Appel à manifestation d'intérêt - Chaire de professeur junior
Fiche projet type

Établissement/organisme porteur : Inserm
Nom du chef d'établissement/d'organisme : Gilles Bloch
Site concerné : Marseille
Région académique : Aix-Marseille Université

Établissements/organismes partenaires envisagés : *INSERM and Aix-Marseille Université*

Nom du projet : Neural regulation of immunity
Mots-clés : Immunology, Neurosciences, Inflammation, Cancer, Immunity, Viral infection, Neuropeptides, Innate immunity, Macrophages, Adaptive immune response

Durée visée : 5 years

Scientific domain : Neuroimmunology

Section (s) CNU/CoNRS/CSS correspondante (s) : CNU 65 and 47-03, CoNRS 27, Inserm CSS 2

Strategy of the host institution: *(15 lignes maximum)*

The host institution aims to strengthen the emerging field of Neuroimmunology.
The survival of living organisms depends on their capacity to develop mechanisms of defense against environmental challenges causing tissue damage, infections and cancer. These protective functions involve both the immune and nervous systems, which have traditionally been considered independent. However, the nervous system has recently been shown to regulate immune functions.
Marseille is a major pole of research in the fields of Immunology and Neuroscience. The aim of this project is to link these disciplines in order to discover unexplored areas at the border between these different biological fields. The research and teaching activities will be developed in the Luminy campus, which brings together the faculty of Sciences of Aix-Marseille University (AMU), many laboratories and research institutes, which cover major scientific disciplines. It includes over 8000 students, 32 research laboratories (CNRS, INSERM, University, INRA, IRD, CEA) (more than 1500 researchers, post-doctoral fellows, engineers...), an incubator and high-tech companies, a training and conference centre, student accommodation.
The Centre d'Immunologie de Marseille-Luminy (CIML) is a mixed CNRS/INSERM/AMU research center located on the Luminy campus. This laboratory is ideally positioned to develop ambitious multidisciplinary approaches. Its international reputation and the research projects it develops in close collaboration with the APHM (assistance publique des hopitaux de Marseille), other research institutes and AMU are major assets for hosting a Chaire de professeur junior (CPJ).

Strategy of the host laboratory :*(15 lignes maximum)*

The Centre d'Immunologie de Marseille-Luminy (CIML) is a research institute internationally renowned in its discipline formed of 16 research teams (200 persons) and 6 advanced technological core facilities. It has developed an organization and practices designed to foster the creativity and risk-taking of its researchers. In coordination with AMU, the CIML has set up a master's and PhD student program. This international partnership between the CIML and the Immunology program at Harvard Medical School in the United States, began in 2009, was renewed in 2019 and expanded to include the Karolinska Institute in Sweden.

Several research teams within the CIML are specialized in Neuroimmunology. This includes the **neural regulation of immunity** team, headed by Sophie Ugolini, which will be hosting the CPJ and which is exploring this new area of biology at the border between Immunology and Neurobiology. With the support of an ERC grant and other funding (from ANR, FRM, ARC, La Ligue contre le Cancer), this laboratory is deciphering the involvement of the nervous system in the regulation of inflammatory and immune responses in infectious or cancer conditions. The team has recently identified novel neuroimmune pathways playing a crucial role in the regulation of infectious diseases, inflammation and tissue repair (J. Exp. Med. 2017, Nature Immunol. 2018, Cell 2019, J. Exp. Med. 2020, Nature 2021, Nature com. 2021, see the publication list below).

The opening of a CPJ within this team will strengthen this emerging and promising field of research within the reserach institute, the Luminy campus and the AMU.

Summary of the scientific project : *15 lignes maximum*

Pain is one of the major signs of inflammation. Following injury or infection, inflammatory mediators activate nociceptive sensory neurons in tissues. These neurons transmit the signal to the brain, eliciting pain. They also release a number of mediators directly at the site of injury, modulating local immune responses. The laboratory of Sophie Ugolini at the CIML, in collaboration with the laboratory of Aziz Moqrich at IBDM (also located in the Luminy campus) recently demonstrated a key role for subsets of sensory neurons in limiting inflammation and promoting macrophage tissue-repair functions. However, the precise mechanisms involved remain poorly understood. The goal of this project is to decipher the role of the nervous system in the regulation of host immune, inflammatory and pro-repair responses, from the molecular to the systemic level. The host laboratory tackle these questions by studying genetically modified mice with ablations, activations or functional inactivations of particular subsets of neurons. These questions are being addressed in models of viral infection, tissue injury and cancer.

