HOSTING RESEARCH LABS

Centre d'Immunologie de Marseille-Luminy

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Founded in 1976, the Centre d'Immunologie de Marseille-Luminy is a research institute internationally renowned in its discipline. From worm to man, from molecules to the whole organism, from nanosciences to system biology, from physiology to pathology the CIML addresses all areas of contemporary immunology, on many models and at various scales. These include the genesis of numerous cell populations, their modes of differentiation and activation, their implication in cancers, infectious and inflammatory diseases, and the mechanisms of cell death.
The CIML brings together 16 research teams and cutting-edge technological platforms and employs around 180 people, including scientists of many different nationalities.
The CIML is located on the Luminy campus of Aix-Marseille University, in the exceptional environment of the Calanques National Park.

Applications at CIML: Send your CV and motivation letter by email to the hosting scientist and Béatrice Nal-Rogier (nalrogier@ciml.univ-mrs.fr)

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Innate immunity in *C. elegans*

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Mechanobiology / aECM / epidermis / skin / cytoskeleton / innate immune system

How is the innate immune response of the epidermis controlled by the mechanical properties of the extracellular matrix? ?

The apical extracellular matrix (aECM) of *C. elegans* exhibits remarkable mechanical properties, reflecting its intricate structure and composition. This protective outer layer is comprised of collagenous proteins forming a complex and periodically organized mesh-like network. aECM damage leads to the reorganization of the cytoskeleton and the activation of immune responses in the underlying epidermis. The mechanical connections between the aECM and the plasma membrane/cytoskeleton are currently uncharacterised. We hypothesise that circumferential periodic collagens increase stretching anisotropy and could sense changes in tension, leading to cytoskeleton assembly. Using a combination of genetics, cell biology and biophysics, we are exploring the links between aECM damage, tension changes, and immune signaling in *C. elegans.* Our studies are expected to give fundamental insights into how the aECM affects immunity in other animals, including mammals.

Body stiffness is a mechanical property that facilitates contact-mediated mate recognition in Caenorhabditis **elegans**. Weng JW, Park H, Valotteau C, Chen RT, Essmann CL, Pujol N, Sternberg PW, Chen CH. **Curr Biol. 2023**

Meisosomes, folded membrane microdomains between the apical extracellular matrix and epidermis. Aggad D, Brouilly N, Omi S, Essmann CL, Dehapiot B, Savage-Dunn C, Richard F, Cazevieille C, Politi KA, Hall DH, Pujol R, Pujol N. **Elife. 2023**

Microtubule plus-end dynamics link wound repair to the innate immune response. Taffoni C, Omi S, Huber C, Mailfert S, Fallet M, Rupprecht JF, Ewbank JJ, Pujol N. **Elife. 2020**

Innate Immunity Promotes Sleep through Epidermal Antimicrobial Peptides. Sinner MP, Masurat F, Ewbank JJ, Pujol N, Bringmann H. **Curr Biol. 2021**

A Damage Sensor Associated with the Cuticle Coordinates Three Core Environmental Stress Responses in *Caenorhabditis **elegans***. Dodd W, Tang L, Lone JC, Wimberly K, Wu CW, Consalvo C, Wright JE, Pujol N, Choe KP. **Genetics. 2018**

Immunosurveillance of the Central Nervous System

Rejane RUA

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My dynamic team focuses on the brain defense system. The variety of immune sentinels at the brain borders, recently discovered, changed our view of brain protection and neuroinflammation by adding new, key players, in the picture. Using spectral and intravital imaging, spectral cytometry, bulk, single-cell transcriptomics, bioinformatics and genetic tools, we are deciphering the role of macrophages located at the brain borders in the protection against infections and in brain development. This is an exciting and blooming field of research at the frontier between neuroscience, virology, immunology and development, and we hope our work will bring new therapeutic approaches in neurodevelopmental (e.g. autism) and neurodegenerative (e.g. Alzheimer's) diseases.

Seletion of publications:

- Rebejac J, Eme-Scolan E, **Rua R**. Role of meningeal immunity in brain function and protection against pathogens**. J Inflamm** (Lond). 2024 Jan 30;21(1):3. doi: 10.1186/s12950-023-00374-7.

