SYSKID - Systems biology towards novel chronic kidney disease diagnosis and treatment

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Chronic kidney disease (CKD) affects up to 10% of the population. Besides eventual progression towards end stage renal disease CKD impacts the patient’s quality of life by causing serious comorbidities including cardiovascular complications and bone metabolism disorders. On the everyday clinical level early stage diagnosis and tailored treatment of CKD are still inadequate. In addition, CKD seems not to have reached its appropriate emplacement in an epidemiological and healthcare perspective yet, and the pathophysiology of the disease on a molecular and cellular level is not well enough understood. Our sysKID consortium was installed for precisely addressing these issues: To unravel the molecular and cellular mechanisms of chronic kidney disease development, combine this information with clinical risk factors, and on this basis delineate chronic kidney disease biomarkers. These markers will allow us to perform preclinical studies of novel therapy approaches for halting disease progression, and will provide us with the materials for development and clinical evaluation of tools for early stage diagnosis as well as prognosis and treatment monitoring. sysKID assures a successful implementation of these goals by a truly international consortium of 25 leading research groups. We combine clinical know how, provide access to a huge chronic kidney disease sample and clinical data pool, and build a Systems Biology framework for chronic kidney disease by integrating molecular and cellular biology, computational biology, statistics and epidemiology. Our expert group is further complemented by a high level advisory board covering science, product development, and the patient’s perspective. sysKID implementation is structured for completing pre-clinical Proof of Concept studies of novel chronic kidney disease therapy regimes, and further for completing clinical evaluation of an epidemiological screening tool as well as of early stage chronic kidney disease diagnostic kits.

Principal investigators

Scientific co-ordinator:
Bernd Mayer (Emergentec Biodevelopment GmbH)

KIDREGEN - Investigating the ability of embryonic stem cell derivatives to improve renal function in a murine model of kidney disease.

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The number of people worldwide with end-stage renal disease (ESRD) is increasing every year. Current treatment options consist of dialysis and transplantation, both of which have significant side effects in terms of quality and quantity of life. Therefore there is an urgent need to develop alternative therapies. My recent work has shown that if mouse embryonic stem cells (mESC) are directed to differentiate to mesodermal cells, they show high potential for integrating into developing nephrons in a mouse kidney rudiment ex vivo. Moreover, the ability of mESC derived mesoderm to generate renal cell types was highly comparable to that of metanephric mesenchyme (MM), which are the cells that give rise to the nephron in the developing kidney. Although these results are encouraging, a key test will be to investigate if the mESC-derived mesoderm cells can generate nephric cell types in a rodent model of kidney disease and if these cells are able to improve renal function. Therefore the aim of this project is to explore the potential for renal replacement therapy from exploitation of the unique properties of mESC. This will be
tested by injecting the stem cells into the tail vein of mice with induced kidney injury, following which, the ability of the cells to generate renal cell types and improve renal function will be analysed. The propensity of the stem cells to generate inappropriate cell types or tumours in the animal model will also be tested. A further objective will be to develop an MRI-based tracking system so that the stem cells can be monitored non-invasively following transplantation. The project will form the basis of a long term collaboration between the applicant and the host group at the University of Liverpool.

Principal investigators

Scientific co-ordinator:
Patricia Ann Murray (The University of Liverpool)

KIDREGEN - Investigating the ability of embryonic stem cell derivatives to improve renal function in a murine model of kidney disease.

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The number of people worldwide with end-stage renal disease (ESRD) is increasing every year. Current treatment options consist of dialysis and transplantation, both of which have significant side effects in terms of quality and quantity of life. Therefore there is an urgent need to develop alternative therapies. My recent work has shown that if mouse embryonic stem cells (mESC) are directed to differentiate to mesodermal cells, they show high potential for integrating into developing nephrons in a mouse kidney rudiment ex vivo. Moreover, the ability of mESC-derived mesoderm to generate renal cell types was highly comparable to that of metanephric mesenchyme (MM), which are the cells that give rise to the nephron in the developing kidney. Although these results are encouraging, a key test will be to investigate if the mESC-derived mesoderm cells can generate nephric cell types in a rodent model of kidney disease and if these cells are able to improve renal function. Therefore the aim of this project is to explore the potential for renal replacement therapy from exploitation of the unique properties of mESC. This will be tested by injecting the stem cells into the tail vein of mice with induced kidney injury, following which, the ability of the cells to generate renal cell types and improve renal function will be analysed. The propensity of the stem cells to generate inappropriate cell types or tumours in the animal model will also be tested. A further objective will be to develop an MRI-based tracking system so that the stem cells can be monitored non-invasively following transplantation. The project will form the basis of a long term collaboration between the applicant and the host group at the University of Liverpool.

