Research Unit Inserm UMR1327
ISCHEMIA « Membrane Signalling and Inflammation in Reperfusion Injuries
University of Tours, Faculté de Médecine, 10 boulevard Tonnellé, 37032 Tours, France
Director : Prof. Sébastien ROGER

The research unit is looking for a highly motivated and highly skilled senior post-doctoral immunologist researcher to apply to the competitive programme from the French **« Fondation pour la Recherche Médicale (FRM) »** called **« Amorçage de jeunes équipes » (Starting Young Teams)** on a project dealing with the**:**

« Role of the purinergic signaling and the Innate Immune response in the early phases after kidney transplantation and consequences on delayed graft function (DFG) and graft rejection ».

If accepted, the FRM offers **a grant of €450 000 for a duration of 3 years,** aiming at covering personnel costs (salary of the team leader, salary of a post-doctoral researcher, an engineer or a technician), material resources (consumable and small equipment) and/or mission expenses (within the limit of €3000 per year). Publication costs are limited to €15,000 for the entire project.

Our goal with this grant is to accompany and prepare the candidate to the **recruitment competition for an Inserm statuary researcher (CRCN) position in the unit.**

Presentation of the research unit

The strategy of the Inserm lab UMR1327 (created as an Inserm unit since January 2024, CSS3 « Physiology and Physiopathology of systems », Thematic Institute « Physiopathology, Metabolism, Nutrition »), is to conduct a **"Bench to Bed, and Back"** translational pathophysiological project aiming at understanding molecular, cellular and tissue mechanisms involved in the worsening of tissue lesions following ischemic/hypoxic and inflammatory episodes, in order to prevent organ dysfunction and disease progression.
The unit, structured as a single team, develops a transversal project to study and understand common bases of signalling pathways involved in cell communication, activation and differentiation induced by ischemia-reperfusion in different pathological contexts, most notably after myocardial infarction, solid organ transplantation (kidney/heart/liver) or in cardiorenal

syndromes. More precisely, members of the unit will work on an original research project studying the involvement of soluble danger signals (extracellular ATP, exosomes, cytokines) released by cells suffering from ischemia-reperfusion, under metabolic and inflammatory challenges, and their role in the activation, polarization and phenotypic switches of all cells within the tissue involved in the response to danger signals, such as cardiomyocytes, (cardio)fibroblasts, epithelial cells, platelets and immune cells.
To address these scientific questions, the research unit has developed transversal methodological tools such as cohorts of patients (participation to the prospective cohort CARIM CARdioprotection in Myocardial Infarction NCT02967965, or the interventional cohort HIBISCUS-STEMI CoHort of Patients to Identify Biological and Imaging markerS of CardiovascUlar Outcomes in ST Elevation Myocardial Infarction NCT03070496, or those available at the CePiBAc platform), biocollections (BioSUPORT from the FHU SUPORT NCT03997253) associated with DNA collection (DC2013-1780) clinical data, pre-clinical models and mathematical modelling of biological systems (*in vitro* and *in vivo*), imaging methodologies for cells, tissues, organs and living organisms (*in vitro*, *ex vivo* and *in vivo*) and adapted analytical tools, *in vitro* models of primary cultures, co-cultures in 2 and 3 dimensions.
Our goal is to ensure a translational strategy, with mechanistic questions evaluated first by *in vitro/ex vivo* experiments and in preclinical models before being proposed for clinical trials, the translation to bedside being possible because of our close ties with clinical units in our University Hospital of Tours.
The Inserm UMR1327 is an active member of the Fédération Hospitalo-Universitaire « SUrvival oPtimization in ORgan Transplantation » (FHU SUPORT) and the « Consortium for Organ Preservation in Europe (COPE2.0) » on organ transplantation, of the European COST Action CA21130 « P2X receptors as a therapeutic opportunity » (PRESTO) and the National « French Purine Club » on purinergic signalling, on the European COST Action CA21147 « European Network on Optimising Treatment with Therapeutic Antibodies in chronic inflammatory diseases » (ENOTTA) and national LabEx MabImprove for "improved antibodies, improved development and improved use" (ANR-10-LABX-53-01) on therapeutic antibodies.