The scientific strategy is based on a holistic approach based on the analyses of both local neuro-immune interactions in tissues, and of systemic regulation. Indeed, pain perception and inflammatory processes also activate a stress response in the central nervous system. This project will, therefore, analyze the modulation of immune responses by local and systemic neuroendocrine pathways. The potential therapeutic value of the findings for treating inflammatory diseases and cancer will be also explored.

Summary of the teaching project : *15 lignes maximum*

Immunology and neuroscience are among the leading disciplines taught at Aix-Marseille University. The objective of by recruiting a researcher on a "Chaire Inserm" will be to promote a strong link between two these disciplines, which will strengthen the Neuroimmunology pole, already being established on the Marseille site. Several professors and assistant professors are critically involved in teaching the L3 and the Master immunology program which is currently organized as a single track "Master in Immunology" covering research and professional training during the M1 and M2 program, and offers students an equal opportunity to orient their future towards academic or industrial research. The reinforcement of Neuro-Immunology teaching will therefore be critical in this system by linking Immunology and Neurobiology Masters. Students will benefit from the latest knowledge to understand the two complex systems that are the immune and nervous systems. These bridges between disciplines will give them the necessary assets to create a French research network that will generate a favorable ground for new discoveries and thus make a major contribution to this rapidly expanding field.

Funding :

ANR package	200k€
Co-funding*	€
Total project	200 k€

*source et montant

Scientific communication and dissemination :

The team obeys to the research practices that are established by CNRS, as well as the different indications provided by professional editors to allow publication in peer-reviewed international journals. The CNRS official guidelines (https://comite-ethique.cnrs.fr/wp-content/uploads/2020/09/COMETS-GUIDE-EN.pdf) are provided to all team members to insure proper information circulation and awareness. The publications of our laboratory describe analysis of data sets gathered by different laboratory members to ensure reproducibility of methodologies and experiences that are repeated the number of times necessary to reach statistical relevance. Application of proper statistical methodology and data analysis are performed under the control of a professional statistician working on the CIML biocomputing, biostatistics and modelling hub. Manuscripts are elaborated by several members of the team and circulated through the entire team to insure proper information dissemination and results validation prior submission. Our laboratory only publishes papers in peer-reviewed journals of high international standards favouring open access and rapid reproduction by other laboratories of our results all our publications are also deposited in the HAL open archives system (https://hal.archives-ouvertes.fr). The results from this project will be disseminated in the scientific community as well as in more general media. Researchers of the CIML are often interviewed by media in France and in the US from the scientific or general press (France Inter, Europe 1, Le Figaro, Science et Avenir, La Provence, Curiaunautes des Sciences…), dissemination will also be done through CNRS and INSERM communications ressources, as well as the CIML Tweeter account and web site.

Open Science :
Enforced by AMU and CNRS, we abide to the conformity to mention all affiliations correctly, and which also includes the deposition of all the manuscripts to the national multidisciplinary scientific open archive database HAL (https://hal.archives-ouvertes.fr). Also, we publish in open access journals like Nature Communication, and preprint servers such as BioRvix or Research square. The materials published are available to the scientific community, when necessary through an MTA, and the CIML frequently supplies mouse lines or other materials to groups outside the CIML. The knowledge, data and tools coming from this project will be shared as early as possible in the Research and Innovation (R&I) process, in open collaboration with all relevant knowledge actors, including academia, industry, public authorities, end users, citizens and society at large.

Science and society :
We expect this interdisciplinary project to reveal new and unexpected neuroimmune pathways involved in the regulation of pathophysiological inflammatory processes, which should provide promising therapeutic perspectives.

Indicators :

Teaching:
Establishment within the Master of Immunology of Aix-Marseille University of a neuroimmunology module shared with the Neuroscience program.

Research:
We aim at publishing high impact articles in first rank journals of the same type that those listed below:

Publication list of the host team (selection):
- Sensory neuron-derived TAFA4 promotes macrophage tissue repair function. Hoeffel G, Debroas G, Roger A, Rossignol R, Gouilly J, Laprie C, Chasson L, Barbon PV, Balsamo A, Reynders A, Moqrich A and Ugolini S. **Nature**. 2021; 594 (7861):94-99. doi: 10.1038/s41586-021-03563-7. (https://rdcu.be/ckUYr) (=> Publication highlighted in Immunity- https://doi.org/10.1016/j.immuni.2021.06.011 and in Nature Reviews Immunol. https://rdcu.be/cmysj)

