GRAFF-DUBOIS Stéphanie, *PhD*

Enseignant-Chercheur en immunologie UPMC/ *Associate professor in immunology UPMC*

Membre d'Equipe Cimi-Paris / ***Cimi-Paris Team Member***

Immunobiologie des infections virales et présentation des antigènes / ***Immunobiology of Viral infections and Antigen presentation***

Bio

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Formation / *Education*

2011	D.U Experimentation animale de niveau I, University of Paris VI (UPMC)
2003	Ph.D. in Immunology (Highest honorable distinction), University of Paris V. fellow of Ministère de la Recherche et des Techniques

Expérience professionnelle antérieure / *Past Professional experience*

Since 2010:	UMR-S 945 team 5 (A. Moris), Hôpital Pitié Salpêtrière, Paris - Immunobiology of antigen presentation (UPMC - MCU)
2008-2010	U698 team 4 (Pr Nicoletti), Hôpital Bichat, Paris - Immunology of graft microenvironment and Lymphangiogenesis
2006-2008	UMRS 872 team 16 (Dr Kaveri) CRC, Paris - Immune intervention on dendritic cell differentiation and maturation; Coordination and immunomonitoring design of a clinical trial including hemophilic patients; Immunology of graft microenvironment (UPMC - MCU)
2005-2006	Immunology department (Dr Abastado) Cochin Institute, Paris - Immunology of tumor microenvironment (Post-doc INSERM)
2004-2005	Unité d'Immunité Cellulaire Anti-virale, (Pr Lemonnier) Pasteur Institute, Paris - Development of two T-cell hybridomas from HLA-transgenic mice as tools for analysis of antigen processing by human dendritic cells (Scientist)
2003-2004	IDM Pharma - immuno-monitoring Plateform. Institut des Cordeliers (Dr Abastado). Paris - Optimization of protocols of immunomonitoring protocols to amplify and detect antigen-specific T cells induced by vaccination with tumor lysate-loaded dendritic cells (Scientist)
2000-2003	INSERM U487 - Laboratory: Cytokines et Immunologie des tumeurs humaines (Dr Kosmatopoulos), Institut Gustave Roussy ; Villejuif - Identification of low affinity epitopes derived from tumor antigen for high efficiency antitumor immunotherapy (PhD student and Master fellowship)

Distinctions - Titres honorifiques / *Honors and Awards*

2012-2016	Award for scientific and teaching activities

Recherche / *Research*

Mots-clés / ***Keywords :*** VIH, Présentation des antigènes, Immunité, Autophagie, Centre Germinatif, cellules T folliculaires, B cell, organes lymphoïdes /

HIV, Antigen presentation, Immunity, Autophagy, Germinal center, Follicular T cells, B cells, Lymphoid organs

Programme en cours / *Current Research*

Les cellules T « helper » folliculaires (Tfh) sont des cellules récemment caractérisées, hautement spécialisées et situées dans les organes lymphoïdes secondaires. Les Tfh fournissent aux cellules B les signaux requis pour leur différenciation et leur maturation tandis que les cellules B induisent une expression soutenue du facteur de transcription Bcl-6 par les Tfh, conduisant à leur différentiation complète. Parmi les signaux fournis par les Tfh, l'Il-21 est nécessaire à la différenciation des cellules B en cellules mémoire.

Dans les infections virales chroniques, la persistance des antigènes viraux induit une différenciation préférentielle des lymphocytes CD4 vers le sous-type Tfh au lieu du sous-type TH1 classiquement décrit comme antiviral. Dans le contexte de l'infection VIH, le flux continu des Tfh au sein des organes lymphoïdes pourrait entretenir le cercle vicieux de l'infection et participer au réservoir VIH dans les organes lymphoïdes.

Même si la plupart des patients VIH développent des anticorps spécifiques du virus, la fonction des cellules B est globalement affectée. Ainsi, seule une fraction des anticorps anti-VIH produits par les cellules B présente une activité neutralisante. Ces anticorps « efficaces » n'apparaissent que tardivement au cours de l'infection et présentent un taux de mutations somatiques très important, suggérant une maturation de la réponse B retardée ou inefficace dans laquelle les Tfh pourraient jouer un rôle central. Nous proposons de caractériser les Tfh provenant de patients VIH et de donneurs sains selon 2 axes : (i) La caractérisation des Tfh comme cibles potentielles du VIH, et(ii) Les conséquences fonctionnelles de l'infection des Tfh sur la maturation des cellules B

T Follicular helper cells (Tfh) are highly specialized CD4 T cells located in spleen and lymph nodes, canonical secondary lymphoid organs that support the initiation of immune response. Within follicles, Tfh control multiple B cell differentiation and maturation steps. Cognate interaction between Tfh and B cells leads to their mutual and interdependent activation. Tfh provide signals required for B cell differentiation into extra follicular plasma cell or germinal center (GC) B cell. In return, B cell help sustains Bcl-6 expression in Tfh, a key transcription factor required for fully differentiation of Tfh into GCTfh. Among signals provided by Tfh, Il-21 is required for the generation of memory B cells.

In chronic viral infections, persistence of viral antigens redirects CD4 T cell differentiation away from antiviral TH1 response toward Tfh. In the context of HIV infection, this continuous renewal of Tfh within lymphoid structures might sustain the vicious circle of HIV infection. Constantly replenished within follicles, the pool of Tfh might be targeted by HIV at the earliest stage of HIV infection thus contributing to the establishment and maintenance of viral reservoirs.

