evotec

DRUG DISCOVERY UPDATES #07

DDup

KIDNEY DISEASES 2.0

Next generation kidney drug discovery

Including:

- *NURTuRE & NEPLEX*
- *NephTec*

evotec — DDup

What's inside this issue?

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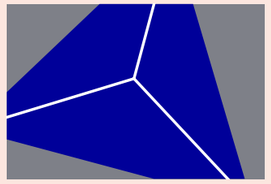

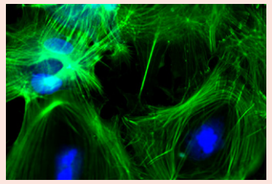

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DEAR FRIENDS
OF EVOTEC

A message from Evotec CEO
Dr Werner Lanthaler

Welcome to this seventh issue of DDup, an Evotec publication providing you with more insights into the company and our research programmes. This edition is dedicated to our highly innovative initiatives in the kidney space where Evotec has positioned itself as a key player since the Cure*Nephron* initiative with Harvard University initiated in 2012. With NURTuRE and NEPLEX we are building highly productive collaborations between Academia and Pharma once again.

Kidney diseases remain an area of high unmet medical need and an enormous burden to healthcare systems, with more than 600 million patients affected by chronic kidney disease (CKD) globally.

Within NURTuRE and NEPLEX we are collaborating with experienced and well-known academic experts and laboratories to lay the foundation for new and more efficient drugs, which are desperately needed to fight this tremendous health threat.

To fully explore the potential of our kidney initiatives we created NephTec, a virtual company within Evotec. This enables unrestricted access to our leading drug discovery infrastructures and proprietary pre-clinical databases, in order to accelerate the search for novel targets and pathways together with our partners.

NephTec, a unique approach, will develop highly innovative patient-centric medication for treatment of kidney diseases. This will be achieved by the systematic, comprehensive and unbiased combination of target identification through phenotypic screens in human systems, an in-depth human systems biology approach (NURTuRE) and patient-based disease models based on human iPSC-derived podocytes (NEPLEX).

We want to especially thank our colleagues and collaborators in Bristol, Cambridge, Bergamo, Birmingham, Geneva, Nottingham and last but not least Kidney Research UK, the coordinator of NURTuRE. This amazing collaborative approach and spirit are a prerequisite to achieve the crucial advances needed to address the burden of CKD, to treat the causes and not only the symptoms of the disease.

Thank you for reading this issue of DDup, for your thoughts, input and hopefully also the cooperation in this field with us. I hope you find this latest edition of DDup of particular interest and as always please do not hesitate to contact us.

Yours sincerely,
for the management of Evotec
Werner Lanthaler,
CEO of Evotec AG

FACTS & FIGURES

CHAPTER 01

Chronic kidney disease (CKD)

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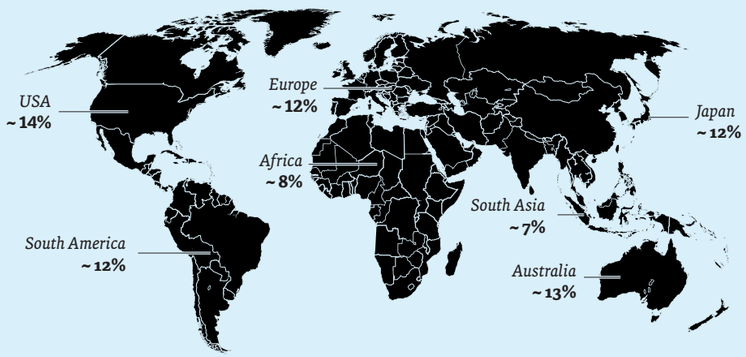
Chronic kidney disease (CKD) comprises a set of heterogeneous disorders that negatively affect the function and structure of the kidney. CKD is characterised by a progressive loss of function and can lead to end-stage renal disease (ESRD), necessitating dialysis or transplantation. The most common causes of CKD are diabetes and hypertension. In cases where damage to the glomeruli allow abnormally large amounts of protein to leak into the urine (proteinuria) patients can develop so called nephrotic syndrome (NS), which over time can also lead to CKD.

MORE THAN 600 MILLION CKD PATIENTS WORLDWIDE



- CKD remains an area of high unmet medical need and no curative or disease modifying therapies are currently available
- CKD is a global epidemic, signified through high prevalence and cost of management
- Disease complexity and failures in drug development call for novel multi-disciplinary approaches and collaborations

CKD IS A SILENT EPIDEMIC

CKD prevalence has increased to global epidemic levels. Approx. 30% of all people in the general population are at increased risk of CKD.

The National Kidney Foundation reports that 1 in 10 people worldwide have CKD. The Center for Disease Control reports 1 in 7 people in the US are afflicted. Of the >600 million people globally affected by CKD, it is estimated that 9 in 10 are unaware of their condition. For this reason, kidney disease is often referred to as a "silent disease".

- An estimated 40 million people in the US and >60 million in Europe have CKD
- Out of the patients that have strongly reduced kidney function but are not on dialysis, 48% are not aware of having kidney disease
- Most (96%) people with mildly reduced kidney function or kidney damage are not aware of having CKD
- More than 660,000 Americans are treated for kidney failure, also called ESRD. Of these, 468,000 are dialysis patients and more than 193,000 have a functioning kidney transplant

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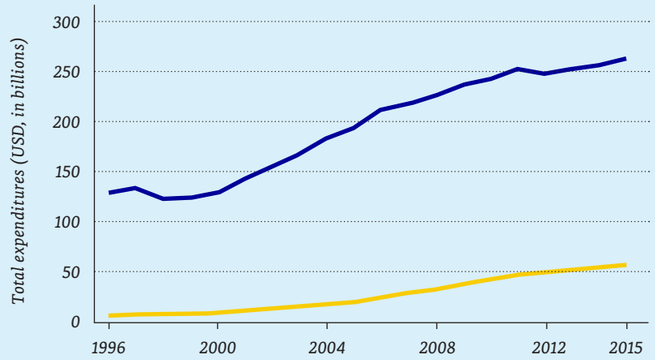
CKD HAS HIGH ALL CAUSE MORTALITY RATES

