POSTDOC, TEAM 1

In vivo evaluation of the role of Langerin+ cells in a mucosal model of primary MCMV infection

PI: Franck HALARY

Our team is interested in studying the biology of DC subsets in animal models or in experimental models of human origin. During the past years, we have endeavored to delineate the interactions between the cytomegalovirus (CMV) and conventional dendritic cells (cDC). We demonstrated the prominent role of the C-type lectin DC-SIGN in the capture and internalization of the virus into monocyte-derived DC, an interesting model of human cDC in vitro. We are now willing to explore in vivo the role of another C-type lectin, the langerin, in the CMV infection. Langerin is known to play a role in the control of very early step of the HIV infection and is conserved in mice. To better understand how the langerin could be instrumental in an in vivo model of CMV primary infection, your mission will be first to set up a model of mucosal CMV infection in mice that has never been described so far. Then, using recombinant MCMV (i.e., able to render fluorescent the infected cells) and langerin-GFP knock-in mice as well as and Langerin KO animals, you will have to explore the role of this lectin at the inoculation site by in vivo imaging and standard confocal microscopy. In addition, you will have to validate in vivo several gene products that already identified as immune-modulatory molecules induced by the CMV in DCs.

You should have a PhD and the desire to undertake a first or second post-doctoral fellowship. You should already have a solid experience in animal experimentation (mice), live/standard imaging, virology, molecular and cellular biology. Extended knowledge in DC biology and more widely in immunology are heavily required. We seek autonomous people (experiment design and paper writing as well) with strong teamwork skills. Fluent English is required.

For more information, please contact by email : **Franck.Halary@univ-nantes.fr**

<u>5 selected publications:</u>

Condamine et al, Tmem176B and Tmem176A are associated with the immature state of dendritic cells. **J Leukoc Biol.** 2010 Sep;88(3):507-15. Epub 2010 May 25.

Plazolles et al, Pivotal Advance: The promotion of soluble DC-SIGN release by inflammatory signals and its enhancement of cytomegalovirus-mediated cis-infection of myeloid dendritic cells. **J Leukoc Biol.** 2010 Oct 12. [Epub ahead of print]

Amara and Halary et al, Method of treating cytomegalovirus with DC-SIGN blockers. **Patent US** 7427469, sept 2008.

Halary F et al, Vd2neg gamma/delta T cells shared reactivity against CMV-infected cells and epithelium-derived tumor cells: implication in mucosal immunity. **J. Exp. Med.,** 2005 May 16; 201(10):1567-78.

Halary F et al, Human cytomegalovirus binding to DC-SIGN is required for dendritic cell infection and target cell trans-infection. **Immunity.** 2002 Nov;17(5):653-64.+ highlights de Nature Reviews Immunology.

POSTDOC, TEAM 2

Role of Aire in the generation and function of CD8 regulatory T cells

PI: Carole GUILLONNEAU, in collaboration with Ignacio ANEGON and Régis JOSIEN

Mutations in the gene Aire are responsible of an Autoimmune PolyEndocrinopathy Candidiasis Ectodermal Dystrophy (APECED) in human characterized by generation of autoreactive T cells against self. Regulatory T cells are an essential component of the immune system to regulate these immune responses. The role of Aire in the generation of CD4 Tregs, the best characterized Treg population, is being intensively studied and even so remains obscure (1-2). In addition, no study to date addresses the role of Aire in the generation of CD8 Tregs. Interestingly, we have recently shown that treatment with CD40Ig, a fusion molecule capable of blocking CD40-CD40L interaction, provides an indefinite extension of graft survival through induction of regulatory $CD8^+CD45RC^{low}$ T cells in rats (3-7).

