institut cochin
CENTRE DE RECHERCHE

Post-Doc position

Title of the project:
Autoimmune T cells in type 1 diabetes
DeARLab R. Mallone & S. You

PROJET/RESEARCH PROJECT

Our research explores the autoimmune pathogenesis of type 1 diabetes (T1D) and the discovery of new T-cell-based biomarkers and therapeutic tools, using both human and mouse experimental systems.

A postdoctoral position is available to work on a project aimed at developing new T-cell biomarkers of islet autoimmunity in T1D. Our recent work (Culina et al., *Science Immunology* 2018; Gonzalez-Duque et al., *Cell Metabolism* 2018) documented that islet-reactive CD8+ T cells circulate at similar frequencies in T1D and healthy donors and display a largely naïve phenotype, suggesting that they are not actively involved in the autoimmune process. The fraction engaged in the disease is instead sequestered in the pancreas and is found enriched in T1D patients. Thus, a universal state of 'benign' autoimmunity exists in all individuals. In liaise with the overall research activity of the Laboratory, this project aims at deciphering the mechanisms that drive the progression of this benign state toward T1D.

The key question addressed by the Postdoc will be whether the beta-cell antigens identified to date are the most relevant targets of the autoimmune response. Indeed, little is known about the epitopes that are naturally processed and presented by beta cells and antigen-presenting cells, which may be modulated by the inflammatory milieu of insulitis. Such modulation may modify this epitope display in terms of both quantity and quality, i.e. by generating neo-antigens through post-translational modifications and neo-sequences generated by mRNA alternative splicing and fusion of non-contiguous peptide fragments. This project will build on parallel efforts in the lab that aim at identifying the peptides presented on the surface of beta cells and dendritic cells, in the frame of HLA Class I and Class II molecules. These peptides are identified using mass spectrometry-based peptidomics techniques. The Postdoc will start by verifying whether these peptides are recognized by T cells (CD8+ and CD4+) in T1D and healthy donors, using the combinatorial HLA tetramer readouts described in our recent publications. He/she will then verify whether these T cells are different according to disease status, in terms of frequency and/or functional profile (e.g. naïve/memory, effector or regulatory). He/she will test the pathogenicity of these T cells by raising T-cell clones against the relevant epitopes and by verifying their cytotoxic activity and other effector functions when put in contact with beta cells. He/she will make use of advanced multiparametric flow cytometry techniques, which we are now translating into CITE-seq formats to improve detection sensitivity and functional profiling of the corresponding T cells.

The ultimate goal is the discovery of new autoimmune biomarkers and of novel therapeutic targets aimed at reverting T1D autoimmunity back to its benign state. The Postdoc will design and set up experiments for the progression of the project. He/she will critically analyze the data obtained, generate reports, and use this information to fine-tune the starting hypotheses and design new experiments.

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• **Knowledge**: A strong expertise in multiparametric flow cytometry, cell sorting, cell culture and previous experience in immunology research is preferred. Fluent English, written and spoken. Applications not fulfilling these criteria will not be considered.
• **Professional skills**: The candidate must be highly motivated and use creative thinking in the resolution of scientific questions. He/she will be able to adapt to rapidly evolving technologies and will have a broad interest for biomedical research. He/she will need to give proof of independent thinking and writing skills and capacity to undertake responsibility as project leader. It is essential that the candidate can work autonomously and as part of a team.
• **Education**: MD/PhD or PhD in biological sciences.

STRUCTURE D'ACCUEIL/LOCATION

The Diabetes & Autoimmunity Research (**DeAR Lab)** "T-cell tolerance, biomarkers and therapies in type 1 diabetes" is part of the Cochin Institute. **The Cochin Institute** is one of the largest biomedical French Research Center located in the center of Paris that provides a multidisciplinary scientific environment and state-of-the-art core facilities. It is affiliated with the French National Institute for Health and Medical Research (Inserm), the Paris Descartes University, the CNRS and the Assistance Publique/Hôpitaux de Paris. It is associated with the Clinical Department of Diabetology of the Cochin Hospital. It belongs to different international consortia such as the European IMI2 Innodia (www.innodia.eu) and the Network for Pancreatic Organ Donors (nPOD; www.jdrfnpod.org).
We offer a stimulating and productive lab environment of young researchers with strong team spirit. This is an excellent career opportunity, as the candidate will have a senior role within the Laboratory and interact with several international collaborators.
Further information. About our Laboratory: www.dearlab.org; about our institute: www.institutcochin.fr.

CONTRAT/FINANCIAL SUPPORT

Type: Temporary positions **Funding**: *Fondation Recherche Médicale*
Employer: INSERM **Beginning**: October 2019 at the earliest
Duration of contract: 12-month contract renewable for up to 3 years.

POUR POSTULER/HOW TO APPLY?

Applicants should send their CV, list of publications, research summary and the names of two references to Roberto Mallone and Sylvaine You: roberto.mallone@inserm.fr, sylvaine.you@inserm.fr

Representative publications of the Laboratory

1) S. Culina*, A.I. Lalanne*, G. Afonso, K. Cerosaletti, S. Pinto, G. Sebastiani, K. Kuranda, L. Nigi, A. Eugster, T. Østerbye, A. Maugein, J.E. McLaren, K. Ladell, E. Larger, J.P. Beressi, A. Lissina, V. Appay, H.W. Davidson, S. Buus, D.A. Price, M. Kuhn, E. Bonifacio, M. Battaglia, S. Caillat-Zucman, F. Dotta, R. Scharfmann, B. Kyewski, R. Mallone, the ImMaDiab Study Group. Islet-reactive CD8+ T cell frequencies in the pancreas, but not in blood, distinguish type 1 diabetes from healthy donors. **Sci Immunol 2018 (cover article).**
2) S. Gonzalez-Duque, M.E. Azoury, M.L. Colli, G. Afonso, J.V. Turatsinze, L. Nigi, A.I. Lalanne, G. Sebastiani, A. Carré, S. Pinto, S. Culina, N. Corcos, M. Bugliani, P. Marchetti, M. Armanet, M. Diedisheim, B. Kyewski, L.M. Steinmetz, S. Buus, S. You, D. Dubois-Laforgue, E. Larger, J.P. Beressi, G. Bruno, F. Dotta, R. Scharfmann, D.L. Eizirik, Y. Verdier, J. Vinh, R. Mallone. Conventional and neo-antigenic peptides presented by beta cells are targeted by circulating naïve CD8+ T cells in type 1 diabetic and healthy donors. **Cell Metab 2018**.
3) Culina S, Gupta N, Boisgard R, Afonso G, Gagnerault MC, Dimitrov J, Østerbye T, Luce, Attias M, Kyewski B, Buus S, Wong FS, Lacroix-Desmazes S, Mallone R. Materno-fetal transfer of preproinsulin through the neonatal Fc receptor prevents autoimmune diabetes. **Diabetes 2015**.
4) Scotto M, Afonso G, Østerbye T, Larger E, Luce S, Raverdy C, Novelli G, Bruno G, Gonfroy-Leymarie C, Launay O, Lemonnier FA, Buus S, Carel JC, Boitard C, Mallone R. HLA-B7-restricted islet epitopes are differentially recognized in type 1 diabetic children and adults and form weak peptide-HLA complexes. **Diabetes 2012**.