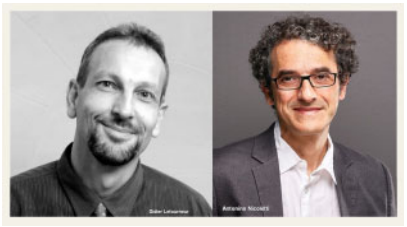
ESC European Society of Cardiology
European Heart Journal (2020) **41**, 2928–2937
doi:10.1093/eurheartj/ehaa256
CARDIOPULSE

Cardiovascular Research Centre of Excellence

The Laboratory for Vascular Translational Science (LVTS)

LVTS is the present avatar of a long standing and highly productive multidisciplinary cardiovascular French institute created in 2005 by Dr Jean-Baptiste Michel and Dr Martine Jandrot-Perrus and headed since 2014 by Dr Didier Letourneur (Director) and Dr Antonino Nicoletti (Deputy Director). https://lvts.fr/



With 150 tenured researchers and engineers and around 60 post-docs, Master and PhD students (*Figure 1*), Laboratory for Vascular Translational Science (LVTS) is affiliated with Inserm and CNRS, the Paris University and University Paris 13 and the Greater Paris University Hospitals (AP-HP).

The Institute is located north of Paris on the Bichat campus that harbours a 900-bed university hospital, a medical school, and a research hub. This location has fostered long-lasting and highly dynamic interactions between the institute and the hospital. These have led to numerous common research projects and the establishment of a cardiovascular (CV) biobank from the collection of a large range of human samples (blood, tissue, and cells) from different forms of CV diseases, including atherothrombotic and non-atherothrombotic diseases (notably thoracic and abdominal aortic aneurysms, carotid artery diseases). The CV biobanking activities are integrated in the national Biobank network (Biobank Infrastructure), which are partners of EU BBMRI (www.bbmri.eu).

LVTS has a pluri- and transdisciplinary approach with the objective to fight vascular pathologies. The medical questions raised pertain to new pathophysiological targets, in order to advance diagnosis and treatment of diseases. The general objectives are the understanding of the physiological mechanisms by basic science approaches but also through large clinical trials, development of new diagnostic (markers and imaging), and new therapeutic/biomaterial strategies: identification of new targets, development of new molecules, validated by clinical trials. To carry out these projects, translational human and technological skills include clinical databases and assays, translational clinical investigations (carotid stenosis, aneurysms, and dissections of the ascending aorta, Biocore), human tissue and cell biobanks, numerous experimental models of disease (transgenic mice, rats, rabbits), new methods in molecular and cell biology (genetics and genomics, proteomics, protein engineering, flow cytometry), chemistry of biopolymers, elaboration of biomaterials and nano systems, and imaging technologies in small animals and in humans [nuclear imaging, ultrasound, and magnetic resonance imaging (MRI)].

Research is performed through six teams (*Figure 2*). Their current research topics are briefly presented in the following paragraphs.

Team 1

The Cardiovascular Immunobiology team (Team 1, G. Caligiuri and A. Nicoletti, Refs[1–5]) works on the mechanisms by which the immune system interacts with diseased vessels and designs new vasculoprotective immune interventions. The main recent contributions from this team have been:

- The decryption of local immune responses around atherothrombotic vessels and description of new pathogenic immune pathways in vascular diseases; we have shown that recruited neutrophils can dictate the issue of complicated atheroma and that their activity is enhanced at sites of plaque erosion and also by infectious agents that harbour tropism for atherothrombotic sites. We are currently trying to dampen the myeloid cell-driven vascular damage in the brain, the heart, the lungs, and the intestine, upon ischaemia–reperfusion. We are investigating the mechanisms through which

Figure 1 Members of LVTS.

periodontal diseases can deflect the innate immune response thereby impacting on the issue of atherothrombotic events.

- The demonstration that CD31 is a pacification molecule of the blood vessel interface thereby showing that it is a promising molecular target in inflammatory and thrombotic diseases; we have filed seven patents, six licensed to Tridek-One Therapeutics, a spin-off of our laboratory that aims at developing first-in-class immunomodulatory products targeting the CD31 pathway to down-modulate inappropriate immune responses.
- The revision of the processes initiating atherogenesis and vascular/valvular calcifications where we have shown that endothelial breaches in territories subjected to high haemodynamic stress allow the entry of red blood cells and constitute a key pathogenic mechanism underlying atherogenesis. In addition to mechanical stress, we are exploring the role of temperature, a neglected feature of inflammation. We have found that temperature is different at sites of atherogenesis and can profoundly impact vascular and immune cell biology.

