BIOMARGIN

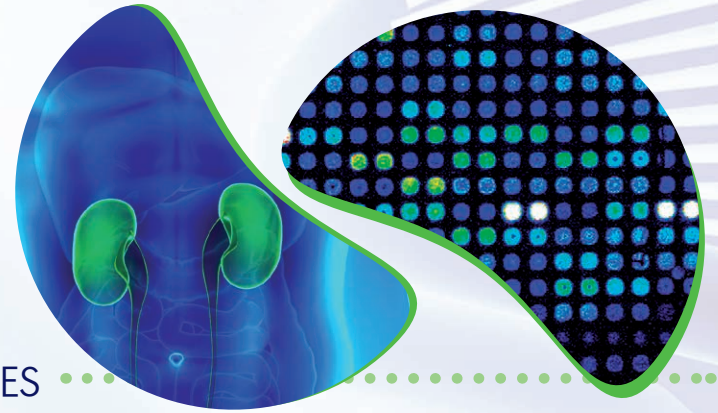
BIOMARKERS OF RENAL GRAFT INJURIES
in kidney allograft recipients

This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no 305499.

CONTEXT

In renal allograft recipients, 10-year graft survival has not improved over the past decades. Histological examination of graft biopsies has long been the gold standard to confirm graft injuries, but biopsies are invasive and histological grading is not very robust. There is thus a need for robust, non-invasive methods to predict and diagnose acute and chronic graft lesions, to improve patient treatment, quality of life and long-term graft survival.

Also, there is an opportunity for better understanding of the immune and non-immune mechanisms of interstitial fibrosis /tubular atrophy and graft loss. Combining all the skills required to build upon previous findings, **BioMargin** will offer such opportunities in renal transplantation by integrating several -omics approaches (mRNA, miRNA, peptides, proteins, lipids and metabolites) in blood, graft tissue and urine, in a well thought out, multistage discovery-to-validation translational programme, following the highest European ethics and regulatory requirements, as well as quality controls and quality assessments at all clinical and analytical steps. It is probably one of the first programmes to pursue such an integrated and systematic research approach. Intellectual property, regulatory and ethical issues will be carefully addressed in order to maximise exploitation of this integrated system for the benefit of the SMEs.



OBJECTIVES

The mission of **BioMargin** is to provide transplant clinicians with validated and easily accessible tools for early prediction of graft lesions and renal function deterioration, offering them the possibility to personalize renal transplant patients' treatment. Indeed, with the development of new immunosuppressive agents, transplant clinicians have multiple therapeutic options and need objective information to choose the most appropriate combination, and/or sequence, for each individual 'case' (defined as the current status of an individual patient).

The practical objectives of **BioMargin** are to:

→ Discover, select and validate:
(1) blood and/or urine biomarkers, at different omics levels, of renal allograft lesions, with good diagnostic performance as compared to biopsy histological analysis ('Gold standard');
(2) mechanism-based classifiers of graft lesions, including intra-graft mRNA or miRNA as well as lipid, peptide and protein localization within the graft, to help histological interpretation of the biopsy; and
(3) early biomarkers of chronic graft dysfunction and ultimately graft loss, less invasive than graft biopsy and with improved predictive values of long-term outcome.

→ Provide clinicians with novel tools (analytical techniques, interpretation algorithms, a dedicated website) to obtain such information in a timely manner, and promote these innovations towards scientific societies and patient associations.

→ Set-up a European research environment for further biomarker research in transplantation, by providing a database of all the biomarker candidates in renal transplantation, either issued from **BioMargin** or previously discovered by **BioMargin** partners and other groups, as well as a **BioMargin** network-biobank of urine and plasma samples from kidney transplant recipients.

STRATEGY

The **BioMargin** consortium will achieve its objectives through the systematic completion of a workplan planned to be able to bring forward all these different approaches and transfer as many as possible of them to the clinics, with some emphasis on urine mRNAs and peptides/proteins, which presently seem to be the most promising.

This strategy explains the multistage workplan, made possible by the existence of large biobanks gathered in similar conditions by four of the **BioMargin** partners (CHU Limoges, MHH, KU Leuven, AP-HP) to start the retrospective. The following steps will be targeted to evaluate the diagnostic and prognostic performance of the biomarker candidates and their clinical validation both in adult and paediatric patients. This will require continuously accruing samples from *de novo* renal transplant patients over the first year post-transplantation in the **BioMargin** biobanks and setting up a European cohort of adult and paediatric renal transplant patients for the collection of urine and blood samples at predefined time points, as well as graft samples in the case of biopsies prescribed locally. At all these steps, the blind histological evaluation of allograft biopsies by expert pathologists will be regarded as the 'gold standard'.

EXPECTED OUTCOMES

BioMargin will contribute with novel early and reliable diagnostic tools to improve the success rate of renal transplantation by prolonging the allograft survival. Early diagnosis means that therapeutic and preventive measures can be initiated at an earlier stage to avoid, stop or reverse the pathological processes ending with graft losses. The validated **BioMargin** biomarkers will enable a closer monitoring of the graft in order to detect acute or chronic injuries earlier, which will translate into earlier intervention and hopefully better long-term outcome. Associated with a closer monitoring of the graft and a shorter reaction time regarding the adaptation of individual patient treatment, the rates of renal graft function deterioration and of graft loss should be reduced. The general condition of the patients will improve, as will their quality of life.