Principal investigators

Scientific co-ordinator:
Patricia Ann Murray (The University of Liverpool)

CX43-CRF - Implication of connexin 43 in chronic renal failure.

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Chronic renal failure (CRF), one of the main causes of disability in western societies, is promoted by a variety of factors including hypertension, diabetes, ischemic, immunological and toxic injury. These factors are linked by their common ability to promote chronic inflammation and fibrosis leading to decline of renal function. Dialysis and transplantation are the only available options that allow survival of patients. Arresting the progression of CRF is one of the major challenges of public health today. Alterations of the expression of the gap junction protein connexin 43 (Cx43) have been associated to the development of inflammation in chronic vascular pathologies. Thus, Cx43 expression was increased during atherogenesis, whereas Cx43 inhibition protected vessels from the development of atherosclerotic plaque. An up-regulation of the Cx43 expression has been also reported in renal inflammation and hypertension suggesting that this connexin may be involved in renal disease. In this project we intend to study the role of Cx43 in CRF and to propose treatments and diagnostic tools targeting this protein to protect against the disease. Thus, in our project: i) we will use the RenTg mice, expressing high steady levels of renin, to study modulation of Cx43 expression during progression of hypertension-induced renal disease; ii) Cx43-specific blockers will be admininister to RenTg mice to see whether decreasing Cx43 expression could reverse the decline of renal function. Cx43 expression will be also reduced genetically by interbreeding the RenTg with the Cx43+/− mice; iii) we will attempt to delineate molecular mechanisms involving Cx43 regulation in endothelial cells in vitro under angiotensin II treatment, a peptide known to participate to renal vascular fibrosis. As perspectives, we will transfer knowledge obtained from this project in humans by testing renal biopsies. Thus, we hope to establish a correlation between Cx43 expression and human CRF.

Principal investigators

Scientific co-ordinator:
Jean-Claude Dussaule (INSERM - Institut national de la sante et de la recherche medicale)

RESCARF - Renal stem cells: possible role in kidney pathologies and as new therapeutic tools

Time period: 2008-10-01 - 2012-09-30
Instrument: Support for Frontier Research (ERC)
Call: ERC-2007-StG

Chronic Kidney Disease (CKD) affects 11% of the adult population and is considered by the WHO as one of the health emergencies of the 21st century. Although cell therapy might be beneficial for CKD, human stem cells that might be used to improve kidney function were so far unknown. Recently, we demonstrated the existence of resident stem cells in the urinary pole of the Bowman?S capsule of adult human kidney and therefore named as adult parietal epithelial multipotent progenitors (APEMP). Injection of APEMP in SCID mice affected by acute renal failure, induced regeneration of tubular structures and reduced morphological and functional kidney damage. More recently, we found that APEMP are highly represented in embryonic kidneys and constitute the common progenitor of tubular cells and podocytes. The first aim of this project is to assess the regenerative properties of APEMP in in vivo models of glomerular injury and their potential use as a novel therapeutic tool to prevent the deterioration of kidney function in chronic renal failure. Second, we will try to identify the mechanisms that regulate the growth, survival, differentiation, and migration of APEMP, which is critical to set up cell therapies of renal injury which should be effective and safe. To this end, the role of different molecular pathways such as Sonic hedgehog, Wnt/beta-catenin, Notch, TGF-beta/BMP and of CXCR4, CXCR7 or CXCR3-B chemokine receptors in the regenerative activity of APEMP will be investigated. Third, to assess whether APEMP directly contribute to kidney regeneration after glomerular or tubular damage, transgenic animals in which APEMP are genetically tagged will be generated. Fourth, by using transgenic animals we will try to understand if an alteration of APEMP growth and/or differentiation is implicated in the pathogenesis of some renal disorders that frequently progress towards end stage renal disease.