According to the 2015 Global Burden of Disease Study, kidney disease was the 12th most common cause of death, accounting for 1.1 million deaths worldwide. Overall CKD mortality has increased by 31.7% over the last 10 years, making it one of the fastest rising major causes of death, alongside diabetes and dementia. In the same study, CKD ranked as the 17th leading cause globally for loss of years of life, an 18.4% increase since 2005, and the third largest increase of any major cause of death. According to the United States Renal Data System, in 2014, adjusted mortality rates for ESRD, dialysis, and transplant patients, were 136, 166, and 30, per 1,000 patient-years, respectively.



Overall Medicare fee-for-service spending for general Medicare population aged 65 and older and for those with CKD, 1996–2015

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CKD IS COSTLY TO HEALTHCARE SYSTEMS AND DRUG DEVELOPERS

- Medicare spending for all patients who had CKD (11% of total) exceeded $ 64 billion in 2015
- When adding an extra $ 34 billion of ESRD costs healthcare expenditures for persons with ESRD, total Medicare spending on both CKD and ESRD was over $ 98 billion
- According to the European Renal Association, about 60 million Europeans have lost some of their kidney function and are at high risk of becoming dependent on renal replacement therapies (dialysis or transplantation)
- Around 350,000 people are on dialysis in the EU alone, which translates into a € 15 billion expenditure for healthcare systems across the EU
- In the past 10 years, only a single drug was approved to slow kidney function decline: Tolvaptan for polycystic kidney disease.
- In a 2017 review of important CKD trials, Pollock et al. showed that 25% of trials for CKD drugs were terminated due to lack of efficacy or safety concerns.

Nephrotic Syndrome (NS)

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NS is characterised by glomerular damage that causes abnormally large amounts of protein to leak into the urine (proteinuria) and over time can also lead to CKD.

- NS in adults is quite rare, the incidence of the condition is approximately 3 cases per 100,000 per year
- NS is one of the most common chronic renal diseases in children. It has an incidence of 2 to 7 per 100,000 population and a prevalence of 16 per 100,000 population, well above the 1 per 1 million incidence of chronic renal failure in children
- NS is an important factor in CKD responsible for 12% of kidney failure in adults and 20% in children

CHAPTER 02

NURTURE CONSORTIUM

A UNIQUE PUBLIC PRIVATE PARTNERSHIP IN KIDNEY DISEASE RESEARCH

Written by members of Kidney Research UK

The UK Renal Research Strategy published in 2016, is a national blueprint of renal research themes and priorities, and it recognised the need for a kidney biobank to provide a resource for fundamental and translational renal research. Under the strategic oversight and management of Kidney Research UK the leading renal research charity in the UK, the National Unified Renal Translational Research Enterprise (NURTuRE) was developed through an innovative collaboration between academic investigators, industry partners and the charity. This collaboration will help to maximise the scientific value and ensure delivery of this high-quality resource.

NURTuRE, is the first kidney biobank for England, Scotland and Wales and it is being jointly delivered through the University of Bristol, led by Moin Saleem, Professor of paediatric renal medicine, and the University of Nottingham, led by Maarten Taal, Professor of medicine. The vision and passion of both professors have been a huge factor in bringing this academic-led cohort and sample collection to fruition. The overall aim is to use multiple approaches to develop novel research and methods to stratify patients and ultimately develop new treatments focussed on high-risk patients, while sparing potentially ineffective interventions to those at low risk.

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HOW DOES NURTURE WORK?

Running over a five-year period, and operating to a standardised protocol, 14 NHS Trusts will collect samples including plasma, serum, urine, DNA and tissue, as well as clinical data from at least 800 patients with idiopathic nephrotic syndrome (INS) and 3,000 patients with stage 3–5 CKD. Some of the most experienced renal units in the UK have been selected to participate in the study and funding is provided for each site to deliver data of the highest standard, with a multidisciplinary team comprising dedicated research nurses, research practitioners, research assistants, laboratory technicians, and doctors.

The UK Renal Registry provides a single data portal linked to tissue imaging, and a combined dataset and web-based database with up to 15 years of tagging.

Elaine Davies, Director of Research Operations at Kidney Research UK says:

'The anonymised data contained within the NURTuRE biobank has the potential to unlock answers to some of the biggest questions about CKD and nephrotic syndrome (NS). The cross-analysis of biological samples alongside clinical data is immensely powerful and unique to the UK. It will enable us to develop new biomarkers to help identify patients who will benefit from better, earlier diagnosis, and develop person-specific new treatments, leading to better health outcomes.'

The biomarker analysis is taking place at the University of Geneva, with histopathological (tissue) storage and analysis at the University of Birmingham, and biofluid storage at the UK national biobank in Milton Keynes.

The NURTuRE collaborators will have access to the samples and associated data when they are available. Access to the data and biosamples will be available to other UK and international investigators from 2019 by application to an independent Strategic Oversight and Access Committee. A unique aspect of the project is that anyone who accesses the samples, agrees to share their analysis after publication, thereby further enriching the resource and helping the progress of renal research.

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THE GOVERNANCE ROLE OF KIDNEY RESEARCH UK

Kidney Research UK's role is to both fund and oversee the governance of the project, to ensure that the responsibilities of the various parties are met. During the extensive period of project set-up the charity undertook due diligence to ensure that the contractual arrangements, staff and processes at participating sites and institutions were of the highest standard for this project, and set-up under any relevant legal/regulatory frameworks.

