EUROPEAN RENAL ASSOCIATION EUROPEAN DIALYSIS AND TRANSPLANT ASSOCIATION	**For Office Use Only** YEAR OF CALL: **2011** **Application No:** Name of Applicant: Approved Denied Amount granted: €

ERA-EDTA SUPPORTED RESEARCH

APPLICATION FORM

By submitting this Application I accept that non-sensitive data (full name and research title) of the winners will be published in *ERA-EDTA website*, *NDT or NDT Plus* (the official publications of ERA-EDTA), *NDT Educational* (the educational website of ERA-EDTA) and *Follow us* (the official ERA-EDTA newsletter).

Main Applicant Signature

Main Applicant: *First name*: **CARMINE** *Family name:* **ZOCCALI** **On behalf of EURECA-m working group**	**Title & Position:** **MD, FASN, Professor of Nephrology (PG)** **EURECA-m Chairman**
Institution: **EURECA-m working group** ERA-EDTA Operative Headquarter Via Spolverini 2, I-43126 Parma, Italy E-mail: eureca-m@era-edta.org; carmine.zoccali@tin.it	

RESEARCH

TYPE			
A) Translational Research Project			**T**
B) Clinical Research Project:	**Collaborative Clinical Trial (CT)**	**x**	**CT**
	Observational Study		**OS**

TITLE:

LUNG WATER by **U**ltra-**S**ound GUIDED **T**REATMENT TO PREVENT DEATH AND CARDIOVASCULAR COMPLICATIONS IN HIGH RISK END STAGE RENAL DISEASE (esrd) PATIENTS WITH CARDIOMYOPATHY (**LUST**)

Lay Title (acronymous):

LUST

Total Amount Requested: 1.647.500 €

In case of acceptance you must recognize this research as an ERA-EDTA mainly/solely supported study.	
Date of application	**19 / 07 / 2011**
Main Applicant Signature	

Proposed Start Date: 01/06/2012 *(dd/mm/year)*

Proposed duration: 24 months

Summary of proposed research *(300 words)* **:**

Extracellular volume expansion and cardiomyopathy are major risk factors for all-cause and cardiovascular mortality in dialysis patients and studies looking at optimization of fluid volume and drug treatment of LV disorders are considered as a research priority in this population.

This is a randomized clinical trial testing whether a treatment policy guided by systematic monitoring of lung water as measured by chest ultrasound (US) may reduce mortality, heart failure, coronary heart disease and/or heart failure in dialysis patients. Lung water assessment by chest US is a quick, reliable, and easy to learn technique that requires just a 2-hours training session.

Patients will be randomly allocated to the US-guided treatment policy and to standard treatment guided by conventional clinical criteria. The treatment policy guided by lung US aims at minimizing lung congestion by appropriate intensification of the UF regimen during dialysis and, whenever needed, by the introduction and/or up-titration of drugs of proven efficacy for the treatment of LV dysfunction in dialysis patients.

Two hundred and fifty patients will be allocated to the active arm of the study (Lung US-guided treatment) and an equal number to the control arm (conventional treatment). The study will have a 80% power for detecting as statistically significant (P<0.05) a 15% difference in the cumulative incidence of the composite outcome "death, myocardial infarction, heart failure" between the two study arms (active 30%, control 45%) over a 2-year follow-up. Other study outcomes will be hospitalization rate and the evolution of cardiomyopathy as measured by echocardiographic indicators of LV systolic and diastolic function.

5 Key words:

1) Lung water
2) Volume expansion
3) LV dysfunction
4) dialysis
5) ESRD

Define relevance in Europe *(300 words maximum)* **:**

Depending on the background dialysis and general population age, from 20% to 40% of prevalent dialysis patients in European countries have a history of cardiac ischemia and/or of heart failure. The risk of death in these patients is more than doubled as compared to that in patients without such complications. Inadequate fluid volume control and/or inadequate treatment of LV disorders are considered as major factors to explain the exceedingly high death risk of ESRD patients with cardiomyopathy.

There is no simple and inexpensive method that may be applied on large scale to guide fluid volume subtraction or to optimize drug therapy in dialysis patients with pre-existing cardio-myopathy. Lung water measurement has now emerged as a valid, costless and fast method that may allow quantification and monitoring of pulmonary congestion, a factor which is considered as a critical element for therapeutic decisions in these patients. Our study aims a testing a treatment policy based on the best available clinical studies in this population and to guide treatment on the basis of the severity of lung congestion.

As 2011, about 480.000 of ESRD patients are maintained on chronic dialysis in Europe. As mentioned, 20% to 40% of dialysis patients in Europe are affected by LV systolic dysfunction (secondary to associated coronary heart disease events and other factors). Thus about 120.000-192.000 dialysis patients exhibit an exceedingly high risk of death for cardiomyopathy. These patients have a mortality rate of about 22.5%/year, which in absolute term is tantamount to 18.000-29.000 deaths/year. If our study is positive, i.e. if the treatment policy in question will reduce the death rate in patients in the active arm of the study from 22.5% to 15.0%/year, the implementation of such a treatment policy will have the potential for preventing about 8.000-19.000 deaths per year in dialysis patients in European countries.

PROPOSED RESEARCH

1. Purpose *(not more than 300 words).*

Volume overload is a leading risk factor for death and cardiovascular events in end stage renal disease (ESRD) patients maintained on chronic dialysis, particularly in those with myocardial ischemia and heart failure which represent a substantial fraction (about 40%) of this population. Early identification of volume overload may prevent cardiovascular sequel in these patients but clinical signs of volume expansion are unsatisfactory to reliably identify patients at risk and to monitor them over time. On the other hand, however reliable, standard techniques for measuring extracellular or circulating (blood) volume do not convey information on fundamental heart function parameters that determine the individual hemodynamic tolerance to volume excess and the response to ultrafiltration, i.e. left ventricular (LV) filling pressure and LV function. Extra-vascular lung water (LW) is critically dependent on these parameters and represents a proxy of both, circulating volume and LV filling pressure and function, and may therefore be a better criterion to identify patients at a higher risk of volume-dependent adverse clinical outcomes and to monitor the effect of therapy aimed at preventing these outcomes. Recently a fast (< 5 min.), easy to learn, simple and non-expensive technique which measures extra-vascular lung water by using standard ultrasound (US) machines has been validated in dialysis patients. Whether systematic measurement of LW by this technique may translate into better clinical outcomes in ESRD patients has never been tested. **The aim of this randomized clinical trial is that of testing a treatment policy guided by extra-vascular lung water measurements by ultrasound (LW-US) to prevent death, decompensated heart failure and myocardial infarction as well as progression of LVH and LV dysfunction and hospitalization in high risk dialysis patients with myocardial ischemia** (a history of myocardial infarction with or without ST elevation or unstable angina, acute coronary syndrome documented by ECG recordings and cardiac troponins or stable angina pectoris with documented coronary artery disease by prior coronary angiography or ECG) **or overt heart failure** (NYHA class III-IV).

2. Background *(not more than 500 words).*

Advancement in dialysis technology and new drug therapies of uremic complications are major achievements of modern nephrology. As a result of progress in the care of ESRD, a continuous increase in survival of dialysis

patients has been documented over the last 13 years in the European Renal Association-European Dialysis Transplant Association (ERA-EDTA) registry (1). Adequate control of fluid balance is a primary goal of dialysis treatment and experience in centres applying strict volume control policies documented a remarkable reduction in mortality in comparison with average mortality rate in well matched cohorts in the USRDS and in the ERA-EDTA Registry (2). Even though specific recommendations in past and current guidelines emphasise the risk of volume overload, the problem still remains pervasive in the dialysis population (3). Unsatisfactory control of volume expansion depends on various reasons encompassing both medical and non-medical factors such as reimbursement of the cost of extra or longer dialyses and other organizational and logistic factors. As to the medical factors, **it is widely agreed that the high prevalence of patients with LV dysfunction and heart failure and the lack of simple, non-expensive, bedside techniques that may serve to estimate and monitor parameters of central hemodynamics for guiding the prescription of ultrafiltration (UF) and drug treatment is a factor of major clinical relevance**.

Extra-vascular lung water (LW), a fundamental component of body fluids volume, represents the water content of the lung interstitium which is strictly dependent on the filling pressure of the left ventricle (4; 5). Chest ultrasound (US) has recently emerged as a reliable technique for detecting LW in intensive care patients (6) and in patients with heart failure (7). The basic principle of this technique is that in the presence of excessive LW, the ultrasound beam is reflected by sub-pleural thickened interlobular septa, a low impedance structure surrounded by air with a high acoustic mismatch. US reflection generates hyperechoic reverberation artefacts between thickened septa and the overlying pleura which are defined “lung comets” (8). These artefacts are easily detected with standard US probes and chest US has been formally validated as a reliable technique to estimate LW in patients with heart diseases (9). This method captures changes in LW which occur across dialysis and the feasibility and repeatability of chest US studies in hemodialysis patients has been recently described (10). However the clinical usefulness of this technique in the everyday care in ESRD patients is still untested and it remains unknown whether systematic application of chest US may translate into better clinical outcomes in these patients. With this background in mind the European Renal and Cardiovascular Medicine (EURECA-m) working group of the ERA-EDTA designed a randomised, multicenter, clinical trial investigating whether a treatment policy based on LW monitoring in haemodialysis patients by chest US is more effective than standard clinical monitoring for reducing death, decompensated heart failure and myocardial infarction and prevent the evolution of LVH and LV dysfunction in patients with myocardial ischemia or heart failure over a 2-year follow-up .

This trial will be the first which formally tests a biomarker as a guide the optimize volume control and drug treatment in high risk dialysis patients. Other promising indicators of fluid volume in dialysis patients - such as body impedance analysis (BIA) or cardiac natriuretic peptides - have never been tested into a clinical trial, which is a basic requirement for recommending systematic use of biomarkers in clinical practice.

3. Plan of investigation including research group strategy

*(not more than **5000** words)*

General aspects

This randomized clinical trial aims at testing whether the application of chest US may reduce mortality, heart failure, myocardial infarction, progression of cardiac disease and hospitalizations in dialysis patients with myocardial ischemia (a history of myocardial infarction with or without ST elevation or unstable angina, acute coronary syndrome documented by ECG recordings and cardiac troponins or stable angina pectoris with documented coronary artery disease by prior coronary angiography or ECG) and/or stage III-IV NYHA heart failure over a 2 years follow-up.

