

Funding: La Fondation Coeur et Recherche

Aiming to Decrease Cardiovascular Mortality Rates by Supporting French Research Teams

Cardiovascular research project leaders who received funding from La Fondation Coeur et Recherche in 2012 describe the funding and their research to Jennifer Taylor, BSc, MSc, MPhil.

La Fondation Coeur et Recherche launched its first call for proposals in 2011, and 7 research projects were awarded €80 000 each. The foundation's priorities are to reduce cardiovascular mortality and support the research of French teams. The results of the 2012 call for proposals will be announced in January 2013. The foundation is committed to funding original collaborative projects that aim to refine epidemiological knowledge and understanding of the determinants of disease and their evolution over time, and to develop new strategies for the diagnosis, treatment, and prevention of cardiovascular diseases. Projects are evaluated by the scientific council of the foundation according to 6 criteria: scientific quality, feasibility, previous work in the project area, quality of the research environment, synergy between the clinical and fundamental, and relevance of the project to the missions and actions of the foundation and the challenges of public health.

Alain Cohen Solal, MD, PhD, FESC, head, Research Medical Unit INSERM U-942 "Heart Failure and Biomarkers," Université Paris VII-Denis Diderot, and head, Cardiology Department, Hôpital Lariboisière, Paris, France



Professor Cohen Solal with colleagues in the lab. Photograph courtesy of Professor Cohen Solal.

Professor Cohen Solal says, "The originality of our team is the unique association of researchers from different departments (cardiology, medical, and surgical intensive care units, and emergency services), preclinical researchers (animal studies), and biologists, including the Biobank team, in a single location at Lariboisière hospital." They are also part of a large international network (Global Research on Acute Conditions Team) of doctors involved in emergency research.

The research is translational, from patients to animal models and vice versa. "We undertook a proteomic analysis that identified several biomarkers of interest, never previously evaluated in this pathology," says Professor Cohen Solal. "Focusing their research on sulfhydryl oxidase 1 (QSOX1), Professor Alexandre Mebazaa, MD, PhD, with

Dr Jane Lise Samuel, PhD, from our team, have shown that although QSOX1 is ubiquitously expressed, its induction in acute dyspnoea is cardiac-specific (humans and rats) and associated with a syndrome of acute heart failure but not stable chronic heart failure. These results open new perspectives, and La Fondation Coeur et Recherche funding is being used for a research project titled 'QSOX1, a Biomarker of Acute Heart Failure.' Such a proteomics approach allows the discovery of at least 3 new plasma biomarkers besides QSOX1, which could represent useful tools for a personalised treatment strategy in cardiovascular emergencies."

Mélèze Hocini, MD, clinical electrophysiologist and associate professor, Haut Lévêque Cardiology Hospital, Pessac, France, and University Victor Segalen, Bordeaux 2, France



Dr Hocini (left, front row) with doctor and nurse colleagues in the lab. Photograph courtesy of Dr Hocini.

Dr Hocini received funding to develop high-resolution 3-dimensional mapping of the sources and substrates of fibrillatory cardiac arrhythmias in the left atria. The experiments will be carried out at the newly established Electrophysiology and Heart Modelling Institute, currently located at the Plateforme Technologique d'Innovation Biomédicale on the grounds of the Xavier Arnoz Hospital in Pessac.

Dr Hocini has a long-term clinical and research partnership with Professor Michel Haïssaguerre, MD (see <http://circ.ahajournals.org/content/114/17/f165>), on all aspects relating to ablation treatment of atrial and ventricular fibrillation as well as sudden cardiac death. Collaborations with basic scientists Véronique Maupoil, PhD, and Ian Findlay, PhD, in Tours, France, will allow an in-depth investigation of the electrophysiological mechanisms underlying arrhythmias. Dr Hocini also maintains critical industrial partnerships to ensure efficient translation into applications and technologies that will benefit patient care. Using a

newly developed catheter, the mechanisms emanating from discrete sources in the pulmonary vein will be described, and structural alterations mediating atrial fibrillation will be identified. Dr Hocini says, “Altogether, the findings could allow the identification of novel, more specific pharmacological targets for atrial fibrillation in the pulmonary veins.”