The study design and protocols are robust, established through both peer and ethical review and permissions tested by patients. The project is built on the funding available across the partnership, and the contracted partners will be held to account by the charity. Dedicated project management support and infrastructures are also in place to ensure clear communications and robust governance around the overall management of the project.

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PATIENT INVOLVEMENT

Patient groups (in particular, the Nephrotic Syndrome Trust and Kidney Research UK's Lay Advisory Committee) have been involved at all stages in the development of NURTuRE. Patients have also had direct input into the study documentation, including patient information sheets and consent forms.

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THE IMPORTANCE OF AN INDUSTRY PARTNERSHIP

Funding for the development of the NURTuRE biorepository comes from Evotec, UCB, AbbVie Inc, Retrophin, and Kidney Research UK with Evotec playing a pivotal role in spearheading the project. Additional funding from the UK's Medical Research Council has been obtained to support genomic and proteomic analyses.

The UK Government's Life Sciences Industrial Strategy and Sector Deal emphasise the importance of industry in driving research and development in the UK, especially in the light of Brexit. Kidney Research UK has brought together a wide collaboration of academia and industry in developing NURTuRE with industry bringing vital investment into the initiative in order to develop and accelerate patient benefit through future drug discovery. There has been a historic lack of investment in drug development in the renal field and how kidney disease is diagnosed in blood. We do not currently have the biological tools to identify patients whose lives are at greatest risk of the disease, to dramatically change their disease outcomes. The NURTuRE biobank will lead to the type of stratified medicine which has the potential to focus efforts to achieve maximum treatment value and save lives, with the added benefit of driving down NHS costs through much more effective targeting of patients most at risk from disease.

Historically, when pharmaceutical companies undertook research they did not always publish results, therefore restricting our collective knowledge of kidney disease and potential treatments. Within NURTuRE however, industry participants are required to share their results, which will serve to accelerate knowledge, understanding and research as a whole.

The overall vision for NURTuRE is that it will provide a springboard to accelerate research in all areas of renal disease, bring further industry investment into the UK, and have a particular focus on methods for improved patient stratification prior to treatment. Plans are already in place to establish similar studies with national biorepositories using the NURTuRE model in other kidney disease areas.

CHAPTER 03

WORLD-CLASS LEADERS

IN KIDNEY DISEASE RESEARCH

Dr Maarten Taal

Professor of Medicine

Maarten graduated from the University of Cape Town Medical School, South Africa, in 1987.

He was appointed Professor of Medicine in the Division of Medical Sciences and Graduate Entry Medicine, University on Nottingham in April 2014, where he leads the Centre for Kidney Research and Innovation. His current research interests include Chronic Kidney Disease Progression, Diabetic Nephropathy, Renal Osteodystrophy and Cardiovascular Disease in CKD patients. He has a career-long interest in CKD, to slow its progression and abrogate the associated risks and co-authored the Renal Association's Clinical Practice Guidelines for CKD. He serves as an Editor for "Brenner and Rector's The Kidney", Section Editor for "Current Opinion in Nephrology and Hypertension" and Academic Editor for "PLOS Medicine". He is Chair of the UK Kidney Research Consortium CKD Clinical Study Group and current President of the British Renal Society.

Dr Moin Saleem

Professor of Paediatric Renal Medicine

Moin graduated from the University of London, GB in 1986 and is currently serving as Head of Bristol Renal. His objective is to understand the fundamental mechanisms of kidney filtration, in order to understand the basis of glomerular disease, the major cause of kidney disease worldwide. The glomerulus is the elemental unit of renal filtration, and the glomerular podocyte is the cell primarily responsible for this complex function. Moin's laboratory (currently >40 researchers) has developed the world gold standard glomerular cell lines, and undertakes research across the spectrum from basic cell and animal biology/physiology to national/international patient cohorts in rare disease including genome sequencing and systems biology approaches. Moin is Chair of the Renal Association Research Committee, and recent Chair of the Paediatric Nephrology national Clinical Studies Group.

5 MINUTES WITH

DR MOIN SALEEM AND DR MAARTEN TAAL ON THE IMPORTANCE OF NURTURE

Cord Dohrmann, CSO of Evotec ("Cord"): Moin, Maarten, why is the NURTuRE study so important?

Moin: In order for industry to discover and translate new therapies into clinical use, a huge unmet need is access to well defined patient cohorts, crucially to include high-quality bio sampling at different time points. The other major aspect is that of collaboration – between academics/clinicians and industry, with open sharing of results and ideas within a well-defined IP framework.

Maarten: CKD affects approximately 10% of the adult population worldwide and is associated with multiple adverse outcomes including end-stage renal disease and increased risk of acute kidney injury, cardiovascular events and all-cause mortality. However, CKD is clinically and pathologically heterogeneous and the majority of those affected are at relatively low risk of these outcomes. Current therapy is limited to control of blood pressure and immunosuppression in selected cases. There is therefore an urgent need for improved methods to stratify patients with CKD according to risk and to identify novel therapies. Lack of effective stratification is arguably the most important barrier to new drug development because of the requirement for large clinical trials with prolonged follow-up. The NURTuRE-CKD project aims to identify novel biomarkers to predict risk and response to therapy in CKD to act as a springboard for the development of new drugs, more efficient clinical trials and personalised medicine.

> **» Lack of effective stratification is arguably the most important barrier to new drug development«**

Cord: What is unique about NURTuRE/different from other initiatives?