Patients with cardiac ischemia and associated LV dysfunction or clinical heart failure represent a relevant segment of the dialysis population with a prevalence ranging from 25% to 40%. These are very high risk patients, with a 2-years death rate of about 45%. Substantial resources are spent in the care of these patients because they require frequent hospitalizations and close clinical supervision. Previous studies showed that dialysis patients with systolic dysfunction may have a substantial improvement in life expectancy with appropriate treatment (11). Tailoring UF and drug treatment according to the individual hemodynamic profile is of obvious importance in these frail, hemodynamic unstable subjects. In this respect echocardiography provides precious information to guide therapy because it allows measurement of the main hemodynamic parameters including LV systolic and diastolic function, LV volume and LV mass. However this technique is fairly

costly and demands a cardiology consultation and therefore it is applied less than needed in the clinical care of ESRD patients. Lung water assessment by chest US is a quick (about 5 minutes) and easy to learn technique that requires just a 2-hours training session. Well conceived introductory programs are available also on the internet (http://www.youtube.com/watch?v=amsULLws8GI).
This technique can be carried out with standard US machines currently applied in internal medicine departments to perform either cardiac or abdominal scans as well as with last generation hand-held US scans (http://www.ge.com/audio_video/ge/health/meet_vscan.html). As discussed, LW by US scans is quantified on the basis of the number of hyperechoic lines (*lung comets*) recorded over the lung (ref. 8, see previous section). The number of these lines (lung comets score) is indeed strictly proportional to LW in patients with cardiac diseases (ref. 9, see previous section) of various severity and appears strongly associated parameters of LV systolic and diastolic function. In dialysis patients the number of lung comets reduces after dialysis and this indicator is strongly associated with ejection fraction, the E/E' ratio (an indicator of diastolic function) and the left atrial and ventricular volume, i.e. the hemodynamic parameters which are most useful to prescribe and monitor UF in dialysis patients (ref. 10, see previous section).

Specific aspects

The trial aims at establishing whether systematic measurements of LW in ESRD patients with myocardial ischemia and/or heart failure and evidence of obvious pulmonary congestion (>15 lung comets) by a simple, low cost US machine (GE VScan, see **Figure 1**) to achieve and maintain the treatment goal of reducing the number of pre-dialysis lung comets by at least the 30% and aiming to post-dialysis values in a range encompassing normal to mildly elevated LW (i.e. <15 lung comets) may translate into better clinical outcomes. LW-US studies will be performed by trained, certified personnel (training will be guaranteed by Eugenio Picano group at CNR - Institute of Clinical Physiology in Pisa). Doctors, nurses and dialysis technicians are eligible for training, according to the local needs/availabilities.

· ***Inclusion criteria***:
- >18 years of age
- On hemodialysis > 3 months prior to study day 1
- A history of myocardial infarction with or without ST elevation or unstable angina, acute coronary syndrome documented by ECG recordings and cardiac troponins or stable angina pectoris with documented coronary artery disease by prior coronary angiography or ECG or dyspnea class III-IV NYHA
- Written consent to take part in the study

· ***Exclusion criteria****:*
- Cancer or other advanced non cardiac disease or comorbidity (e.g. end stage liver failure) imposing a very poor short term prognosis
- Active infections or relevant inter-current disease
- Inadequate lung scanning and echocardiographic studies

· ***The LW-US guided intervention****:*
Patients will be randomized to a lung-US guided treatment policy or to standard clinical care (**Figure 2**).

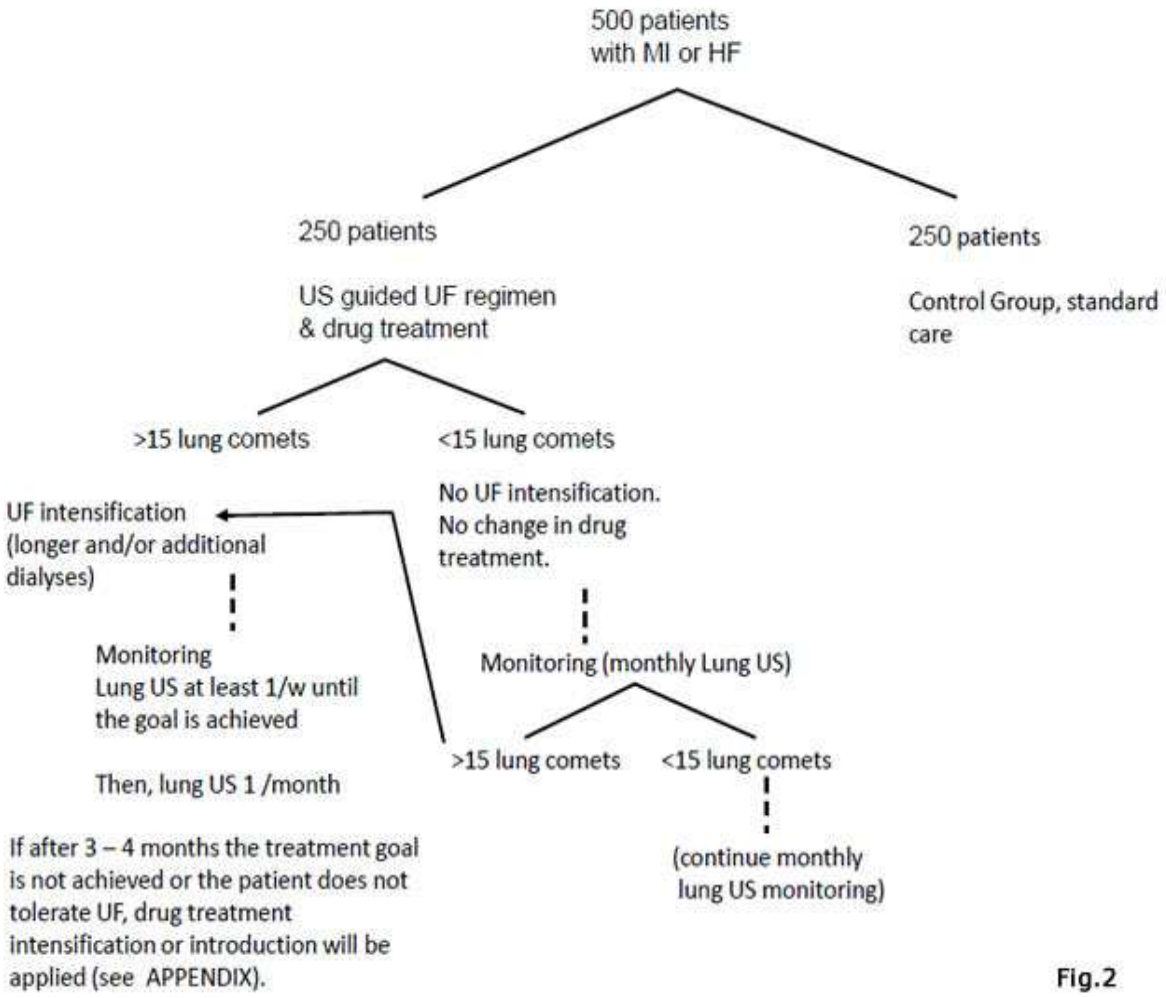

Fig.2

In patients randomized to the active arm of the study, LW-US will be performed before and after dialysis session and their results used to titrate dialysis and drug treatment.
Patients in this arm with moderate to severe lung congestion (>15 lung comets pre-dialysis) LW measurements will be repeated at least once a week until the treatment goal is achieved and once a month thereafter and the same (monthly) monitoring frequency will be adopted also in patients without pulmonary congestion at predialysis baseline (<15 comets). Furthermore **the use of the technique will be allowed whenever its application is deemed useful to assume clinical decisions by attending physicians**. Patients in the active arm of the study without evidence of lung congestion at baseline who will develop pulmonary congestion (i.e. clinical signs and/or >15 lung comets) during the trial will receive the same treatment contemplated for those with lung congestion at baseline (see **Figure 2**).
The treatment goal will be pursued by UF intensification realized either by lengthening the duration of dialysis or by extra-dialyses, according to individual tolerance and feasibility. If the treatment goal will not be achieved within the first 3-4 weeks or intolerance to UF supervenes, adjustment of drug treatment will be considered including the introduction and/or dose adjustments of drugs of proven efficacy like carvedilol and ACE inhibitors or angiotensin II blockers, as recommended by a recent consensus document by KDIGO (Kidney Int 2010; 77: 273–284; **see APPENDIX**). Other cardiovascular and noncardiovascular medications will be maintained unchanged or appropriately adapted in relationship to the individual needs.
Patients in the control arm of the study will be followed up and managed with standard criteria according to

current recommendations (implying optimization of fluids volume control on the basis of clinical criteria and the use of carvedilol, ACE inhibitors/sartans whenever deemed necessary) and the use of LW measurements will not be allowed in these patients.

In all patients entering into the study, both in the active (chest sonography-guided treatment) and control (standard care) arm, a set of **echocardiographic measurements** will be performed following recommendations of American Society of Echocardiography: Ejection Fraction (EF), the ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (E') (E/E' ratio), left atrial and ventricular volume, pulmonary pressure and left ventricular mass Index (LVMI)] along with standard clinical information, a quality of life questionnaire (SF36) and a short questionnaire on depression (CES-D, 20 items) will be collected at baseline and repeated after 6, 12 and 24 months. **The occurrence of clinical events (death, myocardial infarction or de novo heart failure) and hospitalizations will be accurately registered in both study arms.**

Clinical events will be adjudicated by a panel of physicians unaware of the allocation of patients into the trial.

· ***Methods against bias***

As specified, LW-US studies will be performed by trained, certified personnel. Randomization (permuted blocks of random length) stratified by centre and disease severity (angina history without MI, MI, NYHA III-IV) will be adopted. Randomization will be performed at the coordinating centre and communicated to participating centres by e-mail and telephone. Secondary echocardiographic end-points will be analyzed in a central core ab by an observer blinded to patient identity and study condition, as recommended by American Society Echocardiography in the guidelines for use of echocardiography in clinical trials (Gottdiener JS. ASE recommendations in clinical trials. JASE 2004: 17; 1086-1119).

· ***Study outcomes***

The main study end-point is a composite of death, myocardial infarction or de novo hospital admission for decompensated heart failure or acute coronary syndrome. The other study end-points are progression of LVH, left atrial volume (LAV), LV systolic (EF) and diastolic (E/E' ratio) function and pulmonary pressure (at 1 and 2 years) and hospitalizations attributable to cardiovascular causes.

· ***Sample size and power calculation***

The power calculations of the main end-point and of the other end-points are detailed in the Table below. All calculations are based on an expected attrition rate of 30%.