Team 2

The Vascular structural diseases team (Team 2, G. Jondeau and C. Boileau, Refs[6–11]) focuses on the study of pathophysiogenic mechanisms associated with aortic aneurysms, valves and coronary artery disease (CAD) in an uninterrupted continuum from genetics to pathophysiology and patient care. The team focuses on inherited human model diseases: thoracic aortic aneurysms (TAAD) in Marfan's syndrome and associated diseases and autosomal dominant hypercholesterolaemia. These models also provide means to identify the genetic modifiers that account for great clinical variability, between and within families. The identification of these modifiers should enable identification of predictors of disease aggressiveness. Research relies on a close collaboration with the National reference Center for Marfan syndrome (www.marfan.fr) and is part of the national large-scale translational research project CHOPIN (CHolesterol Personalized Innovation, https://rhuchopin.fr/).

- In TAAD, we developed the paradigm shift that TGF-β canonical pathway has a protective effect during aneurysm formation. We are leaders in the discovery of new disease genes involved in familial TAAD. By cross-mapping the results of several genome-wide studies, we detected the existence and mapped 9 modifier loci that are being investigated.
- In familial hypercholesterolaemia (FH), we postulated further genetic heterogeneity and demonstrated the role of rare GOF mutations in the PCSK9 gene. Our work identified a totally unrecognized actor of cholesterol homeostasis and opened up a new field of basic research and the development of anti-PCSK9 agents. Another paradigm shift showed that mutations in the *APOE* gene resulted in FH, as well as the existence of other FH disease genes.

Team 3

The Cardiovascular Bio-Engineering team (Team 3, D. Letourneur, Refs[12–18]) is well-integrated in LVTS research, industrial development, clinical translation, and education. The team has a long-standing expertise in biomaterials and nanotechnologies and is developing research in e-health objects.

- *Biomaterials—3D porous scaffolds for tissue engineering*
  Innovative technology enables the development of different polysaccharide scaffolds for bone regeneration, skin regeneration, three-dimensional cell culture, and cellular or molecular delivery. Thanks to multiphysic and multiscale characterizations, our goal is to develop biomaterials for tissue regeneration *in vivo*. Based on four patents, a company (SILTISS) was created for industrial transfer and is expected to launch clinical trials in 2021.
- *Nanotechnologies for imaging and therapy*
  We have developed a GMP fucoidan and several nanosystems for the early diagnosis of CV diseases with clinical imaging and the establishment of appropriate therapeutic strategies. Fucoidans are marine sulfated polysaccharides and previous studies have demonstrated the capacity of fucoidan to bind to P-selectin as a relevant marker of atherothrombosis and endothelial ischaemia. A