- Rebejac J, Eme-Scolan E, Arnaud Paroutaud L, Kharbouche S, Teleman M, Spinelli L, Gallo E, Roussel-Queval A, Zarubica A, Sansoni A, Bardin Q, Hoest P, Michallet MC, Brousse C, Crozat K, Manglani M, Liu Z, Ginhoux F, McGavern DB, Dalod M, Malissen B, Lawrence T, **Rua R**. Meningeal macrophages protect against viral neuroinfection. **Immunity**. 2022 Nov 8;55(11):2103-2117.e10

- **Rua R**, Lee JY, Silva AB, Swafford IS, Maric D, Johnson KR, McGavern DB. Infection drives meningeal engraftment by inflammatory monocytes that impairs CNS immunity. **Nat Immunol.** 2019 Apr;20(4):407-419

- Kwong B*, **Rua R*,** Gao Y, Flickinger J Jr, Wang Y, Kruhlak MJ, Zhu J, Vivier E, McGavern DB, Lazarevic V. T-bet-dependent NKp46+ innate lymphoid cells regulate the onset of TH17-induced neuroinflammation. **Nat Immunol.** 2017 Oct;18(10):1117-1127

Neuroimmune regulations of tissue regeneration

Guillaume Hoeffel

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Evolving in Sophie Ugolini's Team "Neural regulation of Immunity" in CIML, my research focuses on how immune cells respond to sensory neuron cues in periphery and more generally how the central nervous system orchestrates immune defense. Discovering that macrophages emerged very early during embryonic development changed ours views about how macrophages sense and interact with their surroundings, throughout the lifespan. Tissue-resident macrophages are now considered key players in tissue development, repair and regeneration and we are using spectral/light sheet imaging, high dimensional cytometry, and single-cell transcriptomics, to decipher the non-canonical functions allowing macrophages to regulate tissue homeostasis (e.g. in type 2 diabetes and in cancer). We also observed that the central nervous system can integrate peripheral information upon tissue injuries, and orchestrate the myeloid cell healing responses, suggesting an integral brain-to-periphery axis constantly tuning tissue integrity. Deciphering the nature of peripheral and central neuronal circuits promoting tissue integrity and repair will provide new leads for regenerative medicine strategies.
Neuroimmunologie is an emerging field of research at the crossroad between developmental immunologie and neurosciences, providing exciting opportunities for young and creative minds. The campus is also located in the unique and vibrant environment of Luminy, South of France city of Marseille, allowing adventurous fellows to discover the national park of Calanques.

- **Hoeffel G*#,** Debroas G*, Roger A, Rossignol R, Gouilly J, Laprie C, Chasson L, Barbon PV, Balsamo A, Reynder A, Moqrich A and Ugolini S#. Sensory neurons derived TAFA4 promotes dermal macrophage tissue repair functions. Nature 2021. Jun; 594(7861):94-99. (#co-corresponding author; *co-first author).
- **Hoeffel G*** & Ginoux F*. Fetal Monocytes and the Origins of Tissue-resident Macrophages. Cell. Immunol. 2018 (*co-corresponding author).
- **Hoeffel G,** Chen J, Lavin Y, Low D, Almeida FF, See P, Beaudin AE, Lum J, Low I, Forsberg C, Podinger M, Zolezzi F, Larib A, Ng LG, Chan JKY, Greter M, Becher B, Samokhvalov IM, Merad M, and Ginhoux F. C-Myb+ erythromyeloid progenitors-derived fetal monocytes give rise to tissue-resident macrophages. Immunity. 2015 Apr 21;42(4):665-78.
- Thion MS, Low D, Silvin A, Chen J, Grisel P, Schulte-Schrepping J, Blecher R, Ulas T, Squarzoni P, **Hoeffel G**, Coulpier F, Siopi E, David FS, Scholz C, Shihui F, Lum J, Amoyo AA, Larbi A, Poidinger M, Buttgereit A, Lledo PM, Greter M, Chan JKY, Amit I, Beyer M, Schultze JL, Schlitzer A, Pettersson S, Ginhoux F and Garel S. Microbiome influences prenatal and adult microglia in a sex-specific manner. Cell. 2018 Jan 18 172 (3):500-516. 330:5-15.
- Reynders A*,Anissa Z Jhumka A, Gaillard S, Mantilleri A, Malapert P, Magalon K, Salio C, Ugolini S, Castets F, Saurin AJ, Serino M, **Hoeffel G** and Aziz Moqrich A* Gut microbiota promotes pain chronicity in Myosin1A deficient male mice BioxRiv 2023.