The unit benefits from research supporting activities provided by the Scientific and Technical Platform for Biological Systems Analyses (PST-ASB, https://pst-asb.med.univ-tours.fr) from the University of Tours, mainly located at the Faculty of medicine site, and providing core facilities for Metabolomics analyses, Genomics analyses, Microscopy facilities, Small animal experimentation and Imaging. The unit benefits from Animal facilities, at both the faculty of medicine and the faculty of pharmacy sites (PST-Animaleries), for developing appropriate animal models and setting up preclinical studies. In return, the unit nourishes and participates to the evolution or implementations of techniques and methodologies provided by the platforms, by bringing new projects. The unit also accesses to services provided by the PIXANIM platform (https://www6.val-de-loire.inrae.fr/pixanim_eng), labelled GIS IbiSA and by the INRAE, in co-tutelage of the University and the Hospital of Tours, hosted by the UMR INRAE 0085, UMR CNRS 7247 Physiology of Reproduction and Behaviour (PRC). The platform offers strategies with multiple imaging modalities and molecular analyses to finely phenotype diverse biological systems and characterize the mechanisms explaining these phenotypes. As such it provides solutions for molecular (proteomics/ lipidomics/…), *in vivo/ ex vivo* imaging analyses and interventional activities in large animals (anaesthesia, surgery, imaging, etc). The strong interaction with the PIXANIM platform represents a great opportunity for all project developed in the research unit, especially on those related to ischemia-reperfusion in the context of organ transplantation with the FHU SUPORT. The research unit also works in close collaboration with the CNRS UPS TAAM (Transgenesis and Archiving of Animal Models, http://transgenose.cnrs-orleans.fr), located in the CNRS Orléans "La Source" campus, to develop and promote small animal models (transgenic, syngeneic models, etc…) and dedicated imaging facilities (bioluminescence, infrared fluorescence, ultrasounds, photoacoustic imaging, SPECT, PET and CT Scans). The unit participates to the development of new animal models, as well as new mathematical models for assessing drug efficacy and hypoxia settings in vivo by confronting several imaging modalities.

Recent publications from the research unit :

1. Paris J, Wilhelm C, Lebbé C, Elmallah M, Pamoukdjian F, Héraud A, Gapihan G, Walle AV, Tran VN, Hamdan D, Allayous C, Battistella M, Van Glabeke E, Lim KW, Leboeuf C, Roger S, Falgarone G, Phan AT, Bousquet G. PROM2 overexpression induces metastatic potential through epithelial-to-mesenchymal transition and ferroptosis resistance in human cancers. Clin Transl Med. 2024 Mar;14(3):e1632. doi: 10.1002/ctm2.1632.

2. Joseph A, Harel S, Mesnard L, Rafat C, Knapp S, Rumpler A, Philipponnet C, Barba C, Rebibou JM, Buob D, Hertig A, Vargaftig J, Halimi JM, Arnulf B, Bretaud AS, Joly B, Grangé S, Coppo P.

3. Carfilzomib-associated thrombotic microangiopathy: clinical features and outcomes. Nephrol Dial Transplant. 2024 Apr 24:gfae096. doi: 10.1093/ndt/gfae096. Online ahead of print.

4. Maisons V, Duval A, Mesnard L, Frimat M, Fakhouri F, Grangé S, Servais A, Cartery C, Fauchier L, Coppo P, Titeca-Beauport D, Fage N, Delmas Y, Quérard AH, Seret G, Bobot M, Le Quintrec M, Ville S, von Tokarski F, Chauvet S, Wynckel A, Martins M, Schurder J, Barbet C, Sautenet B, Gatault P, Caillard S, Vuiblet V, Halimi JM; MATRIX Consortium Group. Assessment of epidemiology and outcomes of adult patients with kidney-limited thrombotic microangiopathies. Kidney Int. 2024 May;105(5):1100-1112. doi: 10.1016/j.kint.2024.02.014. Epub 2024 Feb 29.

5. Boulard P, Azzopardi N, Levard R, Cornec JM, Lamamy J, Prieur B, Demattei MV, Watier H, Gatault P, Gouilleux-Gruart V. Albumin influences leucocyte FcRn expression in the early days of kidney transplantation. Clin Exp Immunol. 2024 May 16;216(3):307-317. doi: 10.1093/cei/uxae011.

6. Gourdy P, Schiele F, Halimi JM, Kownator S, Hadjadj S, Valensi P. Atherosclerotic cardiovascular disease risk stratification and management in type 2 diabetes: review of recent evidence-based guidelines. Front Cardiovasc Med. 2023 Sep 26;10:1227769. doi: 10.3389/fcvm.2023.1227769. eCollection 2023.