Maarten: There are many unique features. NURTuRE is a unique partnership between a national research charity (Kidney Research UK), academic and industry investigators. We are utilising the strengths of the NHS as a unified healthcare system to recruit participants from multiple sites across the UK and create a network of centres that can be used to facilitate future trials. Additionally, we will benefit from the participation of the UK Renal Registry, which will collect routine clinical data from all participants and manage the database. Fluid bio-samples and surplus tissue from routine kidney biopsies are being collected to establish the first UK national renal biorepository of samples linked to detailed clinical data. Uniquely, we will make bio-samples and data available to external investigators via an independent access committee to ensure maximal scientific utilisation of this valuable resource. All investigators will contribute new data generated back into the database, creating a resource that continues to grow over time. Finally, Kidney Research UK is supporting the project by providing governance, communications and development support to ensure the long-term sustainability of the project.

Moin: NURTuRE is a novel industry-academic collaboration, built from the ground up by a consortium of academic leaders, clinicians, charities, patients and industry partners. It builds upon existing unique strengths in the UK renal environment, including a mature national

registry (the UK Renal Registry) embedded in the NHS, from which clinical and laboratory data can automatically be collected. In addition, we have a national renal Rare Disease Registry (RaDaR), and a national study of Nephrotic Syndrome (NS), both of which have been running for almost 10 years. Crucially, independent governance is provided by the national charity Kidney Research UK. The exciting development of NURTuRE is the ability to build upon these mature platforms, to establish within a short space of time, bespoke cohorts of patients with renal disease aligned with extensive biosample aliquots and core biomarker datasets. This will be unique in its scope, depth and quality.

Cord: What novel insight do you expect from the NURTuRE CKD cohort (Maarten) and the NS cohort (Moin)?

Moin: The NS cohort has already set out ambitious plans to redefine the disease according to mechanistic insights. We will generate genomic, transcriptomic and laboratory biomarker data (based on our novel podocyte-based assays), and apply machine learning approaches to discover novel disease signatures that correlate with clinical phenotypes. These will guide the introduction of new, mechanism-based therapies for this difficult disease. This part of the work has been funded by a large programme grant from the Medical Research Council.

> »... NURTuRE will generate important new insights into mechanisms of CKD progression and the other associated risks.«

Maarten: We expect that NURTuRE-CKD will generate important new insights into mechanisms of CKD progression and the other associated risks. Early work will focus on a large panel of serum and urine biomarkers but we have also planned projects to investigate the utility of proteomic and genomic approaches to stratification in CKD. Together we anticipate that these biomarkers will make it possible to characterise the dominant mechanism of CKD progression in individual patients to facilitate a personalised medicine approach to therapy.

Cord: When do you think clinical trials and ultimately the patients will benefit from NURTuRE?

Maarten: We hope that within a few years the NURTuRE project will generate novel methods to substantially improve risk stratification in CKD. This will facilitate more efficient clinical trials requiring fewer participants and shorter duration to accelerate new drug development. The fluid biomarker analysis linked to quantitative kidney biopsy analysis may also identify novel therapeutic targets.

Moin: I can envisage clinical trials emerging within the next 5 years. This can include existing therapies, to refine the relevant patient subgroups, as well as repurposing of new compounds or biologic therapies. New targets and compounds will also emerge from the work done within this programme.

Cord: Apart from funding, where do you see Evotec's key contribution?

Moin: Evotec has been a key founding partner from the inception of NURTuRE, to the detailed design and protocol writing, to the follow-on plans for sample and clinical

data analysis. The academic collaboration will continue to benefit patients through discovery and translation in a manner far more rapid and efficient than either partner could achieve alone.

Maarten: Evotec has been involved in NURTuRE from the early stages of development, contributing to the study design and development of rigorous standard operating procedures for specimen handling to ensure a high quality biorepository. Scientists from Evotec have played as key role in designing the panel of biomarkers to be analysed in serum and urine samples. Evotec will undertake its own analysis of bio-samples and has agreed to share all results and contribute the data generated back into the central NURTuRE database to make it available to other partners.

Cord: Are there plans to expand the programme?

Maarten: Yes, we hope that this initial project will be used as an exemplar for future studies to establish biorepositories with linked data in other important disease areas including diabetic kidney disease, acute kidney injury, specific glomerulopathies and renal transplantation. In addition, we envisage that the network of centres with well characterised participants will facilitate the conduct of future clinical trials.

> »The academic collaboration will continue to benefit patients [...] in a manner far more rapid and efficient than either partner could achieve alone.«

Moin: The vision of NURTuRE is to be sustainable for the long-term. Therefore, we are ambitious that now that the proof of concept and first cohorts are successful, new partnerships will rapidly emerge, sit within the NURTuRE infrastructure, and build a number of new and world leading cohorts in renal medicine and transplantation.

Cord: 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 25 years in biomedical research at leading academic institutions and in the biotech industry.

CHAPTER 04

NEPHTEC

INNOVATION IN KIDNEY DISEASE

Kidney disease is a worldwide public health problem with an estimated 10% of the global population affected by CKD. In the United States, the incidence and prevalence of kidney failure is constantly rising, with poor treatment outcomes and high costs. Current management approaches focus on supportive care of kidney disease complications like anemia, hyperparathyroidism or treating underlying diseases like diabetes or hypertension. Patients with CKD are 5 to 10 times more likely to develop cardiovascular disease and ultimately develop ESRD. Despite the significant unmet medical need, there are currently no preventive or disease-modifying therapies to treat these patients. In addition, few biotech and pharma companies work in this field, despite the large target patient population. What are the factors that contribute to this dynamic?

CHALLENGES FOR DRUG DISCOVERY AND DEVELOPMENT IN KIDNEY DISEASE

At the recent CKD summit in Boston, world-renowned experts in CKD discussed several main challenges facing kidney disease drug hunters:

Complex biology involving multiple cell types and multiple pathways along disease progression, early stages of which are asymptomatic and undiagnosed, thus potentially missing an opportunity window for disease modification.

