TranCYST **Tran**slational research (training) in Poly**CYST**ic Kidney Disease

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is an inherited kidney disorder with a prevalence of more than 1:1000, characterized by the development of renal cysts, slowly progressing towards end-stage renal disease. ADPKD is often associated with extra-renal complications, which can be devastating. Current therapy is directed towards limiting the morbidity and mortality from these complications. There are presently no effective specific treatments targeting the renal cystic disease.

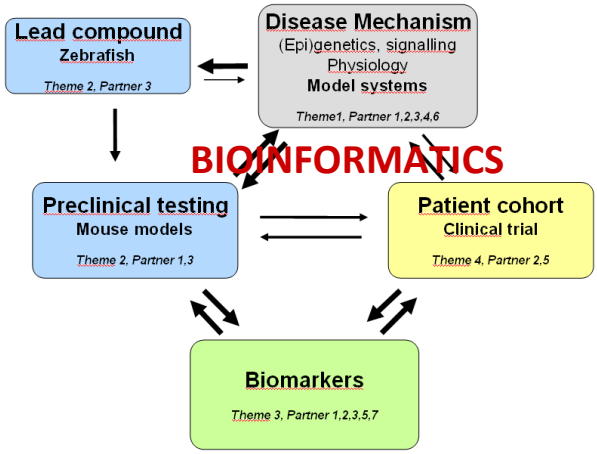
Translational research using innovative approaches from basic sciences to clinical applications are necessary to unravel the disease mechanism and to develop interventions, reliable monitoring of cystic renal disease growth and to slow down renal cystic disease progression. This translation is only possible when basic researchers work closely together with clinical researchers.

ADPKD offers a timely paradigm for multidisciplinary research ideal for clinical translation. Therefore, the aim of TranCYST is to offer a multidisciplinary research training program to young researchers to prepare them to be leading scientists who are able to translate fundamental research questions to the clinic and vice versa, to become the next generation of true translational multidisciplinary (PKD) researchers.

METHODOLOGICAL APPROACH

Building a research and training network

The TranCYST network is collaboration between partners with synergistic and complementary expertise centred around the translational research for Polycystic Kidney Disease. All participating academic partners already operate in multidisciplinary teams in their institutes and have an excellent track record in PKD research, varying from fundamental research to clinical studies.



Research focussing on:

Signal transduction, molecular pathology and/or physiology in cells, zebrafish and mouse models; compound screening, RNA-sequencing, proteomics, bioinformatics, molecular and tissue imaging approaches; molecular biomarkers and clinical trials for ADPKD.

Training:

The extensive research expertise as well as a broader expertise in PKD has been disseminated in the training courses for the young recruited TranCYST researchers. In addition, the associated partners (academic and industrial) add an additional level of complementarities to the training program with respect to extra-renal manifestations, research in commerce and entrepreneurship and ethical aspects from the patient's point of view.

Expected impact and use

Through our multidisciplinary approach we will get more insight into the biological and molecular mechanisms of cyst initiation and progression, in particular the contribution of planar cell polarity, FGF23 and endocytosis. We will identify microRNAs with a significant effect on gene expression and signal transduction. We will optimize and validate zebrafish and mouse models for preclinical drug screening and testing and will identify potential novel drug targets and treatment strategies. In addition, we will identify and implement new tools for early prediction and monitoring of (early) prediction of disease progression, i.e. molecular biomarkers and imaging strategies, in ongoing clinical trials

The TranCYST international training program is directed to train the next generation of young researchers in the field of multidisciplinary medical research of PKD.

TranCYST activities are organized through 4 work packages:

WP1: Management
WP2: Training
WP3: Research
- *Theme 1: Validation of preclinical disease models and new insights into disease mechanisms*
- *Theme 2: Drug screening and testing*
- *Theme 3: Biomarkers and imaging to develop progression markers and define novel endpoints for clinical trials*
- *Theme 4: Registry/biobanking and getting insights from ADPKD clinical trials*

WP4: Dissemination and Outreach

Major research objectives
- Clarify disease mechanisms using state-of-the art technologies in relevant preclinical disease models
- Identify new drug targets and test new treatment strategies
- Implement new tools for early prediction and monitoring of disease progression in ongoing clinical trials

Short term research objectives
- The characterization of cellular cystic changes
- Validation of preclinical disease model and preclinical drug testing
- Identification of new tools for early prediction and monitoring of cystic renal disease progression, as well as evaluating ongoing clinical trials

Bioinformatics and biosemantic approaches will support, enrich and connect the different themes.

RESEARCH ACTIVITIES AND RESULTS (WP3)

At various institutes different animal and cell models are being used to get insight into the disease mechanism and validated for preclinical testing, i.e. the Han:SPRD-Cy rats, several inducible Pkd1 knock-out mice, Hnf1B knock-out mice as well as a Pkd2 zebrafish model. In addition, cell cultures derived from these models are being studied.

We are getting insight into the role of Four-jointed in planar cell polarity in the context of Pkd1 disease progression and tissue damage/repair using single and double knock-out mice. A comprehensive mRNA and miRNA expression profile has been generated in Pkd1 mutant mice and cells. In addition, using publicly available expression profiling studies we have shown that the renal injury signature can be identified in different cystic models. The epigenetic mark on chromatin during mitosis, exerted by HNF1beta, is being unravelled as well as the mechanism of impaired receptor-mediated endocystosis at an early stage of the disease. Progress has also been made in generating and validation of the zebrafish model for PKD and a compound screening is in progress.