Outcome measure	**Hypothesised effects**	**α error**	**Power**	**N (*)**
Cumulative incidence of the composite outcome "*death, myocardial infarction, heart failure*" (%)	**Active arm:** 30% **Control arm:** 45%	0.05	80%	Active arm: n=250 Control arm: n=250
Event rate of hospitalization (%)	**Active arm:** 1.00 hospitalization/patient-year **Control arm:** 1.50 hospitalization/patient-year	0.05	80%	Active arm: n=182 Control arm: n=182
Left atrial volume ($g/m^{2.7}$)	**Active arm:** - 2±17 **Control arm:** 4±17	0.05	80%	Active arm: n=168 Control arm: n=168
E/E'	**Active arm:** -2±6 **Control arm:** 0±6	0.05	80%	Active arm: n=189 Control arm: n=189
LVMI ($g/m^{2.7}$)	**Active arm:** - 2±11 **Control arm:** 3±11	0.05	80%	Active arm: n=102 Control arm: n=102
LVEF (%)	**Active arm:** 3±9 **Control arm:** 0±9	0.05	80%	Active arm: n=189 Control arm: n=189

· ***Study feasibility***

We have already performed a single centre pilot study at the coordinating centre to assess the feasibility of the intervention in a series of 10 patients with moderate to severe lung congestion. The goal of reducing by 30% lung comets was achieved without side effects just with gentle UF. Over 1400 patients are being treated by hemodialysis at participating centres. Given the high prevalence of myocardial ischemia and heart failure in the dialysis population (25%-40%), we foresee no major problem at enrolling the required number of patients (n= 500).

References

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When and how to assess pulmonary congestion in heart failure: pathophysiological, clinical, and methodological implications. Heart Fail 2010; 15:63-72.

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Ultrasound lung comets: a clinically useful sign of extravascular lung water. J Am Soc Echocardiogr 2006; 19:356-363.

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"Ultrasound comet-tail images": a marker of pulmonary edema: a comparative study with wedge pressure and extravascular lung water. Chest 2005; 127:1690-1695.

(10) Mallamaci F, Benedetto FA, Tripepi R, Rastelli S, Castellino P, Tripepi G et al.
Detection of pulmonary congestion by chest ultrasound in dialysis patients. JACC Cardiovasc Imaging 2010; 3:586-594.

(11) Cice G, Ferrara L, Di BA, Russo PE, Marinelli G, Pavese F et al.
Dilated cardiomyopathy in dialysis patients--beneficial effects of carvedilol: a double-blind, placebo-controlled trial. J Am Coll Cardiol 2001; 37:407-411.

APPENDIX

Cardiovascular drugs administration in patients where the treatment goal (LC<15) is not achieved by UF alone (see KDIGO consensus document, Kidney Int 2010; 77: 273–284)

Carvedilol will be started at the dose of 3.125 mg twice a day for two weeks in order to test tolerance to this drug. In patients able to tolerate carvedilol, the dose will doubled at two-week intervals to a target dose of 25 mg twice a day. When the dose increase is not tolerated for the appearance of adverse reactions such as HR >50 beats/min or arterial hypotension (BP>90/60 mm Hg), the dose will be halved (Ref. 11).
If the trial goal (<15 LC) is not achieved and the treatment is tolerated a second drug will be added.

Fosinopril will be started at a dose of 5 mg (QD). Blood pressure will be measured every 30 min for 4–6 h after administration of this dose. Patients who will tolerate the initial dose will enter into a 3- to 6-week up-titration period. The dose will be increased weekly in increments of 5mg until the target dose of 20 mg daily will be achieved. This drug does not require any specific supplement to compensate dialysis losses.
Other options are possible but these will require supplementary doses for dialysis.

Ramipril (trial dose 2.5 mg) titrated to 10 mg QD. Supplement after dialysis 2.5 mg.

Trandolapril (trial dose 1 mg) titrated to 4 mg QD. Supplement for dialysis 0.5 mg.

Lisinopril (trial dose 2.5 mg) titrated to 10 mg QD. Supplement after dialysis 2.5 mg.

Benazapril (trial dose 5 mg) titrated to 20 mg QD. Supplement after dialysis 5-10 mg.
Enalapril (trial dose 2.5 mg) titrated to 10 mg QD. Supplement after dialysis 2.5 mg.

SARTANS may be used as an alternative to ACE inhibitors

Losartan (trial dose 25 mg) titrated to 100 mg QD. NO supplement after dialysis needed.

Valsartan (trial dose 40 mg) titrated to 320 mg QD. "

Irbesartan (trial dose 75 mg) titrated to 300 mg QD. "

Telmisartan (trial dose 20 mg) titrated to 80 mg QD. "

Candesartan (trial dose 4 mg) titrated to 32 mg QD. "

Olmesartan (trail dose 10 mg) titrated to 40 mg QD. "

4. Indication of timescale and milestones to be achieved
(not more than 500 words)

Enrollment phase : 6 months

Study duration: 2 years

Study start and Study : June 2012 - Dec 2014

Echocardiographic data analysis (1 year) June 2013. Deliverable: Echocardiography manuscript by Dec 2013

Time to event analyses, By April 2015. Deliverable: manuscript on the "Effect of LW-US guided intervention on the risk of death and myocardial infarction and heart failure" by July 2015.

5. Detailed justification for support requested: that the work proposed can realistically be carried out in the named establishment, and that the major expense items are essential, particularly justification of expensive salaries

(not more than 500 words)

Coordinating centre
The CNR-IBIM Clinical Epidemiology of Renal Diseases and Hypertension Unit in Reggio Calabria, Italy.
It has several ongoing research projects directly funded by the National Research Council or by the Italian Ministry of Health and two ongoing projects funded by the European Commission.

Training Centre
Eugenio Picano group at CNR Institute of Clinical Physiology in Pisa (involved in several ongoing research projects funded by European Commission, Italian Ministry of health and Tuscany region; also serving as core lab and chest sonography training in USA-based, FDA-monitored trials of new drugs in acute heart failure using ultrasound lung comets as secondary end-point). Picano has 300 ISI articles (impact factor 1,000; ***Hirsh index 49***); coinvestigator is 29 year old cardiologist Luna Gargani (10 ISI articles on Ultrasound lung comets, global impact factor around 30).

EXPERIENCE OF THE STEERING COMMITTEE IN CLINICAL TRIALS IN ESRD

CNR-IBIM Clinical Epidemiology of Renal Diseases and Hypertension Unit in Reggio Calabria, Italy.

Carmine Zoccali MD, ***Hirsh-index 52***
- Steering Committee (Chair) and Principal investigator of the EXCITE study, a study aimed at assessing the effect of physical activity in ESRD (funded by the Italian Ministry of Health)
- Principal Investigator PRIMO study (http://clinicaltrials.gov/ct2/show/NCT00497146)
- Principal investigator, PED-ESRD (Paracalcitol in Endothelial Dysfunction in ESRD)
- Principal investigator Hemofiltration/Hemodiafiltration Hypotension trial (JASN 2010 Sep 2. [Epub ahead of print]

Co- investigator : Francesca Mallamaci MD
- Principal investigator EXCITE
- First author of the paper that validated lung – US in ESRD patients ***Hirsch Index 41***

Co-investigator : Davide Bolignano MD
- Co-investigator of the pilot study made at CNR-IBIM to probe the feasibility of the intervention tested in the present trial

Co-investigator: Giovanni Tripepi, Statistician, Master in Epidemiology (Rotterdam Univ.)
- Author of 144 papers in peer-reviewed journals, most of whom dealing with the clinical epidemiology of ESRD ***Hirsch Index 42***

- Responsible of the local administrative procedures of the CNR-IBIM of Reggio Calabria: Dr Salvatore Capria.

Manhes Hospital and INSERM U970.

Gerard London - ***Hirsch index 69***
- Steering committe and national coordinator of EVOLVE, COSMOS, Monitor-CKD studies
- Principal investigator REASON and EXPLORE studies

Co-investigators : Bruno Pannier - 161 peer reviewed publications

Co-Investigator: Marchais Sylvain - 78 peer reviewed publications

Co-investigator: Alain Guérin - 77 peer reviewed publications

Karolinska Institute

Bengt Lindholm MD -***Hirsh Index 54***
-Principal investigator and/or steering committee member to over 20 clinical trials

Department of Nephrology Saarland University Medical Centre

Danilo Fliser, MD - ***Hirsch Index: 43***
-Steering Committee (Chair) and Principal investigator of the PRIMAVERA study – ongoing (evaluation of the effect of CERA on progression of chronic kidney disease in patients with CKD stage 3-4)
-Principal investigator of the OECD study – ongoing (evaluation of the effect of olmesartan on EPCs and vascular repair in hypertensive patients with CKD stage 1-3)
-Principal investigator of the EPO-NTX study – completed (evaluation of the effect of high dose epoetin on ischemia-reperfusion injury in patients with CKD stage 5D after deceased donor kidney transplantation)
-Principal Investigator of the MIRACEL study – completed (evaluation of the effect of CERA on hemoglobin stability in patients with CKD stage 5D)
-Principal investigator of the HANDOUT study – completed (evaluation of the effect of high dose extracorporeal renal replacement therapy in patients with acute kidney injury (AKI) on the intensive care unit)
-Principal investigator of the PROMETHEUS study – completed (evaluation of the effect of extracorporeal liver support therapy in patients with liver failure on the intensive care unit)
-Principal investigator of the EUTOPIA study – completed (evaluation of the effect of olmesartan on vascular micro-inflammation in patients with hypertension and vascular disease)

Co-investigator: Gunnar Heine, MD
-Principal investigator of the I LIKE HOMe / HOM sweet HOMe / CARE For HOMe studies (epidemiological studies on sonographic markers and cardiovascular/renal outcomes in patients with CKD stage 1-5)
-Senior author of the work that validated DI-RISK (difference of resistive indices in spleen and kidney, a new ultrasound marker of kidney damage)

University of Amiens

Professor Ziad Massy MD, PhD –***Hirsch index 36***
-Global Steering Committee and French national coordinator SHARP trial (International)
-Associate French National Coordinator CKD-Dopps (International)
-Associate Coordinator and President of Scientific committee CKD-Rein (National)
-Principal coordinator NICOREN study (National)

Co-investigator: Sophie Liabeuf

Co-Coordinator of Clinical Research Centre Amiens University Hospital

Department of Renal Medicine and Transplantation, Guy's and St Thomas' NHS Foundation Trust, King's Health Partners Academic Health Science Centre (AHSC), London, UK.