Need for human genetics and genomics approaches to discover and validate disease-relevant targets, interactions and pathways.

Lack of robust translatable systems and pre-clinical models to address CKD's polygenic origin.

Need for more predictive and early biomarkers for patient stratification.

Need for partnerships between FDA and researchers and drug developers to establish regulatory frameworks and surrogate end points correlating with clinical outcomes to speed up drug development.

The above challenges contribute to complex, long and capital-intensive drug development processes riddled with clinical trial failures, and are deterring developers from investing in research in the kidney disease space.

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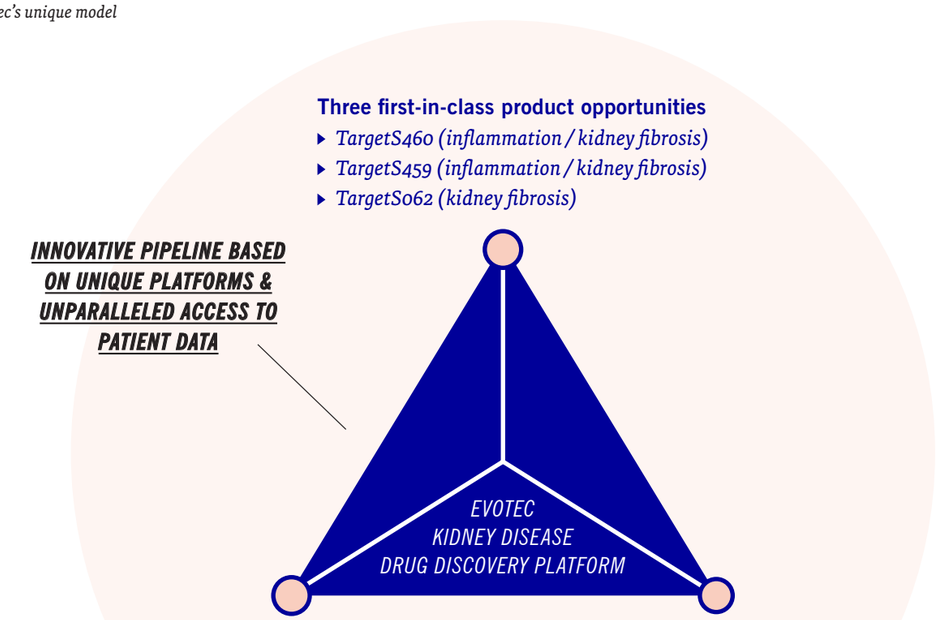
NEPHTEC – A UNIQUE PLATFORM AND BUSINESS MODEL TOWARDS ADDRESSING DRUG DISCOVERY AND DEVELOPMENT CHALLENGES

At Evotec, we have conceptualised NephTec to address several of the challenges above.

NephTec comprises several unique components:

NephTec's unique model



A set of first-in-class drug discovery projects

An unprecedented platform utilising

- Muti-omics capabilities to mine patient-derived insights from the NURTuRE Biobank for target and biomarker discovery and validation
- Relevant human kidney cells and induced pluripotent stem cells (iPSCs) for *in vitro* target identification and validation and drug development
- Nephron-on-a-chip (NEPLEX) – a 3D microfluidics chip aimed to replicate a functional human nephron

A virtual company model brings together world-class academic leaders spearheading NURTuRE, NEPLEX and Evotec's drug discovery and development experts, focused on translational work and patient-centric drug development with significant capital efficiency

NEPHTEC'S PIPELINE

Mechanism	Target	Target ID	Target Validation	H2L	LO	PDC
INFLAMMATION	*TargetS460*	*(In vivo POC achieved, PDC exp. 2019 & IND 2020)*				
	TargetS459					
	NURTuRE blood					
	NURTuRE biopsies					
FIBROSIS	*TargetS062*					
	NURTuRE biopsies					
PODOCYTE FUNCTION	*TargetS064*					
	Podocyte protection					
	Podocyte migration					
	NURTuRE biopsies					

INNOVATIVE PIPELINE WITH FIRST-IN-CLASS OPPORTUNITIES

NephTec is building a complete patient-centric approach to kidney disease. The currently growing pipeline focuses on complex disease mechanisms to address prevention and reversal of kidney cell injury by maintaining podocyte function, reducing inflammation and reversing fibrosis in order to enable the development of first-in-class therapies.

Our most advanced programme to date targeting inflammation, TargetS460 benefits from a proven link to CKD and cardiovascular disease. Upregulation of TargetS460 is involved in the development of kidney disease and human genetic data demonstrates links to elevated risk of cardiovascular disease and delayed graft function in kidney transplantation. Rodent models faithfully recapitulate the kidney contribution of the target and are currently used to select pre-clinical development candidates. The programme is on track to achieve a pre-clinical development candidate (PDC) in 2019 and an investigational new drug (IND) application in 2020.

TargetS459 is another promising biological target with a clear link to kidney inflammation and progression of diabetic kidney disease in patients. We have seen exciting efficacy in rodent models and are continuing to optimise our lead compounds.

TargetS062 is an orphan G-protein coupled receptor (GPCR) with a clear link to kidney fibrosis in several animal models and we are embarking on a first-in-class antibody approach.

Lastly, using/utilising several different approaches, we have identified Target064, an orphan GPCR, with strong evidence for a podocyte-protective role.

NephTec's access to multiple NURTuRE bioanalysis (whole blood, tissue, urine, plasma) alongside clinical data from thousands of CKD and NS patients is enabling us to build a robust platform for target and biomarker identification and validation based on disease-relevant molecular phenotypes. We are currently analysing whole blood samples with our multiomics platform. Discovery and validation of disease biomarkers will aid further refinement of patient populations during clinical development. Therefore, the only patients that would enter a clinical trial are those that will potentially benefit from the therapy, reducing unnecessary drug exposure to those that have an unfavourable biomarker profile. The molecular signatures from disease-relevant stages can also be utilised as pre-clinical and early clinical read-outs for target engagement providing much needed early efficacy signals. Further correlation of these biomarkers to clinical outcomes can provide a basis for collaboration with the regulatory agencies to establish disease relevant surrogate endpoints and improve the clinical development process.