The objectives of this project are to define the role of Aire in the generation and function of naturally occurring and CD40Ig-induced $CD8^+CD45RC^{low}$ Tregs cells in the rat. For this, we propose to use a recently generated model of Aire-deficient rat (unpublished) and to study the generation of subset of CD8 Treg in naïve or transplanted animals. Previously, we also showed that activation of $CD8^+CD45RC^{low}$ Treg cells in animals treated with CD40Ig is donor specific and that $CD8^+$CD40Ig Treg cells express a specific altered Vβ11 repertoire. We will determine whether Aire-deficiency impact on the TCR repertoire selection of natural and induced CD8 Tregs. We will also analyze their suppressive activity in MLR responses and the expression of different molecules.

This study will provide important clues on the role of Aire in the generation and function of regulatory T cells in the rat.

For more information, please contact by email : **Carole.Guillonneau@univ-nantes.fr**

1. Aschenbrenner K, *et al.* (2007) Selection of Foxp3+ regulatory T cells specific for self antigen expressed and presented by Aire+ medullary thymic epithelial cells. *Nat Immunol* 8(4):351-358.
2. Mathis D & Benoist C (2009) Aire. *Annu Rev Immunol* 27:287-312.
3. Guillot C, *et al.* (2002) Prolonged blockade of CD40-CD40 ligand interactions by gene transfer of CD40Ig results in long-term heart allograft survival and donor-specific hyporesponsiveness, but does not prevent chronic rejection. *J Immunol* 168(4):1600-1609.
4. Guillonneau C, *et al.* (2007) CD40Ig treatment results in allograft acceptance mediated by CD8CD45RC T cells, IFN-gamma, and indoleamine 2,3-dioxygenase. *J Clin Invest* 117(4):1096-1106.
5. Guillonneau C, *et al.* (2007) Anti-CD28 antibodies modify regulatory mechanisms and reinforce tolerance in CD40Ig-treated heart allograft recipients. *J Immunol* 179(12):8164-8171.
6. Li XL, *et al.* (2010) Mechanism and localization of CD8 regulatory T cells in a heart transplant model of tolerance. *J Immunol* 185(2):823-833.
7. Guillonneau C, Picarda E, & Anegon I (2010) CD8+ regulatory T cells in solid organ transplantation. *Curr Opin Organ Transplant*. [Epub ahead of print].

POSTDOC, TEAM 4

Mechanisms and induction of liver tolerance in allotransplantation

PI: Sophie CONCHON, in collaboration with Sophie BROUARD

INSERM UMR 643 team #4 (group S. BROUARD) studies the immune mechanisms of operational tolerance and chronic rejection in allotransplantation in human as well as in allograft rodent models.

A postdoc position is available in this team to expand a new research project on immune tolerance in the liver, in the context of allogeneic transplantation of liver, isolated hepatocytes and pancreatic islets. This project involves :
- developing new strategies to induce liver tolerance to allotransplantation,
- analyzing the interactions between hepatocytes & immune cells in models of liver tolerance.

Strategies of in vivo gene transfer, RNA interference, rodent models and clinical collaborations are all important elements of this project.
Highly motivated candidates with training in molecular/cell biology and immunology and good communication skills are encouraged to apply. A background in cell/gene therapy and experience with animal models is advantageous.