Luc Lorgis, MD, PhD, interventional cardiologist, Department of Cardiology, University Hospital, and INSERM U866, Dijon, France; and Pierre Sicard, PhD, postdoctoral research fellow, INSERM 1048, Toulouse, France

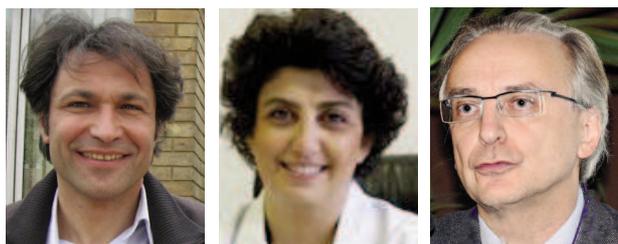


From left to right, Dr Lorgis, Dr Sicard, and Professor Marber. Photographs courtesy of Dr Lorgis.

Drs Lorgis and Sicard are interested in the mechanism involved during the remodelling process after infarction. The funding is being used to study the role of growth arrest and DNA damage protein (Gadd45) in the regulation of mitogen-activated protein kinase during the remodelling process after infarction from mice to humans. The signalling pathways are studied in Toulouse by Dr Sicard and involve molecular, cellular (adult mice, ventricular myocytes), and animal (knockout mice, left anterior descending artery ligation) models. Patients with myocardial infarction are included from the French regional Observatoire des Infarctus de Côte-d’Or survey (Marianne Zeller, PhD, and Professor Yves Cottin, MD, PhD, INSERM U866, University of Burgundy, Burgundy, France) to correlate the circulating Gadd45 gene expression with prognosis after myocardial infarction. In addition, this project will take advantage of the complementary competencies and skills of the Cardiovascular Division at King’s College London, London, England (Professor Michael Marber, MD, PhD).

“The objective of this multicentre and translational project is to understand the potential contribution of Gadd45 to the development of cardiac remodelling after myocardial infarction,” says Dr Lorgis. “This work will be able to identify a possible new therapeutic target that can reduce the development of heart failure.”

Ziad Mallat, MD, PhD, British Heart Foundation Professor of Cardiovascular Medicine, Department of Medicine, University of Cambridge, Cambridge, England Professor Mallat previously conducted studies that unravelled an unsuspected role for B lymphocytes in the development of experimental atherosclerosis. His group has also shown that growth factors and receptors involved in the survival and activation of the B2 cell subset of B cells



From left to right, Professor Mallat, Professor Simon, and Professor Danchin. Photographs courtesy of Professor Mallat.

promote atherosclerosis. More recent studies in Professor Mallat’s lab indicate that B cells also modulate the immune response to myocardial infarction. The aim of the present translational project is to examine the (causal) relationship between specific B cell-activating factors and the occurrence of major cardiovascular events (death or recurrent myocardial infarction) during a 2-year follow-up of patients with acute myocardial infarction.

Professor Mallat is working on this project with Professor Tabassome Simon, MD, PhD, and Professor Nicolas Danchin, MD, PhD, in Paris, France. They have established a national registry of patients with acute myocardial infarction, the French Registry of Acute ST-elevation and Non-ST-elevation Myocardial Infarction. Of the 374 centres in France that treated patients with acute myocardial infarction at that time, 223 (60%) participated in the registry. Among these, 2430 patients (>99% White) contributed to a DNA bank, and 1029 patients contributed to a serum bank. “All measurements have been completed and analyses are underway,” says Professor Mallat. “The discovery that B cell-activating factors may be causally linked to worse outcomes after an acute myocardial infarction should pave the way for testing specific B cell-targeted immunomodulatory therapies at the acute phase of myocardial infarction.”

Vincent Probst, MD, PhD, professor of cardiology and head, Cardiac Intensive Care Unit, National Reference Centre for Hereditary Arrhythmic Diseases and Centre for Sudden Cardiac Death in the Young, University Hospital of Nantes, INSERM Unit 1087, Nantes, France



Professor Probst with colleagues in the lab. Photograph courtesy of Professor Probst.