Principal investigators
RENALSTEM - Developing a stem cell based therapy to replace nephrons lost through reflux nephropathy

Scientific co-ordinator:
Mario Serio (Università degli Studi Di Firenze)

The prevalence of end stage renal disease (ESRD) continues to grow worldwide. Current treatment options for ESRD are peritoneal dialysis, haemodialysis, or renal transplantation, all of which have significant drawbacks both in terms of quality and quantity of life. In children and young adults, the most common cause of ESRD is vesicoureteric reflux (VUR), a condition where urine from the bladder re-enters the kidney. VUR creates an increased risk of urinary tract infection, predisposing to pyelonephritis, renal scarring, and in the most severe cases, ESRD. However, there is usually a time-window of several years from initial diagnosis of VUR to the development of ESRD, which presents an opportunity to design therapies aimed at preventing disease progression by repairing renal tissue before it becomes non-functional. Recent advances in stem cell science and tissue engineering suggests that stem cell based therapies for reflux nephropathy could be feasible. The long-term aim is to explore the potential of resident kidney stem cells for renal replacement therapy in order to prevent susceptible children from developing ESRD. In this project, the potential of resident kidney stem cells will be tested by transplantation into mouse embryonic kidneys ex vivo. To devise a suitable scaffold to, a range of biocompatible polymeric substrates will be fabricated and tested for their ability to support nephrogenesis from disaggregated mouse kidney rudiments in vitro. Finally, we will develop a magnetic nanoparticle-based cell tracking technique that will enable the transplanted cells to be monitored in vivo using magnetic resonance imaging. Results generated by the project will establish if kidney stem cells have potential for future use in regenerative medicine. Should the results prove positive, further work will determine if the isolated kidney stem are capable of generating nephrons in animal models in vivo.

Principal investigators
Scientific co-ordinator:
Patricia Ann Murray (The University of Liverpool)

EUNEFRON - European Network for the Study of Orphan Nephropathies

In this proposal, we have mobilized a critical mass of expertise to investigate, on a Europe-wide scale, the natural history and pathophysiology of rare inherited diseases affecting important structures of the kidney. The project will use and develop multiple models (in vitro and in vivo) with the aim to develop preventive, diagnostic and therapeutic interventions that should alleviate the burden of these diseases, particularly in children. A central part of the proposal is the creation of a European registry and a network of genetic laboratories to foster a tight interaction between physicians and researchers, promote clinical and basic research, and ensure the efficient dissemination of knowledge. By increasing our knowledge of these rare diseases, the EUNEFRON project will also yield new insights into basic processes relevant for the general population (progression of renal disease, blood
pressure control, prevention of renal stones, effect of gender and age, etc?), the complex relationship between different nephron segments, and the multi-systemic involvement of renal diseases.

**Principal investigators**

**Scientific co-ordinator:**
Olivier Devuyst (Universite Catholique de Louvain)

**Other principal investigators:**
Corinne Antignac (INSERM - Institut national de la sante et de la recherche medicale)
Erik Ilsøe Christensen (Aarhus Universitet)
Peter Deen (Stichting Katholieke Universiteit)
Dominik Muller (Charite - Universitaetsmedizin Berlin)
Carsten Wagner (Universitaet Zuerich)
Luca Rampoldi (Fondazione Centro San Raffaele Del Monte Tabor)
William van 't Hoff (University College London)
Elena Levtchenko (Katholieke Universiteit Leuven)

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**CHRONIOUS - An Open, Ubiquitous and Adaptive Chronic Disease Management Platform for COPD and Renal Insufficiency**

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Chronic diseases are those that occur across the whole spectrum of illness, mental health problems and injuries. Management includes medication and/or lifestyle changes such as diet and exercise. At the same time, it should be noted that chronic diseases may get worse, lead to death, be cured, remain dormant or require continual monitoring. CHRONIOUS primary goal is to define a European framework for a generic health status monitoring platform schema addressing people with chronic health conditions. This will be achieved by developing an intelligent, ubiquitous and adaptive chronic disease platform to be used by both patients and healthcare professionals. CHRONIOUS addresses a smart wearable platform, based on multi-parametric sensor data processing, for monitoring people suffering from chronic diseases in long-stay setting. It is constantly monitoring their activity using audio observation methods and activity sensors while at the same time tracking their medical condition via vital signs sensors. Any trait of abnormal health status and possible alerting incidents are detected by CHRONIOUS Intelligence. The system generates alerts in case of invalid medical data or if current activity and behaviour lay outside the well established activity patterns and locomotion behaviour. Furthermore, CHRONIOUS objective is to face Europe?s challenge for delivering quality healthcare to all its citizens by offering a ubiquitous and more personalised care solution that addresses the user needs, personal data security, confidentiality and privacy of information and all that at an affordable cost. Our proposed solution will be applied to the chronic diseases of Chronic Obstructive Pulmonary Disease (COPD) and Chronic Kidney Disease (CKD) and Renal Insufficiency.