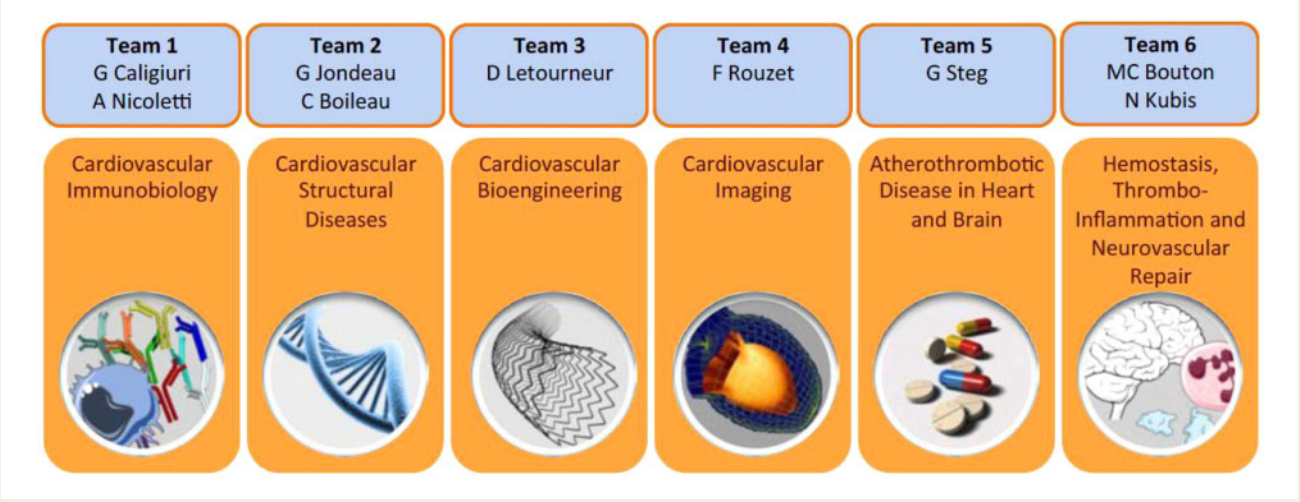


Figure 2 LVTS teams, their leaders, and their research areas.

GMP microdose radiopharmaceutical based on 99mTc-fucoidan has been validated in Phase I and Phase II clinical trials for single-photon emission computed tomography (SPECT) imaging of human thrombosis and heart ischaemia (FP7-NMP-Large-6-'Nanoathero').

We focus on three major areas:

i. The development of soft nanosystems of which the core materials are polysaccharides. These are used as contrast agents for molecular imaging of CV disease by computed tomography (CT), MRI, SPECT, positron emission tomography (PET), ultrasonography, optical imaging, or some combination of these modalities.
ii. The development of ligands able to aim nanoparticles at molecular relevant targets, such as fucoidan for P-selectin.
iii. The development of therapeutic strategies by optimizing loading capacities and physicochemical properties well adapted to antioxidative molecules.

Team 4

The Cardiovascular imaging team (Team 4, F. Rouzet, Refs[19–23]) aims at developing imaging agents and procedures from preclinical proof of concept to clinical validation. The preclinical imaging platform gathers all the modalities dedicated to small animals (ultrasounds, MRI, PET/MRI, SPECT/CT, and a radiolabelling lab) and is a member of the French Life Imaging network. Our team has developed expertise in radiolabelling probes, nanoparticles, or cells with gamma and positron emitters (Gallium-68 and Copper-64) and more recently in multiparametric magnetic resonance (MR). Our research is fuelled by a strong interaction with other teams of LVTS for the development of novel imaging agents and takes advantage of the wide range of fully characterized animal models available onsite for *in vivo* validation (*Figure 3*).

The clinical research including preliminary studies in humans takes place at Bichat hospital. The proximity between LVTS and the hospital facilitates the interplay between clinical challenges and fundamental research. The main research topics of the team are centred on,

(1) biological activities associated with arterial thrombi such as procoagulant activity and serine proteases,
(2) tracking or detection of cells involved in inflammation/infection, and
(3) three tissue biomechanical properties obtained from MR elastography.

We are currently developing a multimodal approach combining the molecular information derived from PET, tissue contrast from MRI, and viscoelastic properties from MR elastography. This comprehensive characterization is developed in animal models of myocardial inflammation and fibrosis and will be translated to humans with the installation of a clinical PET/MR system by the end of 2020.

Team 5

The atherothrombotic disease in heart and brain team (Team 5, P.G. Steg, Refs[24–30]) focuses on clinical epidemiology of CAD (P. Gabriel Steg) and stroke (P. Amarenco), via the design, conduct and analysis of large-scale observational registries and of randomized clinical trials. The team recently received French government funding for an integrated research programme on innovations in atherothrombosis science (RHU IVASC, www.ivasc.eu) which involves ongoing epidemiologic studies and interventional studies to establish the relationship(s) between chronic periodontitis, sleep disordered breathing, and atherothrombosis. The TIA.org registry established the benefit of rapid management of transient ischaemic attacks through specialized centres worldwide, initially and at 5-year follow-up.

Recent trials have studied the impact of lipid lowering interventions after acute coronary syndromes (using alirocumab, a PCSK9 inhibitor, in the ODYSSEY OUTCOMES trial) or after ischaemic stroke in patients with atherothrombosis (comparing two target LDL cholesterol levels, in the TST trial which established the clinical benefit of targeting LDL to <70 mg/dL rather than 100 mg/dL). A large-scale trial, THEMIS (the largest randomized trial in diabetes) established the value of dual antiplatelet therapy with ticagrelor and aspirin in patients with stable CAD and diabetes, particularly if they have a prior history of percutaneous coronary intervention.