Professor David Goldsmith MA MB B Chir FRCP ***Hirsch Index 31***
- Global Steering Committee member for IMPACT-SHPT (Abbott)
- Global Steering Committee member for MONITOR-CKD (Sandoz)
- Chief Investigator for Vitamin D in LVH in CKD patients (clintrials.gov reference number tbc)
- UK National Lead for the COSMOS study (2004-2011)
- Principal/Local Investigator for Genzyme : Sevelamer Carbonate in CKD study; for Shire: Lanthanum Carbonate; for Amgen: EVOLVE; for Wyeth-Pfizer: Sirolimus in renal transplantation.

Renal unit University of Madrid

Professor Alberto Ortiz MD, PhD ***Hirsch Index 29***
-Management Committee COST Action BM0702, Urine and Kidney Proteomics, EUROKUP Core Group Member, Fabry Registry database
-Principal / Local Investigator for Genzyme : Sevelamer Carbonate in PD study

Co- investigator : Emilio Gonzalez Parra MD ***Hirsch Index 9***
- Author of 31 papers in peer-reviewed, English language journals

Co-investigator : Carolina Gracia, MD

Co-investigator : Beatriz Fernandez, MD

Academic Renal Unit University of IASI

Prof. Adrian Covic, M.D., Ph.D., FRCP. - ***Hirsch Index 28***
-member of the steering committee of 4 , phase 2 or 3 ongoing clinical trials
-Principal investigator in 14 clinical trials

Co-investigator: Simona Hogas, MD, Dialysis and Transplantation Center "Dr.C.I.Parhon" University Hospital 50, B-dul Carol I, 700158, Iasi, Romania

Co-investigator: Radu Sascau, MD, Cardiology Center "Dr.C.I.Parhon" University Hospital 50, B-dul Carol I, 700158, Iasi, Romania

Co-investigator: Mihai Onofriescu , MD, Dialysis and Transplantation Center "Dr.C.I.Parhon" University Hospital 50, B-dul Carol I, 700158, Iasi, Romania

Academic Renal unit University of Katowice

Professor Andrzej Wiecek M.D., Ph.D., FRCP (Edin.) - ***Hirsh Index 24***
-Steering Committee of AURORA, SHARP, PEARL 1, and PEARL 2, ORAMA, DIRECT, VitaVasc, PolSenior, EU FP7 (European FP7) Programme: SysKid

Renal Unit, Bellvitge's University Hospital. Barcelona, Spain.

Prof. Alberto Martinez Castelao 58 publications in international , peer reviewed-PubMed indexed- medical Journals
-Principal investigator in AVOID, VITAL, CORDATUS and ESHOL

Co-Investigator: Melilli, Edoardo.PhD; MD

Co-investigator: Rama Arias, Ines.PhD

Co-Investigator: Ortega, Carlos, Pharmacist.

Akdeniz University School of Medicine, Department of Medicine, Nephrology Division, 07070, Campus Antalya/Turkey

Prof. Gultekin Suleymanlar 58 publications in international, peer reviewed-PubMed indexed- medical Journals
-Principal investigator of a population-based survey on Chronic REnal Disease In Turkey--the CREDIT study.

Co-investigator: Ibrahim Demir

SUMMARY OF STUDY COSTS

	Whole study funding (EU)
Participating Centres	
Echocardiography studies (200 EU per single echocardiogram x 500 pts x 4 studies)	400.000
Portable US scanners (GE Vscan 6000 EU per machine x 25 units)	150.000
Enrollment Incentive (500 EU per patient)	250.000
Local ethics committees	75.000
Coordinating Centre (CNR-IBIM)	

Biostatistician (1/4 WTE for 3 years)	45.000
Monitors (either 2 young Clinical Research trainees or 2 certified study nurses for 3 years)	180.000
Data Management [1/2 WTE technician for 3 years]	60.000
WEB site building and materials (CRFs etc.)	40.000
Travel (5 on site visits: 1500 EU x visit x 125 visits in 25 centres)	187.500
Training and certification of the sonographers (1 day visit to the training centre at the CNR institute of Clinical Physiology in Pisa, ITALY, including the cost of the trainer)	70.000
Investigators meetings, teleconferences	90.000
Patients insurance	100.000
Total	1.647.500

6. Does the proposal have commercial potential?

If the trial will provide evidence that measurement of extravascular lung water by US is useful in the clinical care of dialysis patients, simple, small volume sonographs can be specifically adapted for the application in the dialysis population. Sonographs that allow guided introduction of hemodialysis catheters are already being used in many dialysis centers. The development of special sonographs serving the dual scope of guiding the insertion of central (venous) catheters and of measuring LW can be envisaged.

List of Collaborating Researchers and Institutions:

1) **CARMINE ZOCCALI**
Renal and Transplantion Unit, and CNR-IBIM Clinical Epidemiology of Renal Diseases and Hypertension Unit. Ospedali Riuniti, 89124 Reggio Cal. Italy

2) **GERARD MICHEL LONDON**
Manhes Hospital and INSERM U970, 8 rue Roger Clavier and 56 rue Leblanc, 91712 and 75015, Fleury-Mérogis and Paris France

3) **DANILO FLISER**
Department of Internal Medicine IV, Saarland University Medical Centre, Homburg/Saar, Germany

4) **ZIAD MASSY**
Division(s) of Clinical Pharmacology and Nephrology, University Of Picardie and Amiens University Hospital, Amiens University Hospital, INSERM ERI-12/ EA4292. CHU-Amiens South, Av René Laënnec 80054, Amiens Cedex 1, France

5) **DAVID GOLDSMITH**
Department of Renal Medicine and Transplantation, Guy's and St Thomas' NHS Foundation Trust, King's Health Partners Academic Health Science Centre (AHSC), London, UK.

6) **ALBERTO ORTIZ ARDUAN**
IIS-Fundacion Jimenez Diaz, Av Reyes catolicos 2, 28040, Madrid, Spain.

7) **ADRIAN COVIC**
Dialysis and Transplantation Center, "Dr.C.I.Parhon" University Hospital 50, B-dul Carol I, 700158, Iasi, Romania

8) **ANDRZEJ WIECEK**
Institution: Department of Nephrology, Endocrinology and Metabolic Diseases, Medical University of Silesia, Francuska 20/24 Str. 40-027 Katowice, Poland

9) **ALBERTO MARTINEZ-CASTELAO**
Bellvitge´sUniversity Hospital, Feixa Llarga sn 08907, Hospitalet, Barcelona, Spain

10) **GULTEKIN SULEYMANLAR**
Akdeniz University School of Medicine, Department of Medicine, Nephrology Division, 07070, Campus Antalya/Turkey

*Give the following information **for each professional person** involved on the project, beginning with the Applicant. Use continuation pages (**numbered 1, 2, etc**) as necessary following the same format for each person.*

Person N. 1

NAME	TITLE:	DATE OF BIRTH
Carmine Zoccali	**MD, FASN,** **professor of Nephrology (PG)**	27 / 01 / 1947

Place of Birth (Country):	Present Nationality:	Sex
Italy	Italian	M

Degrees/Diplomas	Year Conferred

- Major field of interest:
Cardiovascular complications of CKD, CKD, progression of renal diseases, ESRD,
Hypertension, Clinical Epidemiology of renal diseases

- Summarize the main outcomes of your research work/ programme(s) in the last 5 years (500 words maximum):
work/programme(s) in the last 5 years, overall in the field of this application (500 words maximum, not including the refs in the count):
The research group leaded by dr. Zoccali has recently validated the chest US technique to estimate lung water in dialysis patients (**ref. 1**). Investigators in this group have a longstanding interest on cardiomyopathy and cardiovascular risk in ESRD patients. They were the first that draw attention to proper indexing (by height) of LV mass to optimize the predictive power of this biomarker in ESRD patients and to show the relevance of subclinical alterations in thyroid hormones (low T3, **see ref. 5**), sympathetic over-activity and the accumulation of the endogenous inhibitor of nitric oxide synthase, asymmetric dimethylarginine (ADMA) in the pathogenesis of cardiomyopathy in ESRD. In 2001 this group was the first to report that cardiac natriuretic peptides in ESRD patients largely reflect LV mass and function and that BNP is a strong predictor of death and incident cardiovascular events in this population. Furthermore, the same investigators have recently shown that BNP is strongly associated with left atrial volume as well as with left atrial volume progression in ESRD (**ref. 3**).
All members of the EURECA-m working group (Directors of the 10 participating Units) are internationally recognized clinical investigators with wide experience in cardiovascular and renal medicine. Their Hirsh-Index or (PubMed) publications number is reported in the previous section

References :

Total number of **peer reviewed** publications in Pub Med by dr. C.Zoccali**:** 396

Publications *(List up to 5 recent publications relevant to proposed project)*

1) Mallamaci F, Benedetto FA, Tripepi R, Rastelli S, Castellino P, Tripepi G, Picano E, Zoccali C.
Detection of pulmonary congestion by chest ultrasound in dialysis patients. JACC Cardiovasc Imaging. 2010; 3:586-94.

2) Zoccali C. Left ventricular systolic dysfunction: a sudden killer in end-stage renal disease patients. Hypertension. 2010; 56:187-8.

3) Tripepi G, Mattace-Raso F, Mallamaci F, Benedetto FA, Witteman J, Malatino L, Zoccali C.
Biomarkers of left atrial volume: a longitudinal study in patients with end stage renal disease.
Hypertension. 2009; 54:818-24.

4) Stella P, Manunta P, Mallamaci F, Melandri M, Spotti D, Tripepi G, Hamlyn JM, Malatino LS, Bianchi G, Zoccali C.
Endogenous ouabain and cardiomyopathy in dialysis patients. J Intern Med. 2008; 263:274-80.

5) Zoccali C, Benedetto F, Mallamaci F, Tripepi G, Cutrupi S, Pizzini P, Malatino LS, Bonanno G, Seminara G.
Low triiodothyronine and cardiomyopathy in patients with end-stage renal disease.
J Hypertens. 2006; 24:2039-46

Person N. 2

NAME	TITLE:	DATE OF BIRTH
Alberto Ortiz	**Co-Chief of Nephrology, Fundacion Jimenez Diaz Associate Professor of Medicine, Universidad Autonoma de Madrid**	20 / 07 / 1963
Place of Birth (Country): Madrid (Spain)	Present Nationality: Spanish	Sex Male
Degrees/Diplomas MD PhD	Year Conferred 1987 1991	

- Major field of interest:
Research has focused over the last 20 years on the study of different aspects of CKD in search of novel therapeutic approaches and biomarkers. Specific subjects of study include the pathogenesis of the progression of CKD, dialysis, glucotoxicity, metabolic bone disease and their relationship to cardiovascular injury.