**Principal investigators**

**Scientific co-ordinator:**
Roberto Rosso (TESAN S.P.A.)

**Other principal investigators:**
Daniela Matarrese (Azienda Ospedaliero-Universitaria Careggi)
Xavier Gutierrez (Universitat de Barcelona)
Diseases of the kidney represent a major cause of morbidity and mortality in Europe. The elderly are disproportionately affected, but renal disease is also a condition that severely affects children. An estimated 4.5 Million Europeans suffer from renal disorders. The death rate in patients with renal failure is 20% annually. This disease burden and its challenge for our societies is the focus of this proposal. Elucidation of the human and other genomes heralds a new era in biomedical research offering unprecedented opportunities to understand disease processes and to identify strategies to improve health. We will embrace these opportunities and implement an interdisciplinary research program, the European Renal Genome Project (EuReGene) that integrates European excellence in research relevant to renal development, pathophysiology and genetics. Our goal is to discover genes responsible for renal development and disease, their proteins and their actions. To achieve this goal, we have established a consortium of leading scientists, clinicians and SME partners that will focus on the development of novel technologies and discovery tools in functional genomics and their application to kidney research. We will rely on comparative genomic studies in many systems that provide utilitarian models ranging from zebrafish, to Xenopus, to mice, to rats. Our studies will be performed at different levels including the gene, the cell, the organ and the organism. Ultimately, identification of disease genes will lead to a better understanding of renal disease processes, to improved diagnosis and to new concepts in therapy. Our program will establish a paradigm for an integrated post-genomic approach to analyze renal disease-related developments that may be transferred to other organ systems or disease entities in the future.

Principal investigators
Scientific co-ordinator:
Thomas E. Willnow (MAX DELBRUECK CENTRUM FUER MOLEKULARE MEDIZIN)
Other principal investigators:
Nicholas Hastie (MEDICAL RESEARCH COUNCIL)
Corinne Antignac (INSERM - Institut national de la sante et de la recherche medicale)
Olivier Devuyst (UNIVERSITE CATHOLIQUE DE LOUVAIN)
André Werner Brändli (Eidgenossische Technische Hochschule Zuerich)
Giuseppe Remuzzi (ISTITUTO DI RICERCHE FARMACOLOGICHE "MARIO NEGRI")
Heini Murer (UNIVERSITAET ZUERICH)
Gregor Eichele (MAX PLANCK GESELLSCHAFT ZUR FOERDERUNG DER WISSENSCHAFTEN E.V.)
Seppo Juhani Vainio (OULUN YLIOPISTO)
Thomas J. Jentsch (UNIVERSITAET HAMBURG)
Erik Ilsøe Christensen (AARHUS UNIVERSITET)
Rajesh V. Thakker (THE CHANCELLOR, MASTERS AND SCHOLARS OF THE UNIVERSITY OF OXFORD)
Matthias Kretzler (LUDWIG-MAXIMILIANS-UNIVERSITAET MUENCHEN)
Anders Nykjaer (RECEPTICON APS)

ALDOSTERONE-FELLOW - Molecular determinants of sodium transport: role of a new aldosterone induced gene

Time period: 2005-01-01 - 2006-12-31
Instrument: Marie Curie Actions (MCA)
Call: FP6-2002-MOBILITY-5

