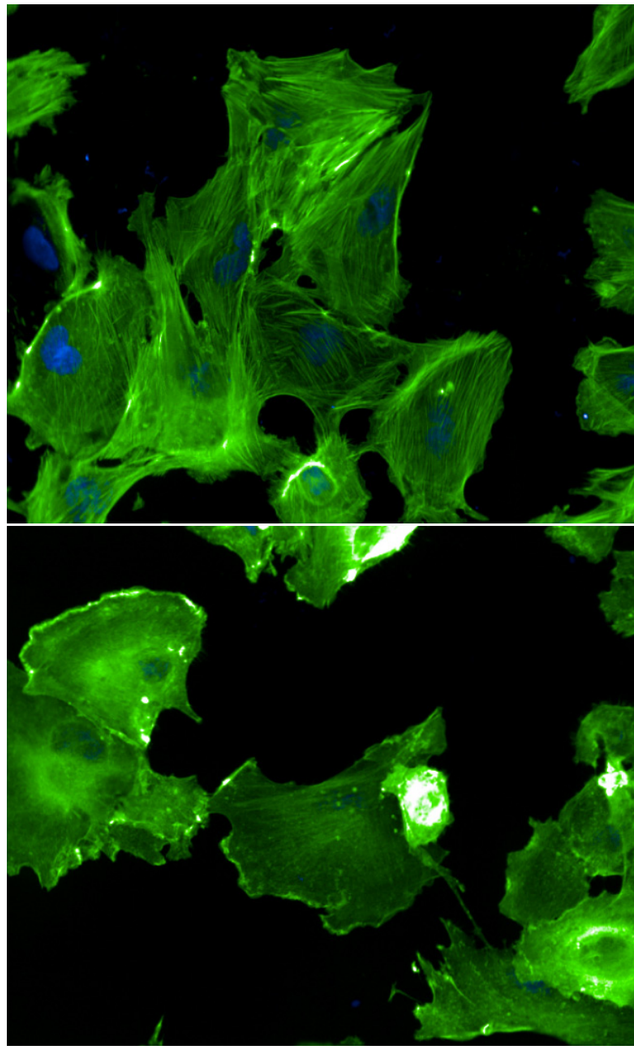
Plasma analysis
- Several hormone plasma levels
- Clinical blood chemistry
- Creatinine & FITC-inulin
- Blood urea nitrogen (BUN)
- Glomerular filtration rate (GFR)
- Disease progression and marker analysis

TRANSLATIONAL TOOLS

Human kidney biobank
- Acute kidney injury samples
- Samples of various degree of kidney fibrosis

Human immortalized primary podocytes
- Apoptosis, actin rearrangement
- (De)differentiation approach

Podocyte actin cytoskeleton: Injured vs control



DR UWE ANDAG

SHORT SUMMARY OF SCIENTIFIC CAREER

Dr Uwe Andag received his PhD in biochemistry from the University of Hannover and the Max-Planck-Institute for Biophysical Chemistry in Goettingen, focusing on biochemical analysis of vesicular trafficking and protein-protein interaction that mediate the fusion of vesicles with target membranes.

In 2002, Uwe joined DeveloGen AG in Goettingen, Germany, as a research scientist focusing on target ID and *in vitro* validation as part of the metabolic disease and beta cell regeneration pipeline. He took over leadership of the *In Vitro Pharmacology* group within DeveloGen shortly after being responsible for more than 20 scientists.

From 2006 to 2010 he joined Sartorius Stedim Biotech where he worked in the R&D department on diagnostic membrane and protein microarray chip development. He then re-joined Evotec Goettingen as the project leader of a newly formed collaboration with AstraZeneca/MedImmune focusing on the development of EVT 770 as well as target discovery and validation in the beta cell regeneration field. More recently, Uwe took over responsibility for the Cure*Nephron* collaboration with Dr Andrew McMahon (Harvard/USC) and Dr Benjamin Humphreys (Harvard University) in the field of kidney disease.

1. **One novel key field of Evotec is kidney disease. What is so special about Evotec's scientific approach?**

Current treatment options for kidney disease are primarily targeting symptoms rather than addressing the underlying causes. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) are used most often for blood pressure control, which can slow further kidney damage. In addition, supplements that support kidney function or generally improve blood parameters are often given to patients. In spite of this, however, many patients experience a progressive loss of kidney function, ultimately requiring dialysis or transplantation. Thus, there is a clear unmet need for disease modifying therapies in this field.

In order to tackle this enormous challenge we will focus on the key cell types of the kidney, as well as certain disease models and technologies for target identification. Our aim is to use the platforms we have developed in-house to identify agents that attenuate or halt the progression of kidney disease, or even reverse it. Our primary goal is to select targets of highest biological and disease relevance; the therapeutic principle is very much of secondary importance as Evotec is equipped to pursue small molecules as well as biologicals be it secreted factors, antibodies or peptides.