Three European SMEs are part of the **BioMargin** consortium, two of which are research companies involved in the biomarkers field and one is a Contract Clinical Research Organization. This will contribute to increasing the competitiveness and boosting the innovative capacity of European health-related industries.

PARTNERS

The **BioMargin** consortium is coordinated by the French National Institute of Medical Research (INSERM – Prof Pierre Marquet) and brings together 13 complementary European partners, including three small and medium enterprises, five academic laboratories, and four University Hospitals, and one technology transfer / management company from four European Member States (France, Belgium, Germany, and Sweden). The partners are highly complementary and the consortium combines all the skills from clinical nephrology, clinical trials, histology, -omics, statistics and mathematical modelling, regulatory and ethical expertise in clinical settings.

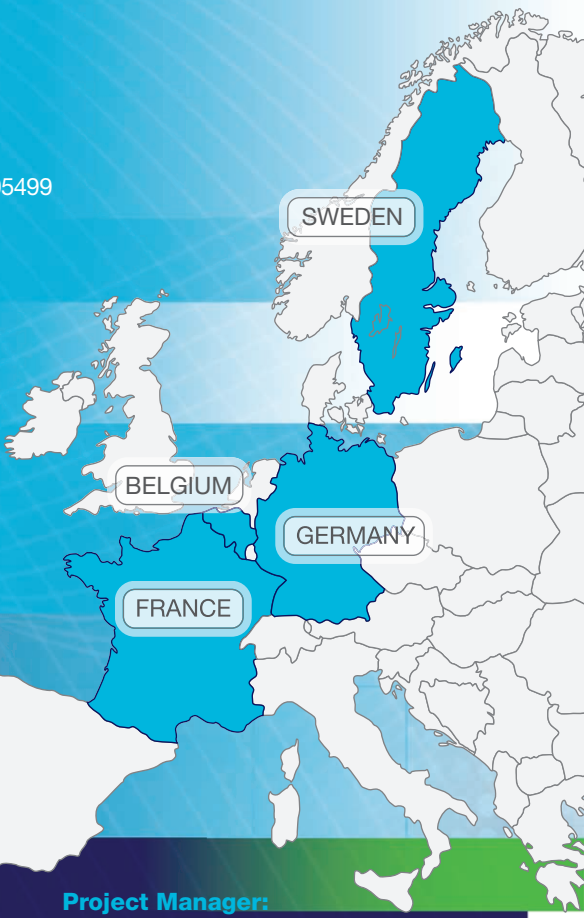
BioMargin combines all the -omics levels (transcriptomics, proteomics, metabolomics, lipidomics) to broaden the range of data that will be compiled and integrated in mathematical models to select and validate the best biomarkers possible. These analyses will be performed on a very large number of samples of urine, blood, and kidney biopsy from patients having received kidney transplants, following a four step plan from discovery to longitudinal clinical validation.

BioMargin CONSORTIUM

COUNTRY	PARTNER INSTITUTION		PRINCIPAL INVESTIGATOR
France	Inserm	INSTITUT NATIONAL DE LA SANTÉ ET DE LA RECHERCHE MÉDICALE	• Prof. Pierre Marquet Limoges • Dr Joost Schanstra Toulouse • Prof. Dany Anglicheau Paris
	InsermTransfert	INSERM TRANSFERT SA	• Dahlia Tsakiropoulos Montpellier
	ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS	ASSISTANCE PUBLIQUE – HÔPITAUX DE PARIS	• Prof. Dany Anglicheau Paris
	cea	COMMISSARIAT À L'ÉNERGIE ATOMIQUE ET AUX ÉNERGIES ALTERNATIVES	• Dr Nora Benhabiles, Dr Etienne Thévenot Saclay
	cnrs	CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE	• Dr Alain Brunelle Gif-sur-Yvette
	Venn Life Sciences Think Research	VENN LIFE SCIENCES	• Aline Schindelé Paris
	UNIVERSITÉ PARIS DESCARTES	PARIS V UNIVERSITÉ PARIS-DESCARTES	• Prof. Olivier Laprévote Paris
	CHU Limoges	CENTRE HOSPITALIER UNIVERSITAIRE DE LIMOGES	• Prof. Marie Essig Limoges
Belgium	KU LEUVEN	KATHOLIEKE UNIVERSITEIT LEUVEN	• Prof Maarten Naesens Leuven
	vito vision on technology	VLAAMSE INSTELLING VOOR TECHNOLOGISCH ONDERZOEK N.V.	• Dr Inge Mertens Mol
Germany	mosaiques diagnostics	MOSAIQUES DIAGNOSTIC GMBH	• Dr Jochen Metzger Hannover
	MHH Medizinische Hochschule Hannover	HANNOVER MEDICAL SCHOOL	• Prof. Wilfried Gwinner Hannover
Sweden	acure omics	ACUREOMICS AB	• Prof. Johan Trygg, Prof. Torbjörn Lundstedt Umeå

BioMargin

- Grant Agreement FP7-HEALTH-305499
- Starting date: 1st March 2013
- Duration: 4 years
- 13 partners including
  3 SMEs
  5 academic laboratories
  4 university hospitals
  1 management company
- 6 000 000 € contribution from the European Commission



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www.biomargin.eu