- Summarize the main outcomes of your research work / programme(s) in the last 5 years (500 words maximum):
Over the past 5 years our research program has resulted in 90 peer-reviewed publications, for a total career
Hirsch Index 29. Main outcomes of the research include:
Clinical. Defining the role of sevelamer in peritoneal dialyiss, characterisation of cell culture and in vivo (animal models, clinical) effects of novel peritoneal dialysis solutions, characterising the natural history and response to therapy of Fabry disease, and identification of novel biomarkers of cardiovascular disease in CKD patients, including TWEAK and MMP-10
Traslational: identification of novel mediators of acute kidney injury that may be therapeutic targets,

preclinical study of TWEAK targeting in renal disease, identification and characterisation of novel mediators of diabetic kidney injury identified from human biopsy transcriptomics including CD74, Basp1 and TRAIL, identification of novel pathogenic mediators of Fabry disease (lyso-Gb3) and its mechanism of action.

References:

Total number of **peer reviewed** publications in Pub Med**: 200**

Publications *(List up to 5 recent publications relevant to proposed project)*

1. Carrero JJ, **Ortiz A**, Qureshi AR, Martín-Ventura JL, Bárány P, Heimbürger O, Marrón B, Metry G, Snaedal S, Lindholm B, Egido J, Stenvinkel P, Blanco-Colio LM. Additive effects of soluble TWEAK and inflammation on mortality in patients undergoing hemodialysis. **Clin J Am Soc Nephrol 2009**;4:110-8
2. Sanchez-Niño MD, Sanz AB, Ihalmo P, Lassila M, Holthofer H, Mezzano S, Aros C, Groop PH, Saleem MA, Mathieson PW, Langham R, Kretzler M, Nair V, Lemley KV, Nelson RG, Mervaala E, Mattinzoli D, Rastaldi MP, Ruiz-Ortega M, Martin-Ventura JL, Egido J, **Ortiz A**. The MIF receptor CD74 in diabetic podocyte injury. **J Am Soc Nephrol** 2009 Feb;20(2):353-62
3. Sanchez Niño MD, Sanz AB, Corina Lorz C, Gnirke A, Rastaldi MP, Nair V, Egido J, Ruiz-Ortega M, Kretzler M, **Ortiz A**. functional genomics identifies BASP-1 as a pro-apoptotic factor in diabetic nephropathy**. J Am Soc Nephrol**. 2010 Apr;21(4):610-21 PubMed PMID: 20110383
4. Wanner C, Oliveira JP, **Ortiz A**, Mauer M, Germain DP, Linthorst GE, Serra AL, Maródi M, Mignani R, Cianciaruso B, Vujkovac B, Lemay R, Beitner-Johnson D, Waldek S, Warnock DG. Prognostic Indicators of Renal Disease Progression in Adults with Fabry Disease: Natural History Data from the Fabry Registry. **Clin J Am Soc Nephrol** 2010 Dec;5(12):2220-8. Epub 2010 Sep 2. PubMed PMID: 20813854
5. Coll B, Rodríguez JA, Craver L, Orbe J, Martínez-Alonso M, **Ortiz A**, Díez J, Borras M, Valdivielso JM, Fernández E, Páramo JA. Serum Matrix Metalloproteinase 10 is associated with the severity of atherosclerosis in patients with chronic kidney disease. **Kidney Int** 2010 Dec; 78(12):1275-80.

Person N. 3

NAME	TITLE:	DATE OF BIRTH
MASSY ZIAD	**Prof**	03 / 08 / 1959

Place of Birth (Country):	Present Nationality:	Sex
Homs (Syria)	French	Male

Degrees/Diplomas	Year Conferred
MD, PhD	1982 and 2000

- Major field of interest:

Cardiovascular disease, vascular calcifications, hyperlipidemia, uremic toxins, oxidative stress, chronic renal failure,
chronic kidney disease, and chronic renal allograft nephropathy

- Summarize the main outcomes of your research work / programme(s) in the last 5 years (500 words maximum):

Cardiovascular calcifications are frequently observed in the general population. They occur with an even higher frequency in patients with chronic renal failure (CRF). Their presence is associated with a major risk of cardiovascular morbidity and mortality. The molecular mechanisms involved in these processes and the multiple consequences of these soft-tissue calcifications have not yet been well established. Our research work, based on cellular models in vitro (osteoclast precursors, vascular smooth muscle cells and circulating monocytes), animal models in vivo (apolipoprotein E gene knock-out mouse with spontaneous development of atherosclerosis, in the presence or absence of superimposed

CRF), and clinical investigation in CRF patient cohorts and in elderly women cohort (EPIDOS cohort), has allowed us to progress in the understanding of the molecular and cellular mechanisms underlying the occurrence of vascular calcifications. Above all, they will help us in the future to identify new therapeutic targets which may lead to the development of innovating strategies for the prevention and treatment of arterial and valvular calcifications. Concerning new therapeutic approaches, we have made important contributions to the prevention of soft tissue calcification in CRF by phosphate binding agents, with the goal to limit the negative effects of uremic toxins on vascular tissues. We also have contributed in an important manner to present knowledge about the role played by the calcium-sensing receptor in the calcification process. The activation of this receptor, in particular by co-agonists such as the calcimimetics, appears to exert a protective action not only in experimental animals, but also in patients with CRF, as recently shown by others.

I carry out epidemiological work evaluating the role of lipids in cardiovascular disease (CVD) in renal transplant recipients (RTR) and Chronic Kidney Disease (CKD). I reported my first meta-analyses related to lipid-lowering therapy in patients with renal disease. The results of this meta-analysis provided a useful framework for choosing lipid lowering therapies, and pointed to areas of future long-term studies in this area. In last few years, I take the role of SHARP National Coordinator for France. SHARP, which has been published recently showing that the reduction of LDL cholesterol with simvastatin 20 mg plus ezetimibe 10 mg daily safely reduced the incidence of major atherosclerotic events in a wide range of patients with advanced CKD.

In conclusion, I have made, both from the point of view of basic research and clinical investigation, important contributions to the mechanisms as well as the prevention and treatment of CVD in CKD patients.

References:

Total number of **peer reviewed** publications in Pub Med**: 199**

Publications *(List up to 5 recent publications relevant to proposed project)*

1) Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, Wanner C, Krane V, Cass A, Craig J, Neal B, Jiang L, Hooi LS, Levin A, Agodoa L, Gaziano M, Kasiske B, Walker R, **Massy ZA**, ……. Collins R; SHARP Investigators. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. **Lancet.** 2011;377(9784):218192. (IF:33.63)

2) Maizel J, Six I, Slama M, Tribouilloy C, Sevestre H, Poirot S, Giummelly P, Atkinson J, Choukroun G, Andrejak M, Kamel S, Mazière JC, **Massy ZA**. Mechanisms of aortic and cardiac dysfunction in uremic mice with aortic calcification.
Circulation 2009; 119(2):306-13. (IF:14.43)

3) Phan O, Ivanovski O, Nguyen-Khoa T, Mothu N, Angulo J, Westenfeld R, Ketteler M, Meert N, Maizel J, Nikolov I, Vanholder R, Lacour B, Drüeke TB,. **Massy ZA**. Sevelamer prevents uremia-enhanced atherosclerosis progression in apolipoprotein E deficient (apoE-/-) mice. **Circulation** 2005; 112;2875-2822 (IF:14.43)

4) Mozar A, Haren N, Chasseraud M, Louvet L, Mazière C, Wattel A, Mentaverri R, Morlière P, Kamel S, Brazier M, Mazière JC, **Massy ZA**. High extracellular inorganic phosphate concentration inhibits RANK-RANKL signaling in osteoclast-like cells. **J Cell Physiol** 2008; 215(1):47-54. (IF:3.986)

5) Ivanovski O, Nikolov IG, Joki N, Caudrillier A, Phan O, Mentaverri R, Maizel J, Hamada Y, Nguyen-Khoa T, Fukagawa M, Kamel S, Lacour B, Drueke TB, **Massy ZA**. The calcimimetic R-568 retards uremia-enhanced vascular calcification and atherosclerosis in apolipoprotein E deficient Apo E (-/-) mice. **Atherosclerosis** 2009; 205(1):55-62. (IF:4.086)

Person N. 4

NAME	TITLE:	DATE OF BIRTH
Covic Adrian Constantin	MD. PhD, FRCP (London), FERA	**06/05/1967**

Place of Birth (Country): Romania	Present Nationality: Romanian	Sex Male
Degrees/Diplomas -graduated University of Medicine and Pharmacy "Gr.T. Popa", Iasi, Romania - Ph.D. dissertation - Professor at the University of Medicine “Gr. T. POPA” Iasi - Vice-Dean of the University of Medicine “Gr. T. POPA” Iasi	Year Conferred 1991 1997 2004 2004	

- Major field of interest:

cardiovascular complications in renal disease
haemodialysis
renal anemia
CKD-MBD
acute renal failure

- Summarize the main outcomes of your research work / programme(s) in the last 5 years (500 words maximum):

Prof. Covic started his clinical and research activity as a fellow in Nephrology in Manchester and Amiens. Later he performed clinical research at the Case Western University in Cleveland, Ohio. He received a Ph.D. on cardiovascular abnormalities and its determinant factors in chronic renal failure in 1997. Since 2007, he is a FRCP (London) and became in 2009 a correspondent member of the Romanian Academy of Medical Sciences.
He is a Full Professor of Nephrology and Internal Medicine at the “Gr.T. Popa” University of Medicine and Pharmacy and the Director of the Nephrology Clinic and the Dialysis and Transplantation Center in Iasi, Romania.
Prof. Covic published more than 200 original and review papers in peer-reviewed journals, 11 books and 22 chapters.
He is a Subject Editor for NDT, an Associate Editor for the International Journal of Urology and Nephrology, and editor / reviewer for several prestigious journals.
His main areas of interest are: cardiovascular complications in renal disease, renal anaemia, CKD-MBD, peritoneal dialysis, and acute renal failure.
Professor Covic is the past president of Romanian Society of Nephrology and a board member of Kidney Disease: Improving Global Outcomes (KDIGO) and European Renal Best Practice. He is currently also the Secretary/Treasurer of the European Renal Association/European Dialysis and Transplant Association (ERA-EDTA), Chair of the International Society of Nephrology's (ISN's) Commission for the Global Advancement of Nephrology (COMGAN) Committee for Central and Eastern Europe and member of the KDIGO Board of Directors.
Due to the large expertise in the field of nephrology/dialysis/cardiovascular complications of renal disease, he has been invited to participate in numerous national and international studies (22 in total), most notable examples being:
International steering committee: COSMOS, AFFYMAX, The European Body Composition Monitoring (EuroBCM) Study Cohort, ORAMA
Principal Investigator: CALMAG, EURO-BCM, HEMATIDE

References:

Total number of **peer reviewed** publications in Pub Med**: 225**

Prof. Dr. Covic Adrian
Search - ISI Web of knowledge 1994-2011:
199 ISI indexed publications, 2048 citations, Hirsch-index: 30

Publications *(List up to 5 recent publications relevant to proposed project)*

1) Covic, A; Kanbay, M; Voroneanu, L; Turgut, F; Serban, DN; Serban, IL; Goldsmith, DJ, Vascular calcification in chronic kidney disease, CLINICAL SCIENCE, Vol 119, 111-121, (2010), Total Citations = 0

2) Gusbeth-Tatomir, P; Covic, A, Causes and consequences of increased arterial stiffness in chronic kidney disease patients, KIDNEY & BLOOD PRESSURE RESEARCH, Vol 30, 97-107, (2007), Total Citations = 21

3) Covic, A; Goldsmith, DJA; Gusbeth-Tatomir, P; Covic, M, Haemodialysis acutely improves endothelium-independent vasomotor function without significantly influencing the endothelium-mediated abnormal response to a beta 2-agonist, NEPHROLOGY DIALYSIS TRANSPLANTATION, Vol 19, 637-643, (2004), Total Citations = 13

4) Goldsmith, DJA; Covic, AC, Meta-Analysis of the Effects of Treating Blood Pressure on Cardiovascular Outcomes of Dialysis Patients, HYPERTENSION, Vol 54, E6-E6, (2009), Total Citations = 2

5) Locatelli, F; Covic, A; Chazot, C; Leunissen, K; Luno, J; Yaqoob, M, Hypertension and cardiovascular risk assessment in dialysis patients, NEPHROLOGY DIALYSIS TRANSPLANTATION, Vol 19, 1058-1068, (2004), Total Citations = 28

Person N. 5

NAME: **DANILO FLISER**		**TITLE:** **PROF. Dr.**	**DATE OF BIRTH:** **13/04/1962**
Place of Birth (Country): Slovenia	Present Nationality: German		Sex: male
Degrees/Diplomas: MD	Year Conferred: 1989		

- Major field of interest:

The major field of interest are different aspects of cardiovascular medicine and progression of chronic kidney disease with particular focus on endothelial and vascular function. Here, the principal work is on endothelial dysfunction and protective mechanisms including endothelial regeneration.

- Summarize the main outcomes of your research work / programme(s) in the last 5 years (500 words maximum):

At the Department of Internal Medicine IV – Renal and Hypertensive Diseases – of the Saarland University Medical Centre we have established two internationally recognized working groups in the field of cardiovascular medicine: one is devoted to clinical research in patients with CKD, whereas the other explores different aspects of endothelial and vascular injury in animal models of CKD.
The former group (under guidance of Associate Professor G. Heine, MD) has recently published several reports in high ranked journals on the role of inflammatory monocytes in the pathogenesis of vascular injury in patients with CKD [***Blood*** (in revision); ***Eur Heart J*** 2011, 32: 84; ***CJASN*** 2011, 6: 505; ***Eur Heart J*** 2010, 31: 369; ***NDT*** 2010, 25: 2265; ***NDT*** 2009, 24: 3480; ***Kidney Int*** 2008, 73: 622; ***Am J Transplant*** 2008, 8: 103] and on the relationship between FGF-23 and cardiovascular morbidity and mortality, and progression in CKD patients [***Eur Heart J*** (in revision), ***NDT*** 2010, 25: 3983; ***JASN*** 2007, 18: 2600]. This working group has also extensive experience with the use of ECHO and kidney ultrasound as diagnostic tools in CKD patients [***Radiology*** (in revision); ***NDT*** 2009, 25: 1294].
The second working group, which was formally established by me already at the Hannover Medical School, is now managed by F. Bahlmann, MD, PhD, and has contributed on microvascular inflammation, derangement of nitric oxide metabolism and the role of endothelial progenitor cells (EPCs) in patients with CKD and in patients with the metabolic syndrome [***NDT*** 2011, 26: 1421; ***PLOS One*** 2010, 5: e11477; ***Atherosclerosis*** 2009, 206: 184; ***J Hypertens*** 2009, 27: 1641; ***Circulation*** 2007, 116: 163; ***FASEB J*** 2006, 20: 994; ***Circulation*** 2005, 111: 2356; ***Hypertension*** 2005, 45: 526; ***Transplantation*** 2005, 79: 941; ***Blood*** 2004, 103: 921; ***Circulation*** 2004; 110: 1103; ***Kidney Int*** 2004, 66: 641; ***Kidney Int*** 2003, 64: 1648]. We were among the first to describe dysfunctional EPCs as a possible cause of endothelial dysfunction and cardiovascular disease in patients with chronic kidney disease. Moreover, we have shown that

pharmacological manipulation of these cells using erythropoietin or angiotensin II receptor blockers can increase the number of functionally active EPCs in CKD patients. Another important field of research are the pleitropic effects of erythropoietin [***Kidney Int*** (in revision); ***Eur J Clin Invest*** 2009, 39: 755; ***JASN*** 2007, 18: 2046; ***Circulation*** 2004, 110: 1006].

Total number of **peer reviewed** publications in Pub Med**: >150**

Publications *(List up to 5 recent publications relevant to proposed project)*

1) Seiler S, Cremers B, Rebling N, Hornof F, Steimle C, Jeken J, Kersting S, Rogacev KS, Scheller B, Böhm M, Fliser D, Heine GH. FGF-23 and left-ventricular dysfunction in subjects with and without renal function impairment. ***Eur Heart J*** (in revision)
2) Rogacev KS, Seiler S, Zawada A, Reichart B, Roth D, Ulrich C, Fliser D, Heine GH. $CD14^{++}16^{+}$ monocytes are independent predictors of cardiovascular outcome in patients with chronic kidney disease. ***Eur Heart J*** 2011; 32: 84-92
3) Lorenzen JM, David S, de Groot K, Bahlmann FH, Bahlmann E, Haller H, Fliser D. Endothelial progenitor cells (EPCs) and survival in patients on maintenance hemodialysis. ***PLOS One*** 2010: 5: e11477
4) David S, Kümpers P, Seidler V, Biertz F, Haller H, Fliser D. Diagnostic value of N-terminal pro b-type natriuretic peptide (NT-proBNP) for left ventricular dysfunction in patients with chronic kidney disease (CKD) stage 5 on hemodialysis. ***Nephrol Dial Transplant*** 2008; 23: 1370-1377

Person N. 6

NAME **Bengt Lindholm**		TITLE: **Professor**	DATE OF BIRTH 05 / 05 / 1946
Place of Birth (Country): Sweden	Present Nationality: Sweden		Sex Male
Degrees/Diplomas MD, PhD	Year Conferred		

- Major field of interest: Dialysis; Cardiovascular disease in CKD: Metabolism, nutrition, and endocrinology in CKD; Inflammation, oxidative stress, genetics, CKD-BMD, and other factors influencing CVD and clinical outcome in CKD and dialysis patients. Fluid and solute removal kinetics in dialysis.

- Summarize the main outcomes of your research work / programme(s) in the last 5 years (500 words maximum): During the last 5 years, research work in the abovementioned areas resulted in 170 PubMed publications co-authored by the applicant and most of which involved close collaboration with Prof Peter Stenvinkel and colleagues as well as international collaboration through visiting post docs from many countries. A main focus of our research is to describe and try to understand causes and risk factors for the high CVD mortality in CKD and dialysis patients including volume overload. Another research line is the detailed description of nutritional, metabolic and endocrine alterations in CKD and links with clinical outcomes. An increasing number of biomarkers have been analyzed in cohorts of carefully phenotyped CKD stage 5 patients.

References:

Total number of **peer reviewed** publications in Pub Med**: 350**

Publications *(List up to 5 recent publications relevant to proposed project)*

1)Hayashi SY, Seeberger A, Lind B, Nowak J, do Nascimento MM, Lindholm B, Brodin LA. A single session of haemodialysis improves left ventricular synchronicity in patients with end-stage renal disease: a pilot tissue synchronization imaging study. Nephrol Dial Transplant. 2008 Nov;23(11):3622-8.

2)Nakashima A Carrero JJ, Qureshi AR, Miyamoto T, Anderstam B, Bárány P, Heimbürger O, Stenvinkel P, Lindholm B. Effect of Circulating Soluble Receptor for Advanced Glycation End Products (sRAGE) and the Proinflammatory RAGE Ligand (EN-RAGE, S100A12) on Mortality in Hemodialysis Patients. Clin J Am Soc Nephrol. 2010 Dec;5(12):2213-9

3) Olauson H, Qureshi AR, Miyamoto T, Barany P, Heimburger O, Lindholm B, Stenvinkel P, Larsson TE. Relation between serum fibroblast growth factor-23 level and mortality in incident dialysis patients: are gender and cardiovascular disease confounding the relationship? Nephrol Dial Transplant. 2010 Sep;25(9):3033-8

4) Carrero JJ, Nakashima A, Qureshi AR, Lindholm B, Heimbürger O, Bárány P, Stenvinkel P. Protein-energy wasting modifies the association of ghrelin with inflammation, leptin, and mortality in hemodialysis patients. Kidney Int. 2011 Apr;79(7):749-56.

5) Meuwese CL, Snaedal S, Halbesma N, Stenvinkel P, Dekker FW, Qureshi AR, Barany P, Heimburger O, Lindholm B, Krediet RT, Boeschoten EW, Carrero JJ. Trimestral variations of C-reactive protein, interleukin-6 and tumour necrosis factor-α are similarly associated with survival in haemodialysis patients. Nephrol Dial Transplant. 2011 Apr;26(4):1313-8.

Person N. 7

NAME	TITLE:	DATE OF BIRTH
GÜLTEKİN SÜLEYMANLAR	**PROF**	02 / 01 / 1957

Place of Birth (Country):	Present Nationality:	Sex
ANKARA-TURKEY	TURKISH	MALE

Degrees/Diplomas	Year Conferred
MEDICAL DOCTOR	1980

- Major fields of interest:

Cardiovascular disorders in chronic kidney disease, renal epidemiology, renal registry on RRT patients, transplantation

- Summarize the main outcomes of your research work / programme(s) in the last 5 years (500 words maximum):

1. Oxidative stress and anti-oxidant mechanisms in CKD requiring RRT
2. A population-based survey of Chronic REnal Disease In Turkey--the CREDIT cohort study; phase I completed in 2009, phase II is going on
3. Managing the National Renal Registry System in Turkey on behalf of TSN
4. Establishment of Transplantation Institute at Akdeniz University

References:

Total number of **peer reviewed** publications in Pub Med**: 59**

Publications *(List up to 5 recent publications relevant to proposed project)*

1) Dursun B, Dursun E, **Suleymanlar G**, Ozben B, Capraz I, Apaydin A, Ozben T. The effect of hemodialysis on accelerated atherosclerosis in diabetic patients: correlation of carotid artery intima-media thickness with oxidative stress. J Diabetes Complications. 2009 Jul-Aug;23(4):257-64. Epub 2008 Apr 16.