HOSTING RESEARCH LABS

Centre de Recherche en Cancérologie de Marseille

https://www.crcm-marseille.fr/en/

The Centre de Recherche en Cancérologie de Marseille (**CRCM**) was created in 1972 and comprises now 22 teams and 15 technological platforms (in total 450 people). Research at the CRCM addresses basic aspects of cancer initiation and development by identifying molecular alterations and understanding their functional consequences in *in vitro* and *in vivo* settings. The contribution of the tumoral microenvironment and immune system is another important area of research at the CRCM. This research is performed at the molecular and cellular levels, using cellular, organoïd/tumoroïd or organism model systems including yeast and mouse models. Another strong asset of the CRCM is translational and clinical research, which aims to identify prognostic and diagnostic biomarkers and to launch innovative clinical trials tightly linked to bench activities, in collaboration with Institut Paoli-Calmettes (IPC) and Assistance Publique des Hôpitaux de Marseille (APHM), and biotechs founded by CRCM/IPC researchers.
The CRCM is located on the sites of Institut Paoli-Calmettes, of the Luminy campus of Aix-Marseille University, and at the Faculty of Pharmacy on the Timone campus.

Applications at CRCM: Send your CV and motivation letter by email to paula.michea-veloso@univ-amu.fr

Targeting Signalling Networks and Microenvironment in Cancer, CRCM

Name of hosting Scientists:
Co-PIs of the Team:

Jean Paul BORG, PhD
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We investigate the molecular and cellular circuits operating mode of action in the tumor microenvironment in the crosstalk between cancer cells and distinct cell types, such as immune cells, and its remodelling upon drug treatment. We do so employing *ex vivo* and *in vivo* sophisticated approaches, such as organoids/tumoroids and spontaneous cancer mouse models, principally on **triple negative breast cancer, hepatocarcinoma, colorectal cancer, melanoma and lung cancer**. To decipher the composition of the tumor infiltrate, we utilize single cell omics, spectral cytometry and spatial microscopy. Signalling networks operating in the tumor are identified integrating biochemical with proteomics approaches. The data generated are integrated and compared to human databases, and then validated in human samples.

The main axes of the team are :

Aim 1. Modelling and targeting crosstalks between cancer cells and their tumor microenvironment: towards translational perspectives. Exploring new candidate genes/mechanisms in the crosstalk between cancer cells and their microenvironment, particularly with immune cells.

Aim 2: Membrane signalling pathways in tumor cells. Focusing on still uncharacterized signalling pathway in cancer: VANGL2, MINK1, PTK7, ADAMTSL5

https://www.crcm-marseille.fr/en/teams/research-teams/jean-paul-borg/

Selected publications

- Walton A., et al, #, Thomé V.#, et al. (2024) ***J. Biol. Chem.,*** *in press.* #co-first authors.
- Ganier L., et al. (2022) ***ASC Chem Biol,***
- Arechederra et al. *(2021)* **Journal of Hepatology**
- Castellanet et al. (2021) . **Theranostics,**
- Lamballe et al. (2021). **Advanced Science,**
- Santoni M.-J. *, Kashyap R., Camoin L., and Borg J.-P. * The Scribble family in cancer: twentieth anniversary. (2020) Invited review in ***Oncogene,*** *co-corresponding authors.
- Fan et al. *(2019).* **Journal of Hepatology,** 70(3): 470-482 (2019). PMID: 30529386.
- Michea P # , Noël F #, et al. (2018). **Nat Immunol**. #co-first authors
- Puvirajesinghe T.M, et al. (2016) ***Nat. Commun.***, 7:10318.