For more information, please contact by email : **Sophie.Conchon@inserm.fr**

POSTDOC, TEAM 5

Identification of seric factors involved in idiopathic nephrotic syndrome

PI: Ludmilla LEBERRE, in collaboration with Jacques DANTAL

The idiopathic nephrotic syndrome is a major challenge in nephrology, mainly in pediatrics. It is a clinical entity defined by the association of a selective albuminuria, leading to hypoalbuminemia and characteristic, but nonspecific, glomerular lesions called minimal change disease or focal and segmental glomerulosclerosis. Resistance to the current treatments leads to the appearance of a chronic renal dysfunction requiring frequent hemodialysis and/or renal transplantation. The mechanism of this disease is unknown but some clinical observations, such as immediate recurrence of the initial disease on the graft after renal transplantation, highly suggest the presence of an extra-renal circulating factor that deteriorates renal filtration. Our hypothesis is that this albuminuric factor is produced by the immune system. We have indeed demonstrated in patients that immuno-adsorptions of sera with Protein A or anti-human immunoglobulins affinity columns restaure the glomerular permeability. These clinical observations argue for the role of Igs in this disease. These Igs may target auto-antigens or act as a factor's transporter. A differential proteomic analysis is now required to identify such albuminuric factor(s). Moreover, in order to further define the physiopathological mechanisms, we now work with the Buffalo/Mna rat that develops a spontaneous disease that is very close to the human disease.

The principal aim will be to perform an exhaustive analysis of proteins bound to anti-Igs or Protein A columns of sera from recurring vs. non recurring INS patients and healthy individuals, using the proteomic platform Biogenouest. Then, the proteins selectively identified in recurring patients will be further analysed by Elisa, Western Blot and RT-PCR from sera, tissues or cells of our patient cohort. Finally, the pathologic involvement of the identified protein(s) will be investigated *in vivo* with the Buffalo/Mna rat and *in vitro* with human podocyte cell lines.

For more information, please contact by email : **Ludmilla.Leberre@univ-nantes.fr**

5 selected publications:

Dantal, Godfrin, Koll, Perretto, Naulet, Bouhours, Soulillou. Antihuman immunoglobulin affinity immunoadsorption strongly decreases proteinuria in patients with relapsing nephrotic syndrome. J Am Soc Nephrol., 1998, 9(9):1709-15.

Le Berre, Godfrin, Lafond-Puyet, Perretto, Le Carrer, Bouhours, Soulillou and Dantal. Effect of plasma fractions from patients with focal and segmental glomerulosclerosis on rat proteinuria. Kidney Int., 2000, 58: 2502-2511.

Le Berre, Godfrin, Perretto, Smit, Buzelin, Kerjaschki, Usal, Cuturi, Günther, Soulillou and Dantal. Extrarenal effects on the pathogenesis and relapse of idiopathic nephrotic syndrome in Buffalo/Mna rats. J. Clin. Invest., 2002, 109 (4): 491-8.

Le Berre, Hervé, Buzelin, Usal, Soulillou and Dantal. Renal macrophage activation and Th2-polarisation precedes the development of nephrotic syndrome in Buff/Mna rats. Kidney Int, 2005, 68 (5) : 2079-90.

Le Berre, Bruneau, Naulet, Renaudin, Buzelin, Usal, Condamine, Soulillou and Dantal. Induction of T regulatory cells attenuates idiopathic nephrotic syndrome. JASN 2009, 20(1): 57-67.

POSTDOC, TEAM 6

Neuroimmune signaling in neuron survival and axonal outgrowth

PI: Héléne BOUDIN

INSERM UMR 643 team #6 (P. NAVEILHAN) studies neuroimmune interactions involved in neuronal differentiation in the context of intracerebral transplantation. Neuroinflammation induces both detrimental and beneficial effects on neuronal survival and repair. Therefore, therapies targeting the beneficial aspects of neuroinflammation may substantially stimulate mechanisms of tissue repair in neurodegenerative diseases and brain injury. In the course of experiments designed to inhibit the immune response induced by intracerebral neuron transplantation, we have identified an immunoregulatory molecule as a promoter of neuronal survival and/or axonal sprouting. The aim of the project is to test the regenerative action of this molecule on injured neurons and to decipher the mechanisms underlying this effect. This work could lead to new therapeutic strategies targeting neuroimmune signaling to improve neuronal regeneration. This project will be conducted in collaboration with B. VANHOVE (team 3) and A. NICOT (team 4).

Highly motivated candidates with training in molecular/cell biology and neurobiology are encouraged to apply. A background in neuronal cell culture will be appreciated.

For more information, please contact by email : **Helene.Boudin@univ-nantes.fr**