2) Fellström BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, Chae DW, Chevaile A, Cobbe SM,

Grönhagen-Riska C, De Lima JJ, Lins R, Mayer G, McMahon AW, Parving HH, Remuzzi G, Samuelsson O, Sonkodi S, Sci D, **Süleymanlar G,** Tsakiris D, Tesar V, Todorov V, Wiecek A, Wüthrich RP, Gottlow M, Johnsson E, Zannad F; AURORA Study Group. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med. 2009 Apr 2;360(14):1395-407. Epub 2009 Mar 30.

3) Kocak H, Gumuslu S, Sahin E, Ceken K, Ermis C, Gocmen AY, Yakupoglu G, Ersoy FF, **Suleymanlar G**, Tuncer M. Relationship between carotid artery intima-media thickness and brachial artery flow-mediated dilation in peritoneal dialysis patients. Int Urol Nephrol. 2009;41(2):409-16.

4) Dursun B, Dursun E, **Suleymanlar G**, Ozben B, Capraz I, Apaydin A, Ozben T. Carotid artery intima-media thickness correlates with oxidative stress in chronic haemodialysis patients with accelerated atherosclerosis. Nephrol Dial Transplant. 2008 May;23(5):1697-703. Epub 2008 Jan 3.

5) **Süleymanlar G**, Utas C, Arinsoy T, Ates K, Altun B, Altiparmak MR, Ecder T, Yilmaz ME, Camsari T, Basçi A, Serdengeçti K. A population-based survey of Chronic REnal Disease In Turkey--the CREDIT study. Nephrol Dial Transplant. 2011 Jun;26(6):1862-71. Epub 2010 Nov 4.

Person N. 8

NAME	TITLE:	DATE OF BIRTH
Alberto MARTINEZ CASTELAO	**MD; PhD**	26 / 06 / 1948

Place of Birth (Country):	Present Nationality:	Sex
Spain (León)	Spanish	Male

Degrees/Diplomas	Year Conferred
PhD; MD; Associated Prof	1973;1982;1997

- Major field of interest:

Diabetic nehropathy; CV risk factors; CKD progression; anaemia; dyslipidaemia; OL HDF; immunosuppression

- Summarize the main outcomes of your research work / programme(s) in the last 5 years (500 words maximum):

- GEENDIAB, Spanish Group Diab. Neph. Study: CALVIDIA, MERENA, NADIR-3; PROGRESER (this is starting now, n= 800 p, comparing progression factors in diabetic vs non-diabetic CKD-3 patients).

- Spanish Renal Health Strategies. Design and collaborative studies. EPIRCE (n= 2740 p). EROHOSP, (.EROCAP, n= 6700 Primary Care attending p).

- Atherosclerosis Observatory Program: NEFRONA study. multicenter Spanish Study (> 2000 CKD patients, stages 2-5D) ongoing in 50 centers, with a control group (n= 1000 p).

- EMITRAL study: vascular calcifications & atherosclerosis in CKD-5T (renal transplant patients), ongoing.

- Anemia studies in CKD 3-5D. AMG-114. AMG-163, CORDATUS, STELLATA, EMERALD…

- Diabetic Neph. International trials: RENAAL, AVOID, ALTITUDE and others.

- CKD detection in PC sites: Consensus Doc SEN-SEMFYC (Primary Care Ph). Consensus Doc SEN- SEQC (estimation of GFR).

References:

Total number of **peer reviewed** publications in Pub Med**: > 150 (see as Martínez Castelao A; and Castelao AM)**

Publications *(List up to 5 recent publications relevant to proposed project)*

1) Martínez-Castelao A, Sarrias X, Bestard O, Gil-Vernet S, Serón D, Cruzado JM, Moreso F, Díaz-Noguera A, Grinyó JI elasticity measurement in renal transplant patients under anticalcineurin immunosuppression. Transplant Proc 20 3788-90.

2) Gerth W, Remuzzi G, Viberti G, Hannedouche T, Martínez-Castelao A, Shainfar S, Carides GW, Brenner B: Losartan re burden and cost of ESRD: public halth implications from the RENAAL study for the European Union. Kidney Int 2002 82): S-68-S-72.

3) Martínez Castelao, A; Górriz JL, García-López F, López-Revuelta K, Cruzado JM: Perceived health-related quality comorbidity in diabetic patients starting dialysis (CALVIDIA study). J. Nephrol 2004; 17:544-551.

4) Martínez-Castelao A, Hernández D, Pascual J et al. Detection and treatment of post Kidney Transplant hyperg Spanish multicenter cross-sectional study. Transplant Proc 2005; 37 (9): 3813-3816.

5) Mann J, Kessler M, Villa G, Martinez-Castelao A, Feldt-RasmussenB, Cruz J, Hörl W, Mattin C, Prami C, Wilke M. Da alfa once every two weeks for treatment of anemia in dialysis patients: a combined análisis of eight multicenter Nephrol 2007; 67(3): 140-148.

6) Ramos R, Martínez-Castelao A. Lipoperoxidation and hemodialysis. Metabolism Clin Exper. 2008; 57:1369-1374.

7) Kessler C, Martínez-Castelao A, Siamopoulos K, Villa G, Spinowitz B, Dougherty FC, Beyer U. C.E.R.A. once every patients with chronic kidney disease not on dialysis: the ARCTOS extension study. Hemodial modial Int 2009; 1: 1-7

Person N. 9

NAME	TITLE:	DATE OF BIRTH
Gérard Michel LONDON	**MD**	03 / 04 / 1943

Place of Birth (Country):	Present Nationality:	Sex
France	French	Male

Degrees/Diplomas	Year Conferred
MD	1966

- Major field of interest:

Pathophysiology of cardiovascular disease in hypertension and renal diseases

- Summarize the main outcomes of your research work / programme(s) in the last 5 years (500 words maximum):

The principal outcomes in my research is the pathophysiology and clinical consequences of arterial disease and functional abnormalities in CKD and ESRD patients. The focus is principally the changes in mechanical properties of the arterial system (stiffness, wave reflections and impedances mismatches) and their influence on cardiac structure and function. We were the first to demonstrate the arterial stiffening in ESRD patients and their predictive value for CV morbidity and mortality. We demonstrated the association between arterial stiffening and calcifications with adynamic bone disease and the role of calcium overload associated with calcifications in the present of low bone turnover. We also demonstrated for the first time the association between low vitamin D status and abnormal arterial and endothelial function in CKD patients. The second field of interest concerns the endothelial function in

ESRD patients.

References:

Total number of **peer reviewed** publications in Pub Med**:** 327 (London G or London GM)

Publications *(List up to 5 recent publications relevant to proposed project)*

1) Clin JASN 2011 (in press) Flow mediated dilation in ESRD patients.
Werbeke F, Pannier B, Boutouyrir P, Laurent S, London GM

2)Kidney Int. 2010 Feb;77(4):273-84
Blood pressure in chronic kidney disease stage 5D-report from a Kidney Disease: Improving Global Outcomes controversies conference.
Levin NW, Kotanko P, Eckardt KU, Kasiske BL, Chazot C, Cheung AK, Redon J, Wheeler DC, Zoccali C, London GM.

3) J Am Soc Nephrol. 2008 Sep;19(9):1827-35.
Association of bone activity, calcium load, aortic stiffness, and calcifications in ESRD.
London GM, Marchais SJ, Guérin AP, Boutouyrie P, Métivier F, de Vernejoul MC.

4) Hypertension. 2007 Apr;49(4):902-8. In vivo shear stress determines circulating levels of endothelial microparticles in end-stage renal disease.
Boulanger CM, Amabile N, Guérin AP, Pannier B, Leroyer AS, Mallat CN, Tedgui A, London GM.

5) J Am Soc Nephrol. 2007 Feb;18(2):613-20.
Mineral metabolism and arterial functions in end-stage renal disease: potential role of 25-hydroxyvitamin D deficiency.
London GM, Guérin AP, Verbeke FH, Pannier B, Boutouyrie P, Marchais SJ, Mëtivier F.

6) Blood Purif. 2011;31(1-3):107-12. Central artery pulse pressure in end-stage renal disease: the roles of aortic diameter, aortic stiffness and wave reflection.
Pannier B, Guérin AP, Marchais SJ, Safar ME, London GM.

Person N. 10

NAME	TITLE:	DATE OF BIRTH
David Goldsmith	**Reader / Dr**	29 / 08 / 1959

Place of Birth (Country):	Present Nationality:	Sex
UK	UK	Male

Degrees/Diplomas	Year Conferred
MA MB BChir FRCP (Lond) FRCP (Edin) FASN	1983 onwards

- Major field of interest: Hyperparathyroidism, calcification, hypertension, left ventricular mass

- Summarize the main outcomes of your research work / programme(s) in the last 5 years (500 words maximum):

Cardiovascular disease and chronic kidney disease share many risk factors, both genetic and environmental, and many of the promoters and accelerators for one also aggravate the other. Renal failure, and albuminuria, independently and equally, impact negatively on cardiovascular disease; kidney patients have 10-100 fold increased death rates compared to age-matched non-CKD patients and most of this excess mortality is cardiovascular. Some of the therapies for one also help the other – ACEI, ARBs, statins to name but three – so there is every reason to study, in chronic kidney disease, dialysis and after renal transplantation, how kidney and cardiovascular functions can be preserved or improved.

Central to these deranged processes are vessel function (stiffness, endothelial function) and structure (calcification); and how these interact with and are modified by endogenous factors (eg FGF-23, inflammation) and exogenous factors (vitamin D therapy).

(a) I have just got two grants to pursue groundbreaking work examining the role of repletion of deficient native vitamin D in reducing left ventricular hypertrophy in subjects with CKD; we are using cutting-edge MR-based LV measurements with Professor Reza Razavi from Imaging. There is only one other such study registered with clintrials.gov. In addition, we will be examining the effect of vitamin D repletion on markers of cardiac fibrosis, and also, the immunity-inflammation axis which is persistently deranged in CKD subjects. In studying a potentially cheap intervention like colecalciferol in a group of patients who represent around 3-5% of the UK population we could find something which could translate to public health benefit, for our challenged local population and beyond. There is increasing academic interest in the multiple pleiotropic effects of vitamin D in KCL, KHP and beyond – for example, dermatology, asthma and allergy, and transplantation tolerance laboratories. I would harness this burgeoning group interest in this important biological area and form a cross-specialty vitamin D research working group to ensure that good ideas, and new techniques and approaches, are not silo-ed.