The epithelial Na+ channel (ENaC) plays a major role in the homeostasis of extracellular Na+ and consequently of blood volume and pressure. Its importance is underlined by its genetic linkage to two renal diseases, pseudohypoaldosteronism type I, and of Liddle's syndrome, which are both caused by mutations in the genes encoding ENaC. ENaC, which facilitates entry of Na+ into the cell, is the rate-limiting step of Na+ reabsorption. It is highly regulated by a variety of factors, including aldosterone and vasopressin, but the molecular mechanisms of their action are still poorly understood. Aldosterone induces and/or represses a number of genes, which consequently lead to the stimulation of transepithelial transport. We have identified a novel protein, NDRG2 (N-myc Downstream Regulated Gene 2) whose expression is very early stimulated by aldosterone, both in established cell lines, and in the kidney and colon of rats. NDRG2 belongs to a family of genes of unknown function, which is conserved in plants, invertebrates and mammals, suggesting important functions. Its identity with MESK2, a gene recently identified in Drosophila, suggests that it may be involved in the Ras/MAPK signaling pathway. Our preliminary data suggest that aldosterone does influence Ras activity, and co-expression of NDRG2 with ENaC into Xenopus laevis oocytes elevates ENaC activity as compared to control oocytes. My project will be focussed on the analysis of NDRG2 function, in cell cultures, and in vivo by transgenesis. We will use conditional systems (tet inducible and HoxB7 promoter kidney-targeting in mice, Tamoxifen-sensitive Cre-Lox in cells) to evaluate the consequences of NDRG2 overexpression on renal collecting duct differentiation, polarity and sodium transport capacities. Constructs have been made, cell transfection is in progress and mouse generation will be initiated in March 2004. We will search for alterations in sodium transport after NDRG2 overexpression.

Principal investigators
Scientific co-ordinator:
Nicolette Farman (INSERM - Institut national de la sante et de la recherche medicale)
ADDNET - Paradigm shift from kidney biopsies to advanced molecular diagnostics from patient urine

**Time period:** 2004-01-01 - 2006-12-31

**Instrument:** Specific Targeted Research Project (STREP)

**Call:** FP6-2002-LIFESCIHEALTH

**BACKGROUND:** Proteinuria is a sign of kidney involvement in association with common infectious, inflammatory, immunological or metabolic (diabetes) diseases. When persisting, proteinuria leads to scarring and end-stage kidney disease requiring dialysis or renal transplantation. Both treatments are chronically debilitating, increase risk for severe secondary complications and are extremely expensive. Altogether, kidney complications constitute more than 15% of total health-care costs in most Western countries, mainly due to increasing prevalence of diabetes-associated kidney disease. **PROBLEM:** Earlier diagnostics is urgently needed to target intensive treatment efforts and to avoid the projected explosive increase in the number of kidney patients in near future. Due to the demographic trends, kidney diseases are a particular problem for Europe. At present, the diagnostics include serum markers (mostly non-sensitive, non-specific) and urine analysis (too late markers) but relies mainly on patient kidney biopsy samples. Although accurate, this procedure is severely inconvenient, invasive and carries a notable risk for complications. **SOLUTION:** We propose to use the latest molecular information of verified pathogenetic routes, proprietary bioinformatics platforms, well established in vivo models as well as extensive human sample repositories together with the SME activities to establish and validate new diagnostics. This includes the identification of an expanding set of key molecular markers directly from patient urine to yield novel measurables for early and accurate non-invasive diagnostics. With the set of markers accurately reflecting pathophysiologic changes we expect to replace the traditional kidney biopsies with more patient-friendly, accurate and economical diagnostics directly from urine, easily accessible source. Development will also allow construction of distant monitoring diagnostic platforms to prevent permanent kidney.

**Principal investigators**

**Scientific co-ordinator:**
Harry Holthöfer (HELSINGIN YLIOPISTO)

**Other principal investigators:**
Klaus-Robert Müller (FRAUNHOFER GESELLSCHAFT ZUR FOERDERUNG DER ANGEWANDTEN FORSCHUNG E.V.)
Per-Henrik Groop (SAMFUNDET FOLKHAELSAN I SVENSKA FINLAND R.F.)
Jesus Egido (UNIVERSIDAD AUTONOMA DE MADRID)
Kimmo Kaski (HELSINKI UNIVERSITY OF TECHNOLOGY)
Eric Fung (CIPHERGEN BIOSYSTEM A/S)

NMDANOARF - Role of NMDA receptors on experimental renal failure. Relationship with NO