In addition, we intend to identify and develop novel and more sensitive biomarkers that allow us to stratify patient population more clearly in terms of which parts of the kidney and cell types are primarily affected as well as allow us to track progression of the disease at higher resolution.

2. **What can you contribute to finding new drugs in this highly interesting field of regenerative medicine?**

It is my primary responsibility to help define the most important projects of the Cure*Nephron* clearly, make sure that research plans are implanted and coordinated effectively across sites and motivate the team across borders and even continents to outperform and overachieve on our goals. Evotec has assembled a team of scientists that is very strong in pre-clinical drug discovery covering target identification, target validation as well as hit-to-lead programs.

In addition, the initiation and successful progress of programs in the field of regenerative medicine, especially beta cell regeneration, has led to the generation of a broad knowledge in developmental biology, genetics and pathway analysis. This includes establishing and running a range of key *in vitro* and *in vivo* models for individual disease areas.

Combining this expertise with excellent assay development, capacities to perform high throughput screens (HTS) & high content screens (HCS) and medicinal chemistry capabilities enables us, at Evotec, to efficiently develop novel therapeutic options in the field of kidney disease.

Furthermore, the collaboration and frequent exchange of knowledge with two scientific leaders of the kidney disease area, Benjamin Humphreys and Andrew McMahon, will allow us to be confident in the route we take, as we will have the benefit of clinical input. It's a very exciting task for me to oversee and coordinate the work of this multiple-sites driven Cure*Nephron* program in order to generate significant and appreciated progress in the development of drugs for treatment of patients suffering from kidney disease.

3. **How will your collaboration with the Harvard/USC/Brigham and Women's Hospital operate?**

It is a great honour and enormous pleasure to work with highly accomplished scientists and clinicians as Andy and Ben. They are truly world-leading experts in their field and represent a never ending fountain of knowledge and deep understanding of kidney biology, physiology and disease etc. Our collaboration with Harvard/USC/Brigham and Women's Hospital is following a very similar route to the one we have taken with the Cure*Beta* program, a proven model of successful collaboration between industry and academia. Like Cure*Beta*, the structure of the Cure*Nephron* program will be based on pooling our resources with resources of scientific academic leaders in the field of kidney disease.

We will share our discovery and development efforts allowing us to establish a comprehensive and unbiased approach for target identification and validation in various fields of kidney disease, with each party contributing their specific expertise, technologies, and capabilities. This will include high resolution expression analysis in several relevant disease models, screening for protective and regulatory factors in embryonic kidneys (regenerative approach) as well as HTS on key cell types of the kidney to identify novel small molecule targets. These models have already yielded several candidate targets as well as example compound classes that are able to protect kidney cells against certain injuries. Small molecule screening on selected kidney cells will take advantage of Evotec's leading HCS capabilities, the Opera™.

The goal of the Cure*Nephron* program is to build a strong scientific team in the field of kidney disease and together pursue a systematic approach based on top class science and technology that, in contrast to current therapy, will lead to discovery of disease modifying drugs. In order to achieve this, in addition to our external partners, the team consists of key scientists from different areas within Evotec.

The focus of the collaboration will be the discovery of innovative drugs that target protection and/or regeneration of key cell types of the kidney by a range of mechanisms, a very challenging, but also exciting mission.

evotec

1) INTEGRATED SERVICES

- Target-to-IND integrated platform
- Hit identification
- Medicinal chemistry
- Structural biology and computational chemistry
- *In vitro* and *in vivo* biology
- ADMET

2) ASSAY DEVELOPMENT AND SCREENING

- Assay development
- High throughput screening
- High content screening
- NMR and label-free screening
- Secondary screening and profiling
- Screening library
- Ion Channel drug discovery
- GPCR drug discovery

3) FRAGMENT-BASED DRUG DISCOVERY

- Proprietary high throughput fragment screening platform
- Biochemical, NMR and SPR screening technologies
- Fragment library
- Structural biology
- Computational chemistry
- Fragment optimisation

4) MEDICINAL CHEMISTRY AND EARLY DEVELOPMENT

- Medicinal chemistry
- Computational chemistry
- Structural biology
- Compound library synthesis
- Chemistry and early development support

5) ADMET

- *In vitro, in vivo* and *in silico*
- Safety pharmacology
- Metabolite detection

6) CELLULAR TARGET PROFILING AND PHOSPHOPROTEOMIC

- Cellular target profiling
- KinAffinity
- PhosphoScout
- Epigenetics target profiling
- Epigenomics analyses
- Quantitative proteomics analyses

7) COMPOUND MANAGEMENT

- Compound identification, selection, procurement
- High throughput compound analysis
- Multi-format plating and reformatting
- Storage and processing
- Disaster recovery and business continuity