7. Faucher Q, Chadet S, Humeau A, Sauvage FL, Arnion H, Gatault P, Buchler M, Roger S, Lawson R, Marquet P, Barin-Le Guellec C. Impact of hypoxia and reoxygenation on the extra/intracellular metabolome and on transporter expression in a human kidney proximal tubular cell line. Metabolomics. 2023 Sep 13;19(9):83. doi: 10.1007/s11306-023-02044-4.

8. Kaczmarek M, Halimi JM, de Fréminville JB, Gatault P, Gueguen J, Goin N, Longuet H, Barbet C, Bisson A, Sautenet B, Herbert J, Buchler M, Fauchier L. A Universal Bleeding Risk Score in Native and Allograft Kidney Biopsies: A French Nationwide Cohort Study. J Clin Med. 2023 May 17;12(10):3527. doi: 10.3390/jcm12103527.

9. Maisons V, Halimi JM, Fauchier G, de Fréminville JB, Goin N, Gueguen J, Gatault P, Sautenet B, Angoulvant D, Herbert J, Bisson A, Ducluzeau PH, Fauchier L. Type 2 diabetes and cardiorenal syndromes. A nationwide French hospital cohort study. Diabetes Metab. 2023 May;49(3):101441. doi: 10.1016/j.diabet.2023.101441. Epub 2023 Mar 15.

10. Yin Y, Wei L, Caseley EA, Lopez-Charcas O, Wei Y, Li D, Muench SP, Roger S, Wang L, Jiang LH. Leveraging the ATP-P2X7 receptor signalling axis to alleviate traumatic CNS damage and related complications. Med Res Rev. 2023 Sep;43(5):1346-1373. doi: 10.1002/med.21952. Epub 2023 Mar 16.

11. Al-Hajj S, Lemoine R, Chadet S, Goumard A, Legay L, Roxburgh E, Heraud A, Deluce N, Lamendour L, Burlaud-Gaillard J, Gatault P, Büchler M, Roger S, Halimi JM, Baron C. High extracellular sodium chloride concentrations induce resistance to LPS signal in human dendritic cells. Cell Immunol. 2023 Feb;384:104658. doi: 10.1016/j.cellimm.2022.104658. Epub 2022 Dec 20.

12. Chadet S, Allard J, Brisson L, Lopez-Charcas O, Lemoine R, Heraud A, Lerondel S, Guibon R, Fromont G, Le Pape A, Angoulvant D, Jiang LH, Murrell-Lagnado R, Roger S. P2x4 receptor promotes mammary cancer progression by sustaining autophagy and associated mesenchymal transition. Oncogene. 2022 May;41(21):2920-2931. doi: 10.1038/s41388-022-02297-8. Epub 2022 Apr 11.

13. Mewton N, Roubille F, Bresson D, Prieur C, Bouleti C, Bochaton T, Ivanes F, Dubreuil O, Biere L, Hayek A, Derimay F, Akodad M, Alos B, Haider L, El Jonhy N, Daw R, De Bourguignon C, Dhelens C, Finet G, Bonnefoy-Cudraz E, Bidaux G, Boutitie F, Maucort-Boulch D, Croisille P, Rioufol G, Prunier F, Angoulvant D. Effect of Colchicine on Myocardial Injury in Acute Myocardial Infarction. Circulation. 2021 Sep 14;144(11):859-869. doi: 10.1161/CIRCULATIONAHA.121.056177. Epub 2021 Aug 23.

14. Jiang LH, Caseley EA, Muench SP, Roger S. Structural basis for the functional properties of the P2X7 receptor for extracellular ATP. Purinergic Signal. 2021 Sep;17(3):331-344. doi: 10.1007/s11302-021-09790-x. Epub 2021 May 13.

Contacts :

Prof. Philippe GATAULT (PU-PH Néphrologie), philippe.gatault@univ-tours.fr
Prof. Sébastien ROGER (PU Physiologie), sebastien.roger@univ-tours.fr

Applications, before 15 July 2024 :

- A Full CV including publications and all research valorizations
- A Motivation Letter
- A short Proposal for a research project (3 pages at max) including a title, methodologies and models, and expected results
- Recommendation letters are welcome

Calendar :

- Submission of the full project to the FRM : 06 September 2024
- Selection of projects : 08 October 2024
- Position starting between October 2024 and January 2025