Kidney function, assessed by estimated glomerular filtration rare (eGFR) does not reflect fully the disease burden expressly at the early disease stage. Therefore, multiple urinary markers for tubular injury and their association with disease burden in ADPKD patients at early disease course have been measured. It can be concluded that the urinary biomarkers osmolality, UACR and KIM-1 have the property to assess disease state at early ADPKD stage. For an unbiased analysis a urinary peptidomic pattern in urine is being established. Using samples from patients a model with 52 peptides was developed and validated.

Total kidney volume, earlier identified as a potential imaging biomarker, is currently used for volume estimation in ADPKD on acquired CT or MR images. Image based methods for absolute and relative changes in total kidney, renal cyst and parenchymal volume are being implemented and optimized for different patient cohorts.

A harmonized ADPKD biobank that includes standardized, quality-controlled biomaterials for translational research is being collected.

TRAINING

The core of the TranCYST training course program of is formed by four training modules that together cover the full spectrum of education within the translational research field of polycystic kidney disease (modules I and II), as well as training in transferable skills (modules III and IV). Apart from this dedicated training program, all researchers are enrolled in the Graduate Schools of the participating academic partners.

So far, three training courses have been organized:

The first Training Course was organized on 11 September 2013 (P3-UK). Several topics were covered by TranCYST PI's. The Visiting Scientist, Vicente Torres, presented an introduction on 'Signal transduction in PKD'.

The second Training Course was the FASEB meeting on 'Polycystic kidney disease: from molecular mechanism to therapy' (3-8 August 2014), where molecular mechanisms and clinical aspects of PKD were covered. A separate training on 'Project Management' was organized on August 4 (P1-LUMC).

The third Training Course took place on 22 November 2014 (P1-NL), with topics not only covering science but also related issues as 'Commercial Exploitation of Knowledge and Intellectual Property', 'Entrepreneurship', 'Careers in Industry'.

Two scientific symposia have been organized: 'Clinical and scientific advances in the management of patients with ADPKD' on 12-13 September 2013 (P3-UK) with 4 TranCYST PI's as speaker and contributions of Vicente Torres (VS), Joost Drenth (AP1) and Tess Harris (AP5).

An international FASEB symposium on' Polycystic Kidney Disease: From Molecular Mechanism to Therapy' was co-organized by P1-LUMC. The meeting took place in Barga (IT), 3-8 August 2014. A range of internationally renowned PKD specialists, including 4 TranCYST partners, Vicente Torres (VS) and Joost Drenth (AP1) presented lectures.

The third symposium is planned for January 2016 and will include presentations of AP2, 3 and 5.

DISSEMINATION RESULTS

Publications

- Petzold K, … , Ong AC, Devuyst O, Rotar L, … , Remuzzi G, … , Serra AL. *Building a network of ADPKD reference centres across Europe: the EuroCYST initiative.* Nephrol Dial Transplant, 29: 26-32, 2014.
- Rotar L, Serra AL, Petzold K. *Tolvaptan zur Therapie der autosomal-dominanten polyzystischen Nierenerkrankung - aktueller Stand.* Schweiz Med Forum 14: 350-351, 2014.

PROJECT COORDINATOR

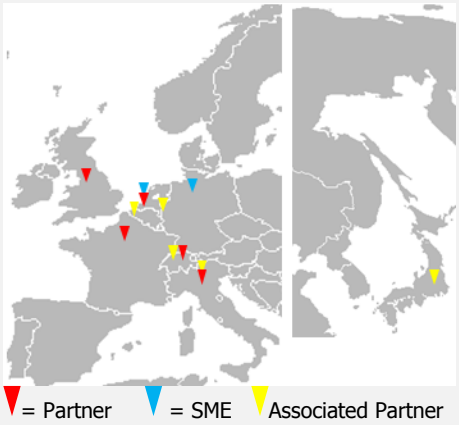
Prof.Dr. Dorien Peters
Dept. of Human Genetics
Leiden University Medical Center
Albinusdreef 2
2333 ZA Leiden (NL)

E-mail: d.j.m.peters@lumc.nl
Website: www.trancyst.eu

TranCYST PARTNERS

1. Leiden University Medical Center (NL)
   Dorien Peters, coordinator and PI
   Peter-Bram 't Hoen, PI
   Babs Teng, project manager
2. University of Zürich (CH)
   Olivier Devuyst, PI
   Andreas Serra, PI
3. University of Sheffield (UK)
   Albert Ong, PI
   Freek van Eeden, PI
4. INSERM (FR)
   Marco Pontoglio, PI
5. IRFMN (IT)
   Giuseppe Remuzzi, PI
   Norberto Perico, PI
6. ServiceXS (NL) - SME
   Bart Janssen, PI
7. Mosaiques (DE) - SME
   Harald Mischak, PI

Associated Partners:
AP1: Un. Med. Ctr. Nijmegen (NL); AP2: Un. Antwerp (BE); AP3: Otsuka Pharm. (JP); AP4: Orobix (IT); AP5: PKD Int. (CH)



MANAGEMENT

The TranCYST project is funded with € 2.7 million through the EU 7th framework program. A supervisory board consisting of all PIs meets at yearly management meetings: Kick-off, 28 FEB 2013 (AT), 1st Annual Meeting, 12 Sep 2013 (UK); Mid Term Meeting, 21 Nov 2014 (NL) and regular web-based meetings.

RECRUITMENT

9 ESRs and 1 ER were recruited, 7 female and 3 male, 6 from EU Member States, 1 from EU Candidate State and 3 from Third Countries.