**Instrument:** Marie Curie Actions (MCA)

**Call:** FP6-2002-MOBILITY-12

N-methyl-D-aspartate receptor (NMDA-R) is an amino acid receptor and membrane calcium channel. NMDA-R is activated by binding of co-agonists, L-glutamine and L-glycine. In the brain, calcium entry via NMDA-R activates type I nitric oxide synthase (NOS I). The kidney also contains NOS I and vasodilates in response to L-glycine. We recently demonstrated that NMDA-R are expressed in kidney cortex, where they exert a tonic vasodilatory influence and may account for the vasodilatory response to glycine infusion. Nitric oxide is a gas that exerts, among others, vasodilatory effects in the kidney. Me and others have demonstrated a role of nitric oxide in several types of acute
renal failure, from aminoglicoside-induced, to ischemic in nature. Also, in a recent paper, I suggested a role for nitric oxide in renal mass reduction due to uninephrectomy. Glycine infusion has been proven to be beneficial in several renal conditions, but the mechanism by which this happens is yet to be elucidated. From cyclosporine nephrotoxicity to ischemic renal failure, increases in glycine availability lead to improvements in renal function. Furthermore, use of NMDA antagonists has been proven to reduce ischemic damage in the brain and aminoglicoside ototoxicity. Thus, the relationship between NMDA-R and NO in the kidney in normal and pathological conditions is an exciting field that could lead to new therapies in the treatment of renal diseases.

**Principal investigators**

**Scientific co-ordinator:**
Elvira Fernandez Giraldez (FUNDACIÓN DR. PIFARRÉ. HOSPITAL UNIVERSITARIO ARNAU DE VILLANOVA)

**KIDSTEM - Developing a stem cell based therapy to replace nephrons lost through reflux nephropathy**

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The aim of this project is to design a stem cell-based therapy to prevent end-stage renal disease caused by reflux nephropathy in children. The two main reasons to focus on this condition are that it is the major cause of kidney failure in children and young adults and secondly, the disease typically takes several years to reach end stage, allowing time for therapies to repair damage kidneys before they become completely non-functional. Recent advances in stem cell science and tissue engineering present an unprecedented opportunity to design a stem cell therapy for this clinical problem. This project will investigate the properties of several different stem cell types (embryonic stem cells, kidney stem cells, amniotic fluid stem cells and mesenchymal stem cells) in order to determine which is most appropriate for the generation of functional kidney tissue. To do this, novel biomaterials will be designed that will provide a substrate both for the generation of kidney progenitor cells and for their transplantation.

**Principal investigators**

**Scientific co-ordinator:**
Patricia Ann Murray (THE UNIVERSITY OF LIVERPOOL)

**Other principal investigators:**
Giovanni Camussi (UNIVERSITA DEGLI STUDI DI TORINO)
Carsten Werner (LEIBNIZ-INSTITUT FUER POLYMERFORSCHUNG DRESDEN E.V.)
Markus Hengstschlaeger (MEDICAL UNIVERSITY OF VIENNA)
Jamie A. Davies (THE UNIVERSITY OF EDINBURGH)
Giuseppe Remuzzi (ISTITUTO DI RICERCHE FARMACOLOGICHE "MARIO NEGRI")

**STAR-T REK - Set up and comparison of multiple stem cell approaches for kidney repair**

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With the increasing rate of end-stage renal failure and limited alternatives for its treatment, potential regenerative approaches for kidney damages are urgently needed. Because of the complexity of the organ, the development of stem cell therapies for kidney is still in its infancy. Identifying which cell types are capable of beneficial effects is the critical step required to realize the potential of this therapeutic approach. Three possible sources of stem cells can be envisioned for the development of this type of treatment: (i) bone-marrow-derived stem cells, (ii) renal adult stem cells, and (iii) fetal renal stem cells. The focus of this project is to assess the regenerative potential of stem cells derived from different sources and investigate the possible obstacles to their utilization, as well as their potential side effects in preclinical models of acute and chronic renal failure. Indeed, the clinical usefulness of the treatment, as well as the need to understand currently discrepant results, require comparative experimental studies that have never been performed before either in SC therapy of kidney injury, or in that of other organs. Hopefully, this comparison will allow to set up standardized protocols of SC isolation and administration for phase I/II trials in patients affected by acute and chronic renal failure.

**Principal investigators**

**Scientific co-ordinator:**  
Paola Romagnani (UNIVERSITA DEGLI STUDI DI FIRENZE)