Fuelled by multiple strategic collaborations, NephTec is poised to accelerate drug discovery and development and deliver novel therapeutic approaches, utilising a sophisticated pipeline and translational strategy to serve kidney disease patients worldwide.

Iva Toudjarska *received her PhD in Molecular Genetics from Medical University, Sofia and Bulgarian Academy of Sciences and her MBA in Corporate Entrepreneurship from F.W. Olin Graduate School of Business at Babson College. In 2003, after working with Dr David Bartel at the Whitehead institute for Biomedical research, MIT, Iva joined Alnylam Pharmaceuticals as one of the founding employees.*

During her nine-year tenure at Alnylam, as part of a multi-disciplinary team, she advanced several programmes to the clinic, most notably ALN-RSV (a virology programme) and ALN-VSP (an oncology programme). She led the evaluation and initiation of two hematology programmes ALN-AT3 for the treatment of hemophilia (currently in Phase III) and ALN-TMP for the treatment of beta-thalassemia.

In 2013, Iva transitioned into consulting. As part of Putnam Associates' team, she informed strategic insights and decisions pertaining to new product development, portfolio prioritisation, clinical development, and commercial opportunity assessments for large pharma clients. At Halloran Consulting, she led the development strategy practice, and working with investors, start-ups and mid-size biotech companies to create pre-clinical, clinical and regulatory strategy and plans.

Iva joined Evotec in 2018 as an SVP, BRIDGEs North America & NewCos, and is leveraging her experience as an entrepreneurial leader and partnering with nephropathy scientists to advance the aggressive platform and pipeline development goals.

CHAPTER 05

NEPLEX: 3 QUESTIONS

TO DR NELE SCHWARZ

SHORT SUMMARY OF SCIENTIFIC CAREER

Dr Nele Schwarz received her PhD in molecular endocrinology from Queen Mary College London, University of London, UK focusing on the role of endocrine receptors and accessory proteins in the adrenal gland.

In 2006, Nele joined the Institute of Ophthalmology, University College London, UK as a postdoc to investigate the at that point unknown function of an important protein in retinal disease. Nele helped unravel the function of several retinal disease proteins by developing iPSC-derived retina cell models and testing therapeutic approaches. Her proven track record in the iPSC field includes research papers in Human Molecular Genetics, Cell Stem Cell and the American Journal for Human Genetics.

In 2016, Nele was awarded a senior research fellowship from the eye charity Fight for Sight where she investigated the role of cilia proteins in retinal disease. Since joining Evotec Goettingen in 2017 as a research scientist, Nele has taken on the project lead for NEPLEX, as well as an iPSC based Retina project.

1 What is new about Evotec's scientific approach to understanding kidney disease?

In many research areas, *in vitro* cell models to study disease are becoming increasingly complex, as standard 2D cultures with one cell type do not replicate the intricacies of organs or tissues. Communication between different cell types, as well as biomechanical stimuli of the extracellular environment are important parameters for disease development and progression, as well as identification and evaluation of therapeutic compounds.

Therefore, *Ne*phron-on-a-chip with cellular and extracellular matrix com*plex*ity, or NEPLEX for short, is an exciting project that aims to replicate a functional human nephron in a 3D environment on a microfluidics chip. For this purpose, the design of the nephron chip recapitulates the functional architecture of two important parts of the nephron: the glomerulus, which is important for the filtration of blood and the proximal tubule, which plays a major role in the reabsorption of water, ions and other molecules. The glomerulus module will consist of iPSC-derived podocytes and a well-characterised glomerular endothelial cell line. For the proximal tubule part, we will culture proximal tubule epithelial cells on top of an extracellular matrix with an adjacent channel containing microvascular endothelial cells as a blood vessel substitute. The cells will be cultured under flow in a 3D environment to mimic the complexity of the human nephron, whilst providing controllable environmental conditions at the same time. This approach will enhance our understanding of the influence of microenvironments on differentiation, maintenance and function of nephron tissues.

2 How can the microfluidics chip contribute to disease understanding and aid the discovery of new compounds?

Translating observations made in rodents to human patient situations is a huge hurdle in many disease areas, in particular in the field of kidney diseases. Many clinical trials failed because molecules that showed impressive activity in animal models were not efficacious in patients. Consequently, academic institutes as well as industry recently increased their efforts to develop human organ-on-a-chip platforms, which can simulate human tissue- and organ-level physiology. The technology aims to recreate minimal functional units of an organ by adapting microfluidics-based bioreactors to mimic 3D architecture and flow conditions for cell and tissue culturing. The tailored complexity of the nephron-chip provides a novel tool to study induction and progression of human kidney injuries *ex vivo*, for example cell death caused by diabetic nephropathy. In addition, using iPSC-derived podocytes in the microfluidic chip allows the modelling of glomerular disease with iPSC from patients, replicating more accurately kidney disease development and progression. With a better understanding of these processes, we also have a higher chance of developing disease-relevant assays for drug screening to develop therapies for patients. In addition, the nephron-on-a-chip model will also be an important tool for cellular toxicity assays. This is especially relevant as nephrotoxicity accounts for 9% of clinical trial failures and the demand is high for *in vitro* models to screen drugs before they go into clinical trials to increase the chance for successful outcomes. With the recreation of functional tri-layered tissue-structures under flow in the nephron-on-a-chip device, we are getting a step closer to better understand complex organs *in vitro*, which will aid the discovery and development of therapeutic compounds for patients.