Team 6

The Haemostasis, Thrombo-Inflammation, Neurovascular Repair team (Team 6, M.C. Bouton and N. Kubis, Refs[31–35]) focuses its research on the interaction between actors of haemostasis and thrombo-

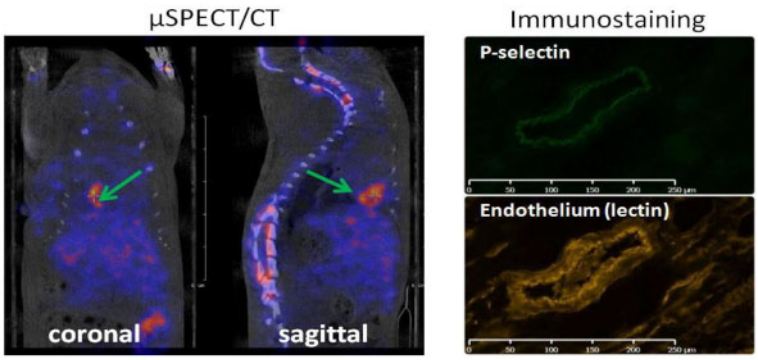


Figure 3 Radiolabelled Fucoidan SPECT/CT in a rat model of myocardial ischaemia–reperfusion. Fucoidan is a P-selectin-targeted imaging agent designed to identify the biological imprint of a transient ischaemic episode a few hours after its resolution. A focal uptake of the imaging agent is detectable at the left ventricular apex (green arrow) 2 h after reperfusion (left panel). Immunostaining demonstrates the endothelial expression of P-selectin (green fluorescence) at the endothelial surface (lectin) in the area at risk (right panel).

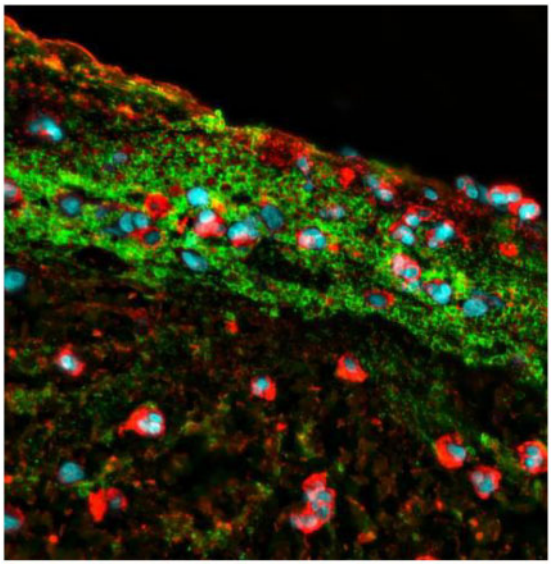


Figure 4 Thrombus retrieved by mechanical thrombectomy from patients with ischaemic stroke. Platelets (green) and neutrophils (red) immunostaining.

inflammation in the vessel wall to extend knowledge on cardio- and neurovascular diseases. The main themes of the team are:

- *Heart failure:* Increased protease activities within the myocardium is involved in the development of heart failure. We have previously demonstrated that protease nexin-1, a major tissue antiprotease, constitutes a key factor in the responses of vessels to injury, via its antithrombotic and antifibrinolytic properties. We now aim to determine its potential role in cardiac pathophysiology.
- *Intracranial aneurysm:* The pathophysiology evolution of intracranial aneurysm events seems driven by complex cellular interactions between different cell types including platelets, leucocytes, and vascular cells. Our main objective is to decipher platelet mechanisms during intracranial aneurysm formation and rupture.
- *Stroke:* We investigate how cellular actors of inflammation and molecular actors of haemostasis contribute to the pathophysiology of ischaemic stroke. Our approach combines the analysis of thrombi and plasma samples recovered from stroke patients (*Figure 4*), and the use of animal models. We showed that
- thrombi from patients have thrombolysis- resistant areas,
- large vessel occlusion triggers downstream micro thrombosis, and
- DNAse can help improve thrombolysis.

Our work has set the basis for the development of clinical trials developing a personalized stroke care in emergency situations (BOOSTER consortium) and testing the efficacy of new drugs such as a novel anti-platelet drug (Phase Ib/IIa clinical trial ACTIMIS, Acticor Biotech, a spin-off company located in LVTS and created by Dr Martine Jandrot-Perrus, https://acticor-biotech.com/).

References

References are available as supplementary material at *European Heart Journal* online.

Conflict of interest: none declared.

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