- Nociceptive sensory neurons promote the CD8 T-cell response to HSV-1 infection. Filtjens J, Roger A, Quatrini L, Wieduwild E, Gouilly J, Hoeffel G, Rossignol R, Daher C, Debroas G, Henri S, Jones CM, Malissen B, Mackay LK, Moqrich A, Carbone FR and Ugolini S. **Nat Commun**. 2021.;12(1):2936. doi: 10.1038/s41467-021-22841-6 (https://rdcu.be/ckO2B)

- β2-adrenergic signals downregulate the innate immune response and reduce host resistance to viral infection. Wieduwild E, Girard-Madoux MJ, Quatrini L, Laprie C, Chasson L, Rossignol R, Bernat C, Guia S, Ugolini S. **J Exp Med.** 2020, 217(4). pii: e20190554. doi: 10.1084/jem.20190554.

- Endogenous glucocorticoids control host resistance to viral infection through the tissue-specific regulation of PD1 expression on NK cells. Quatrini L, Wieduwild E, Escaliere B, Filtjens F, Chasson L, Laprie C, Vivier E and Ugolini S. **Nature Immunol.** 2018 (9):954-962. doi: 10.1038/s41590-018-0185-0. (=> Publication highlighted in Nature Immunology (19), 2018:902–911)

- Host resistance to endotoxic shock requires the neuro-endocrine regulation of group 1 innate lymphoid cells. Quatrini L, Wieduwild E, Guia S, Bernat C, Glaichenhaus N, Vivier E and Ugolini S. **J. Exp. Med.** 2017 Dec 4;214(12):3531-3541. doi: 10.1084/jem.20171048

- Cell cycle progression dictates requirement for BCL2 in Natural Killer cell survival. Viant C, Guia S, Bernat C, Delconte R, Roger M, Simon V, Goh W, Jiao Y, Grabow S, Kile B, Strasser A, Gray D, Belz GT, Beutler B, Vivier E, Ugolini S*, Huntington ND*. **J. Exp. Med.** 2017 Feb;214(2):491-510. * equal contribution and corresponding authors

- SHP-1-mediated inhibitory signals promote responsiveness and anti-tumour functions of natural killer cells. Viant C, Fenis A, Chicanne G, Payrastre B, Ugolini S*, Vivier E*. **Nat Commun.** 2014, 30; 5:5108 equal contribution and corresponding authors

- Neutrophil depletion impairs natural killer cell maturation, function and homeostasis. Jaeger, B, Donadieu, J, Cognet, C, Bernat, D Ordoñez-Rueda, V Barlogis, N Malhaoui, A Fenis, B Beaupain, C Bellanné-Chantelot, M Bajénoff, B Malissen, M Malissen, Vivier E and Ugolini S. **J. Exp. Med.**, 2012, 209:565-80

- Tuning of natural killer cell reactivity by NKp46 and Helios calibrates T cell responses. Narni-Mancinelli E, Jaeger BN, Bernat C, Fenis A, Kung S, De Gassart A, Mahmood S, Gut M, Heath SC, Estellé J, Bertosio E, Vely F, Gastinel LN, Beutler B, Malissen B, Malissen M, Gut IG, Vivier E and Ugolini S. **Science**, 2012, 335:344-8

- Activating receptor confinement at the plasma membrane controls natural killer cell tolerance. Guia S., Jaeger B.N., Piatek S., Mailfert S., Trombik T., Fenis A., Chevrier N., Walzer T., Kerdiles Y.M., Marguet D., Vivier E., Ugolini S. **Science Signaling**, 2011, 4(167):ra21

Patents

- International patent application WO2019/180150 entitled " METHODS FOR MODULATING INNATE LYMPHOID CELL ACTIVITY, ANTIBODY DRUG CONJUGATES AND USES IN THERAPY"
- International patent application WO2020/064907 entitled " METHODS AND PHARMACEUTICAL COMPOSITION REDUCING SKIN INFLAMMATION" ,
- International patent application PCT/EP2021/052548 entitled " METHODS AND PHARMACEUTICAL COMPOSITION FOR TREATING INFLAMMATORY DISEASE"

We have filed 3 patents with Inserm-Transfert (IT, which insures a very proactive watch on the valorization of CIML's research) and meet every 6 months the IT intellectual property manager, our team is rather privileging the engagement into collaborative partnerships. Intellectual property issues pertaining to the products which might be generated from the collaborative projects are tightly negotiated in the corresponding contracts with the support of IT legal departments.