3 What will your collaboration with the NEPLEX consortium look like?

The NEPLEX consortium consists of scientists from three different universities in Europe. Dr Yan Yan Shery Huang is a Lecturer in Bioengineering at the University of Cambridge. Her research focusses on translational bioengineering research, especially 3D bioprinting/biomicrofabrication and developing organ-on-chips for high-throughput drug testing. Dr Huang and her group are currently developing the glomerular part of the microfluidic device.

Prof Moin Saleem from the University of Bristol is the Head of Bristol Renal, a world-renowned group researching glomerular disease. Moin has great expertise in all aspects of renal disease and made many key contributions in the field, such as discovering novel biological aspects of podocytes in health and disease. Moin and his team are providing and characterising renal cell types, as well as assisting Dr Huang with the development of the proximal tubule part of the chip.

Dr Christos Xinaris from the Mario Negri Institute, Bergamo, Italy, is a world leading researcher in kidney organoids and stem cells, and has successfully generated functional kidney organoids *in vivo*. Christos' expertise of iPSC differentiation into nephron cells provides valuable scientific insight that will drive the project forward.

Being able to unite all this expertise in one collaboration is a great achievement and important step for Evotec to advance our understanding of kidney disease. The strengths of the academic contributions in kidney disease, bioengineering and iSPC know-how cannot be emphasised enough.

We will share our discovery and development efforts allowing us to establish a comprehensive and unbiased approach to developing a unique nephron-on-a-chip device, with each party contributing their specific expertise, technologies, and capabilities. This will include in-depth characterisation of available cell lines and ECMs, as well as developing iPSC-derived podocytes that are as close to the *in vivo* situation as possible.

NURTURE: 3 QUESTIONS

CHAPTER 06

TO DR PHILIPP SKROBLIN

SHORT SUMMARY OF SCIENTIFIC CAREER

Dr Philipp Skroblin received his PhD in biochemistry from the Free University Berlin and the Max Delbrück Center for Molecular Medicine Berlin, where he analysed PKA and GSK3β signalling pathways.

From 2012 to 2016, Philipp was a postdoc in the Cardiovascular Proteomics group of Prof.Manuel Mayer at King's College London. In the context of cardiovascular and metabolic disease, he worked on the analysis of circulating biomarkers and microRNAs as well as on the proteomic and transcriptomic characterisation of vascular and hepatic tissues and cells. Apart from gaining an in-depth knowledge of omics techniques, especially in RNA biology and transcriptomics, Philipp acquired expertise in working with clinical samples and data from patient and population-based studies. His research has been published in major journals including Circulation Research, Diabetes and the Journal of Clinical Investigation.

In 2016, Philipp joined Evotec in Göttingen as a Research Scientist and project lead for NURTuRE. Since October 2017, Philipp has also been the Head of Expression Profiling at Evotec-Goettingen and supports transcriptomics, genotyping, and molecular biology in various projects.

1 What is so exciting about NURTuRE?

We have been involved from the very early planning phase, long before patient recruitment started. This ensures highest quality and consistency of samples that are being prepared according to industry standard. To my knowledge, there has never been such a large-scale blood transcriptome analysis in kidney disease. We will generate blood transcriptome data for up to 4,000 patients at 2 timepoints and matched kidney transcriptome data for approximately 20% of patients. This large-scale transcriptomic analysis of kidney disease patients by itself is already very special but pairing this with state-of-the-art clinical, biomarker and imaging data as well as a life-long follow-up of the patients makes it truly unique and powerful. We also have a number of world leaders in kidney disease research on board. Not only NURTuRE will benefit from this network, but for Evotec it is a perfect add-on to our existing databases and platforms in the field.

The involvement of patient representatives is absolutely fantastic and inspiring. It definitely helps to raise awareness, especially among potential participants. Moreover, it vividly reminds us researchers, from both academia and industry, of what we are all striving for: improving the lives of people who suffer from kidney disease.

From my own personal perspective, it is amazing to have the chance to work on a project like NURTuRE, which ticks all the boxes for me: a disease area with a high unmet medical need and close links to cardiovascular and metabolic disease, clinical data and samples, multi-omics analyses, a combination of basic research and drug discovery. And, having lived in London for four years, it is great to get the chance to travel to the UK on a regular basis.

2 Please explain your role and responsibilities within NURTuRE.

I coordinate all activities within Evotec that are related to NURTuRE. This comprises hiring and managing members of the NURTuRE team, being responsible for sample logistics, establishing assays and platforms (e.g. for automated RNA isolation), coordinating research activities internally and with external partners as well as setting up a database that integrates external data with our in-house results. I also represent Evotec's interests at NURTuRE Joint Steering Committee meetings and I critically review and contribute to any new plans and strategies that affect all partners of the consortium.

All of this is already a lot of work but the exciting (and very difficult) part of my job is just starting: literally mining the data, finding new targets or biomarkers, developing new concepts and strategies. With the help of our kidney and bioinformatics teams, I am convinced that we will learn a lot from NURTuRE.

3 Tell us about your vision – what do you expect from NURTuRE?

At this point, it is really hard to tell where the journey will take us. We are aiming to discover new therapeutic targets for kidney disease, which would be absolutely amazing. Coming from well-characterised large-scale human patient data, the relevance of targets in human disease can increase the success of translatability to patients compared to targets identified in animal models or cell culture models. But there is so much more we can discover and most of it will help to advance personalised medicine in the field of nephrology. This could involve the discovery of novel blood-, urine- or tissue-based biomarkers and their use to identify patients that are suitable for a specific treatment.