Further important research questions which would flow from the work I am now embarking upon would include – interactions between FGF-23 (a novel phosphatonin with important impacts on LV morphology, the skeleton, survival, and something that we here at GSTFS have made significant published and presented contributions to) and vitamin D levels and synthesis, impact of vitamin D supplementation on endothelial function and aortic compliance, and impact of vitamin D supplementation on vascular calcification (using techniques developed from the ARTISTIC study).

(b) allied to (a) above, I am actively now co-ordinating a research project with Professor Catharine Shanahan, Professor of Cellular Signalling at the James Black building King's College Denmark Hill Campus, King's College London. Professor Shanahan has developed advanced techniques to study arterial structure and function in cardiovascular, renal and diabetic diseases. In particular, small arterial sections harvested at intra-operative biopsies can be studied both functionally and structurally in the laboratory. The extent and type of calcification can be measured, calcifying vascular cells obtained from the vessel media, and the effect of serum/plasma samples on in vitro models of calcification can be ascertained. This work has successfully been undertaken on paediatric kidney patients, but we want to extend this, in part using a biobanking approach (blood, urine, vessels harvested at clinically opportune moments), to adult patients to allow us to study a range of potential compounds acting as active inhibitors of vascular calcification – this would potentially then allow translation from bench to bedside, and be of therapeutic potential in cardiovascular medicine, diabetes and chronic kidney disease.

References:

Total number of **peer reviewed** publications in Pub Med**:**

Publications *(List up to 5 recent publications relevant to proposed project)*

1) Kanbay M, Solak Y, Covic A, Goldsmith D. Sudden Cardiac Death in Patients with Chronic Kidney Disease: Prevention Is the sine qua non. Kidney Blood Press Res. 2011;34(4):269-76. Epub 2011 Jun 21. PubMed PMID: 21691130.

2) Mactier R, Davies S, Dudley C, Harden P, Jones C, Kanagasundaram S, Lewington A, Richardson D, Taal M, Andrews P, Baker R, Breen C, Duncan N, Farrington K, Fluck R, Geddes C, Goldsmith D, Hoenich N, Holt S, Jardine A, Jenkins S, Kumwenda M, Lindley E, Macgregor M, Mikhail A, Sharples E, Shrestha B, Shrivastava R,Steddon S, Warwick G, Wilkie M, Woodrow G, Wright M. Summary of the 5th edition of the Renal Association Clinical Practice Guidelines (2009-2012). Nephron Clin Pract. 2011;118 Suppl 1:c27-70. Epub 2011 May 6. PubMed PMID: 21555900.

3) Riegersperger M, Covic A, Goldsmith D. Allopurinol, uric acid, and oxidative stress in cardiorenal disease. Int Urol Nephrol. 2011 Jun;43(2):441-9. Epub 2011 Mar 10. PubMed PMID: 21547469.

4) Manghat P, Souleimanova I, Cheung J, Wierzbicki AS, Harrington DJ, Shearer MJ, Chowiencki P, Fogelman I,

Nerlander M, Goldsmith D, Hampson G. Association of bone turnover markers and arterial stiffness in pre-dialysis chronic kidney disease (CKD). Bone. 2011 May 1;48(5):1127-32. Epub 2011 Jan 31. PubMed PMID: 21281749.

5) Molnar MZ, Czira ME, Rudas A, Ujszaszi A, Haromszeki B, Kosa JP, Lakatos P, Beko G, Sarvary E, Varga M, Fornadi K, Novak M, Rosivall L, Kiss I, Remport A, Goldsmith DJ, Kovesdy CP, Mucsi I. Association between the malnutrition-inflammation score and post-transplant anaemia. Nephrol Dial Transplant. 2011 Jun;26(6):2000-6. Epub 2010 Nov 29. PubMed PMID: 21115668.

Person N. 11

NAME	TITLE:	DATE OF BIRTH
Andrzej Więcek	**Professor**	24/11/1955
Place of Birth (Country): Poland	Present Nationality: Polish	Sex male

Degrees/Diplomas	Year Conferred
- specialist in internal medicine	1986
- specialist in nephrology	1993
- specialist in Hypertensiology	2000
- specialist in transplantology	2002
- specialis in angiology	2002
- full Professor of internal medicine and nephrology	1996
- Fellow of the Royal College of Physicians of Edinburgh	2005
- member of the Polish Academy of Arts and Science	2011
-Doctor honoris cause of the Semelweis University in Budapest - Hungary	2011

- Major field of interest:
Pathogenesis and clinical aspects of primary and secondary forms of arterial hypertension, hormonal abnormalities in uremia, kidney transplant and hypertensive patients, endocrine function of the kidney and adipose tissue, clinical aspects of anemia management in CKD patients. Fetal programming of kidney development

- Summarize the main outcomes of your research work / programme(s) in the last 5 years (500 words maximum):

We have documented that the kidney is an important organ producing many hormones and also participating in the biodegradation and elimination of them. These results were very important in the better understanding of the pathogenesis of hormonal abnormalities present in patients with end stage kidney disease. We have also documented the important role of kidney ischemia in patients with renovascular hypertension in the biodegradation and elimination of several hormones as well as in the activation of the sympathetic nervous system. These results are important in the clarification of the pathogenesis of renovascular hypertension and ischemic nephropathy. We have also documented that hormones produced by the fat tissue are involved in the pathogenesis of arterial hypertension in chronic

kidney disease. In our clinical studies we have shown that many antihypertensive drugs may significantly influence the secretion of hormones and cytokines produced by the fat tissue. Such an influence may in some extend explain the protective action of these drugs on the cardiovascular system or eventually their adverse effects. Being member of the Steering and writings Committees of the AURORA and SHARP studies I was involved in the clinical evaluation of the influence of LDL cholesterol level decrease on cardiovascular outcomes in patients with chronic kidney disease. Finally in some experimental studies we have documented the important role of cigarette smoke condensate and nicotine as well as some immunosuppressive drugs used after kidney transplantation not only on kidney development during the fetal live but also on the development of arterial hypertension during their adult life

References:

Total number of **peer reviewed** publications in Pub Med**: 350**

Publications *(List up to 5 recent publications relevant to proposed project)*

1) The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, Wanner C, Krane V, Cass A, Craig J, Neal B, Jiang L, Hooi LS, Levin A, Agodoa L, Gaziano M, Kasiske B, Walker R, Massy ZA, Feldt-Rasmussen B, Krairittichai U, Ophascharoensuk V, Fellström B, Holdaas H, Tesar V, Wiecek A, Grobbee D, de Zeeuw D, Grönhagen-Riska C, Dasgupta T, Lewis D, Herrington W, Mafham M, Majoni W, Wallendszus K, Grimm R, Pedersen T, Tobert J, Armitage J, Baxter A, Bray C, Chen Y, Chen Z, Hill M, Knott C, Parish S, Simpson D, Sleight P, Young A, Collins R; SHARP Investigators.Lancet. 2011 Jun 25;377(9784):2181-92

2) The dysfunctional endothelium in CKD and in cardiovascular disease: mapping the origin(s) of cardiovascular problems in CKD and of kidney disease in cardiovascular conditions for a research agenda. Fliser D, Wiecek A, Suleymanlar G et al. Kidney Int Sup 2011; 1: 6-9.

3) Switching epoetin alfa and epoetin zeta in patients with renal anemia on dialysis: Posthoc analysis. Więcek A, Ahmed I, Scigalla P, Koytchev R. Adv Ther. 2010 Dec;27(12):941-52.

4) A super-agonist of growth hormone-releasing hormone causes rapid improvement of nutritional status in patients with chronic kidney disease. Niemczyk S, Sikorska H, Wiecek A, Zukowska-Szczechowska E, Załecka K, Gorczyńska J, Kubik M, Czerwieńska B, Gosek K, Veldhuis JD, Wagner DA, Gaudreau P, Hakonen T, Kay SW, Jouhikainen T, Schaefer F. Kidney Int. 2010 Mar;77(5):450-8.

5) Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. Fellström BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, Chae DW, Chevaile A, Cobbe SM, Grönhagen-Riska C, De Lima JJ, Lins R, Mayer G, McMahon AW, Parving HH, Remuzzi G, Samuelsson O, Sonkodi S, Sci D, Süleymanlar G, Tsakiris D, Tesar V, Todorov V, Wiecek A, Wüthrich RP, Gottlow M, Johnsson E, Zannad F; AURORA Study Group. N Engl J Med. 2009 Apr 2;360(14):1395-407.

Is any other body supporting research relating to this work currently? YES NO X
(If YES, state organisation, support & tenure)

_____
_____
_____

Has this application been submitted elsewhere? YES NO X

Do you intend to submit this application elsewhere ? YES NO X

(If YES to either please state which organisation and date when the decision is expected)

_____
_____
_____

Date expected ...../...../.....….

Ethics:

Are patients or control volunteers involved with the proposed project? YES X NO

Are Human Tissues involved with the proposed application? YES NO X

Are animals involved with the proposed application? YES NO X

(If YES, an Ethical Committee Letter of Approval is required and a copy of the letter must be attached to this application or date of expected approval detailed)

Tick box if attached ☐ Date expected ...../...../.....….

DETAILS OF CAPITAL EQUIPMENT ALREADY AVAILABLE

Surface area of laboratory: **____sqm**

Number of people working: **____**

Equipment:

1) _____
2) _____
3) _____
4) _____
5) _____
6) _____
…

Details of Consumable, Supplies already available:

1) _____
2) _____
3) _____
4) _____
5) _____

REQUEST FOR CONTRIBUTION
(in Euro)

	YEAR 1	YEAR 2	YEAR 3
Personnel/Expertise (one line for each type)			
Study Monitors	60.000	60.000	60.000
Data manager	20.000	20.000	20.000
Biostatistician	15.000	15.000	15.000
Equipment			
Portable US Scanners	150.000		

Other expenses			
Enrollment incentive	250.000		
Echocardiography studies	300.000	100.000	
Web site building and materials	40.000		
On site visits	75.000	75.000	37.500
Training and certification of sonographers	70.000		
Investigators meetings and teleconferences	30.000	30.000	30.000
Local Ethycs Committees	75.000		
Patients insurance	100.000		
TOTAL PER YEAR	1.185.000	300.000	162.500

GRAND TOTAL OF THE PROJECT	**1.647.500**

Main Applicant's title, first name, family name

Prof. CARMINE ZOCCALI

Main Applicant signature