Although most of HIV infected patients develop virus specific antibodies, defects in global B cell functions are reported. Indeed, only a fraction of these antibodies displays antiviral activity such as neutralization; Moreover, HIV-specific neutralizing Abs (nAbs) arise late in the course of infection and present a broad rate of somatic mutations suggesting a delayed or inefficient B cell maturation in which Tfh might play a central role.

We propose to characterize Tfh from the spleen of HIV infected individuals. We propose to identify Tfh as potential targets of HIV infection and to provide first hints towards their functional capacities.

Domaines d'applications / *Fields of application*

Infections virales, HIV / *Viral infections, HIV*

Antiviral/tumoral immune response, Follicular helper T cell, epitope mapping

Contrats de recherche récents / *External peer-reviewed funding*

2012-2014 ANRS T follicular helper cells in HIV-1 infection

Valorisation des résultats / *Exploitation of results*

Brevets / Patents : 3

- Patent No. EP 2041160 (filing date 07/12/2007)- Identification, optimization and use of cryptic HLA-B7 epitope for immunotherapy. Co-inventors : Kosmatopoulos K., Graff-Dubois S., Menez-Jamet J.
- Patent No. US 8003773 (filing date 07/12/2007)- Polynucleotides encoding MHC class I-restricted hTERT epitopes, analogues thereof or polyepitopes. Co-inventors : Demoyen PL, Garcia Pons F., Olivier Adotevi O., Cardinaud S., Neuveut C., Kosmatopoulos K., Graff-Dubois S., Menez-Jamet J.
- Patent No. EP 1485719 International Publication Number: WO/2003/083124 - Peptide epitopes common to antigens of the same multigene family. Co-inventors : Kosmatopoulos K., Graff-Dubois S. (2003/10/9)

Enseignement / *Teaching*

Encadrement / *Supervision*

PhDs	Angeline Rouers , since 2013 (Interactions entre les cellules B et les lymphocytes T folliculaires dans l'infection VIH)
Master	Master 2 Immunothérapies & Bioingenierie, UPMC (from 2008 to now)
	Advanced courses in Cytometry, UPMC (from 2011 to now)
	Tolerance Immunitaire workshop, UPMC (2009-2011)
Antérieurs / *Completed*	Master : Lucie Colineau (2013), Julian Buchrieser (2012), Nassima Chouaki (2010))

Autres activities / *Other teaching activities*

- Coordinator of Master 2 "ImmunoThérapies et Bioingénierie", specialité Immunologie, Master BMC, UPMC
- Advanced courses in Cytometry
- Lectures: fundamental immunology, Biotechnology industry - Academic interfacePreparation to competitive examinations: fundamental immunology
- Veterinary school admission
- CAPES/aggregation
- Lectures (M1 + M2)
- Member of Faculty Evaluation Committees (Master programs, PhD)

Publications

Publications les plus représentatives / *Selected publications*

- Thaunat O, Graff-Dubois S, Fabien N, Duthey A, Attuil-Audenis V, Nicoletti A, Patey N, Morelon E. A stepwise breakdown of B-cell tolerance occurs within renal allografts during chronic rejection. **Kidney international** 2012 Jan;81(2):207-19.
- Cardinaud S, Consiglieri G, Bouziat R, Urrutia A, Graff-Dubois S, Fourati S, Malet I, Guergnon J, Guihot A, Katlama C, Autran B, van Endert P, Lemonnier F a, Appay V, Schwartz O, Kloetzel PM, Moris A. CTL escape mediated by proteasomal destruction of an HIV-1 cryptic epitope. **PLoS pathogens** 2011 May;7(5):e1002049.
- Thaunat O, Patey N, Caligiuri G, Gautreau C, Mamani-Matsuda M, Mekki Y, Dieu-Nosjean M-C, Eberl G, Ecochard R, Michel J-B, Nicoletti A, Graff-Dubois S. Chronic rejection triggers the development of an aggressive intragraft immune response through recapitulation of lymphoid organogenesis. **Journal of immunology** 2010 Jul;185(1):717-28.

- Thaunat O, Graff-Dubois S, Brouard S, Gautreau C, Varthaman A, Fabien N, Field A-C, Louedec L, Dai J, Joly E, Morelon E, Soulillou J-P, Michel J-B, Nicoletti A. Immune responses elicited in tertiary lymphoid tissues display distinctive features. **PloS one** 2010 Jan;5(6):e11398.
- Lengagne R, Graff-Dubois S, Garcette M, Renia L, Kato M, Guillet JG, Engelhard VH, Avril MF, Abastado JP, Prévost-Blondel A. Distinct Role for CD8 T Cells toward Cutaneous Tumors and Visceral Metastases. **Journal of Immunology.** 2008 Jan 1;180(1):130-7.
- Gross DA, Graff-Dubois S, Opolon P, Cornet S, Alves P, Bennaceur-Griscelli A, Faure O, Guillaume P, Firat H, Chouaib S, Lemonnier FA, Davoust J, Miconnet I, Vonderheide RH, Kosmatopoulos K. High vaccination efficiency of low-affinity epitopes in antitumor immunotherapy. **Journal of Clinical Investigation.** 2004 Feb;113(3):425-33
- Graff-Dubois S, Faure O, Gross DA, Alves P, Scardino A, Chouaib S, Lemonnier FA, Kosmatopoulos K. Generation of CTL recognizing an HLA-A*0201-restricted epitope shared by MAGE-A1, -A2, -A3, -A4, -A6, -A10, and -A12 tumor antigens: implication in a broad-spectrum tumor immunotherapy. **Journal of Immunology.** 2002 Jul 1;169(1):575-80

Nombre total de publications : **35**

Original Article n = 21

Total citations: 1081

H-Index : **14 (from google scholar)**