Diagnosis, prognosis and treatment of CKD is based mostly on well-established markers of kidney function (glomerular filtration rate) and damage (leakage of blood plasma proteins into urine) as well as histopathological assessment of kidney biopsies. However, this approach does not fully reflect the multitude of kidney disease subtypes and etiologies. We need to develop a molecular classification of kidney disease, which will open the door to new, tailored therapeutic approaches – and NURTuRE may be the key. When you think of oncology, the major breakthroughs in cancer treatment in the past 20 years were due to identifying molecular targets and hitting these in the right patient subpopulation. We need something similar for kidney disease; there will be no one-size-fits-all solution.

LONG-TERM VISION
IN KIDNEY DISEASE

CHAPTER 07

Dr Uwe Andag

With the expansion from diabetes and metabolic diseases into the area of diabetic complications, in particular kidney diseases in 2012, Evotec made a significant strategic investment. The Cure*Nephron* collaboration with Ben Humphreys and Andy McMahon from Harvard University was successful to establish and validate a unique drug discovery platform in the field of kidney disease. And as a result Evotec was successful to achieve three significant Pharma partnerships. – with AstraZeneca initiated in 2013, with Pfizer initiated in 2015, and with Bayer initiated in 2016. A cornerstone within Evotec has been Dr Uwe Andag, who is instrumental in building the above-mentioned alliances and building the kidney disease platform.

Uwe is leading a team of drug discovery and development experts and collaborators in the nephrology field and established NURTuRE, a patient-derived biobank, high-content screening platforms, *ex vivo* models as well as key *in vitro* and *in vivo* models as robust and reproducible platforms to enable development of novel therapeutics.

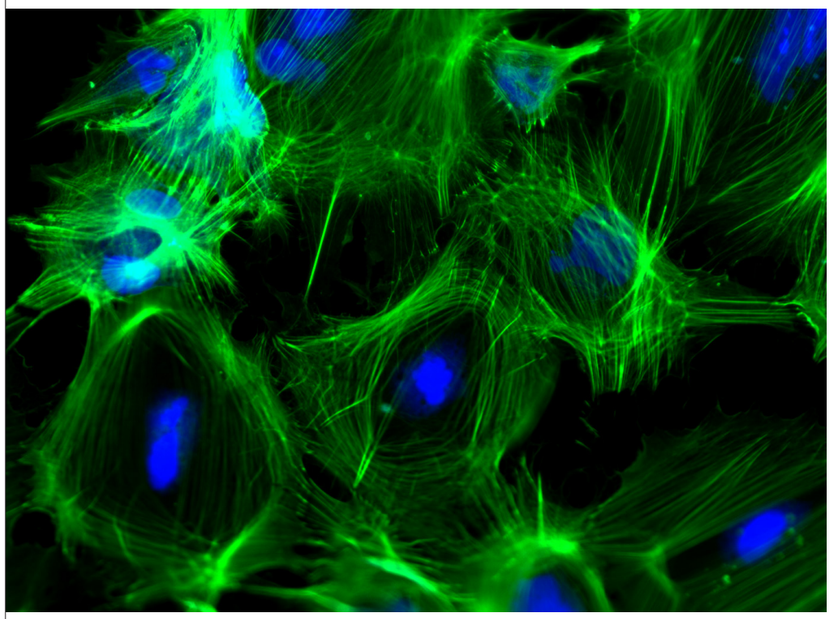
Evotec continues to invest in kidney research and discovery efforts and is well positioned to address the challenges facing the CKD community.

Complex disease biology and the need for genetics and genomics approaches to kidney disease are main hurdles that NURTuRE biobank coupled with our powerful proprietary PanHunter bioinformatics platform for multi-omics data mining can address. Being able to define CKD patient subpopulation based on molecular profiling and identifying disease relevant targets will strengthen translational efforts. This patient-centric approach will discover new mechanisms of disease that will enable the development of first-in-class novel therapies.

Now, with very promising recent data from human trials with SGLT2 inhibitors, the community has realised that it is possible to slow down the disease progression of CKD, which is re-igniting interest in kidney disease drug development. Even though these advancements are encouraging, it is important to understand that the observation comes from retrospective analyses of a cardiovascular outcome trial in Type 2 Diabetes Mellitus patients (EMPA-REG outcome) instead of a prospective CKD / DKD trial.

Thus, in order to enable positive clinical CKD trials in the future it is essential to generate a significant translational package during early drug discovery. Well validated targets addressing specific patient populations and the ability to identify sensitive predictive and prognostic biomarkers to stratify and guide clinical trials with the future drug candidates will be paramount. With NephTec's platform, Evotec is following this human-centric target identification and validation approach. On the basis of already existing pre-clinical in-house databases, platforms and experience, NURTuRE and NEPLEX are adding highly innovative novel approaches that will enable drug discovery based on human data and *ex-vivo* functional organ-on-a-chip systems. The use of a nephron-on-a-chip system that includes iPSC-derived cells will change the way we do drug discovery in the kidney disease field. It will not only improve the drug discovery process by eliminating potentially nephrotoxic compounds early on in the drug development process thus bringing safer therapies to patients faster and reducing the cost of failure. Having relevant cell and tissue markers in a functional glomerular flow system enabled for high-throughput analyses will also enable improved understanding of the mechanism of action of kidney therapeutics and allow for improved translational efforts.

Our long-term vision in kidney disease starts with the patient and ends with the patient. Through enabling patient-driven research and drug discovery and development via NephTec and utilising NURTuRE and NEPLEX consortiums we are aiming to establish a unique CKD database, robust platforms for patient-driven target and biomarker identification and validation and innovative and robust platforms to improve the success rate of the drug development process creating unprecedented capabilities in the field of kidney disease.



iPSC-derived podocytes share the same characteristics of podocytes in vivo, for example actin stressfibers as indicated by Phalloidin staining (green), cell nuclei are stained with DAPI (blue).

For any further questions on Evotec's kidney disease projects, please contact:

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