Professor Probst received funding for a genetic study of atrial fibrillation and has initiated an exome sequencing project on a unique family of 21 members, of whom 7 presented with early onset atrial fibrillation. All family members were evaluated by a 12-lead electrocardiogram, echocardiogram, 48-hour Holter electrocardiogram monitoring, electrocardiogram

with high amplification of the P wave, and lab studies. Exome sequencing was performed on 3 distantly related patients using a whole-exome capturing kit, followed with next-generation sequencing on a sequencer. Exome data identified an average of 7950 variants per individual. After filtering for rare variants shared by all 3 family members, 13 candidate genes remained, 5 of them showing clear expression in the human atria. All variants are missense mutations, segregate in the family, and are located in highly conserved residues among different species.

Professor Probst says, “The next steps will be to screen additional probands for the subset of candidate genes and perform functional analysis in the zebrafish using the morpholino knockdown approach.”

Philippe Rouet, PhD, director of research at INSERM, head of team 7 “Obesity and Heart Failure: Molecular and Clinical Investigations,” Cardiovascular and Metabolic Research Institute, INSERM UMR 1048, Toulouse, France



Dr Rouet (right) with Professor Galinier in front of the hospital. Photograph courtesy of Dr Rouet.

Dr Rouet is using the funding to validate novel urinary biomarkers of heart failure. The project involves cardiologist Professor Michel Galinier, MD, PhD, head of the Cardiology Department and his team at Rangueil University Hospital, Toulouse and basic scientists Professor Harald Mischak, PhD, University of Glasgow, Glasgow, Scotland, Franck Desmoulin, PhD, INSERM UMR 1048 team 7, and Fatima Smih, PhD, INSERM UMR1048 team 7. Dr Rouet says, “The limitations of current biomarkers have led us to look for additional biomarkers that would allow easier screening for heart failure.” Indeed, the brain natriuretic peptide concentration of $\approx 30\%$ of patients admitted to emergency care for acute dyspnoea is in a “grey zone” that does not help with diagnosis. However, prompt treatment is important for the prognosis of the disease.

Dr Rouet and his team are searching for new heart failure biomarkers in urine and plasma from patients using capillary electrophoresis coupled to mass spectroscopy. “The choice of this method relies on its high sensitivity and high throughput and also on our experience with this approach,”

he says. “This led us to propose a set of new putative biomarkers that will be validated using multiple reaction monitoring through mass spectroscopy analysis or immune methods within a large population of patients. These new biomarkers will help the clinician diagnose heart failure and could propose new pathways involved in heart failure by deciphering the molecular mechanisms associated with the new biomarkers. The latter could lead to the proposal of new therapeutic strategies.”

Franck Thuny, MD, PhD, FESC, assistant professor of cardiology and specialist in valvular heart diseases and echocardiography, Departments of Cardiology, Timone and Nord University Hospitals, Aix-Marseille University, Marseille Cedex, France



Dr Thuny with some of the principal investigators. From left to right: Dr Thuny, Professor Habib, Dr Frederique Gouriet, Dr Jean-Paul Casalta, Dr Laetitia Tessonnier, and Dr Sandrine Hubert. Photograph courtesy of Dr Thuny.

“With Professor Gilbert Habib, MD, and Professor Didier Raoult, MD, PhD, we have created a unique multidisciplinary ‘endocarditis team’ allowing a translational research on the management of this disease,” says Dr Thuny. “This team includes specialists in cardiology, infectious diseases, cardiac surgeons, radiologists, and nuclear medicine. Our group has provided numerous original articles on this topic, and we actively participated in the recent European guidelines on the prevention, diagnosis, and treatment of infective endocarditis.”

La Fondation Coeur et Recherche has provided funding to cover research expenses and the salary of a clinical research assistant to enable Dr Thuny and his colleagues to conduct a study on the use of ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography for diagnosing prosthetic valve endocarditis. The poor prognosis of this condition is associated with deficiencies in identifying prosthetic and periprosthetic damage via echocardiography. Dr Thuny says, “We hope to demonstrate a role for this technique in early diagnosis, especially in the case of initial negative echocardiography results.”

Jennifer Taylor is a freelance medical journalist.

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