Antibody Therapeutics and Immunotargeting, CRCM

Name of hosting Scientist

Patrick Chames, PhD

PI (Research director)

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The ATI team explores the potential of single domain antibodies (nanobodies) for the generation of innovative multispecific immunomodulators and the targeting of payloads for cancer immunotherapies. The main interest of our lab is to use antibody engineering solutions to generate innovative molecules able to efficiently modulate the anti-tumor immune response through the recruitment and activation of immune cells using multispecific cell engagers, multispecific immune checkpoint inhibitors, or through the vectorization of radionuclides and nanoparticles.
https://www.crcm-marseille.fr/en/teams/research-teams/patrick-chames/

T. Briolay et al., International Journal of Nanomedicine. 19, 633–650 (2024).
A. Benloucif et al., Front Immunol. 14, 1200652 (2023).
A. Tapia-Galisteo et al., OncoImmunology. 11, 2034355 (2022).
J. Meng et al., Nat Chem Biol. 18, 894–903 (2022).
A. Raynaud et al., OncoImmunology. 10, 1854529 (2021).
J. Haubrich et al., Proc Natl Acad Sci U S A. 118, e2105848118 (2021).
F. Hartung et al., Front Pharmacol. 11, 686 (2020).
J. Del Bano et al., Front Immunol. 10, 1593 (2019).

Team, PI: LIGNITTO

Hosting scientist:
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FOCUS of the LAB

Lung cancers are characterized by deregulation of the Ubiquitin-Proteasome System (UPS), which critically contributes to their mechanisms of pathogenesis. Specifically, ~30% of Lung Tumors sustain their growth by selecting somatic mutations that block the UPS-mediated degradation of the transcription factor NRF2. Stabilization of NRF2 reprograms key metabolic and signaling events, which drive tumor progression, resistance to therapy, and ultimately poor prognosis in patients. Deciphering the specific mechanisms of pathogenesis induced by NRF2 upregulation is therefore critical to develop effective therapies targeting specific liabilities of these tumors and improve patient outcomes. Yet, these mechanisms are incompletely understood.
Our studies in Lung Cancers identified an unprecedented pro-tumorigenic mechanism caused by the NRF2-driven alteration of heme metabolism. In particular, we demonstrated that heme imbalance affects the UPS-mediated protein degradation and ultimately drives the progression of Lung Cancers with stabilized NRF2. Starting off these results, we hypothesize that the heme-UPS axis has a central role in the pathogenesis of these tumors and can be used to develop new genotype-specific therapeutics.
To pursue this hypothesis, our research uses a multistep strategy combining proteomics, biochemistry and mouse genetics to address the 3 following biological questions:

Question-1: How are proteins degraded via the heme-UPS pathway?
Question-2: What are the mechanisms allowing the heme-UPS system to control protein degradation?
Question-3: What is the role of the heme-UPS axis in Lung Cancer mechanisms?

Our research aims to advance our understanding of the mechanisms of cellular proteolysis by deciphering how heme controls protein degradation via the UPS; but not only that. Our research aims to unravel the mechanisms linking UPS deregulation to the metabolic reprogramming driven by NRF2, which ultimately sustains Lung Tumor malignancy.

Lignitto L., LeBoeuf S.E., Homer H., Jiang S., Askenazi M., Karakousi T.R., Pass H.I., Bhutkar A.J., Tsirigos A., Ueberheide B., Sayin V.I., Papagiannakopoulos T., and Pagano M. Nrf2 activation promotes lung cancer metastasis by inhibiting the degradation of Bach1. Cell. 2019 Jul 11;178(2):316-329.e18.

Lignitto L., Arcella A., Sepe M., Rinaldi L., Delle Donne R., Gallo A., Stefan E., A. Bachmann V., Oliva MA., Storlazzi CT, L'Abbate A., Brunetti A., Gargiulo S., Gramanzini M., Insabato L., Garbi C., Gottesman M.E., and Feliciello A. Proteolysis of MOB1 by the ubiquitin ligase praja2 attenuates the Hippo pathway and supports glioblastoma growth. Nat. Comm. 2013;4:1822.

Lignitto L., Carlucci A., Sepe M., Stefan E., Cuomo O., Nisticò R., Scorziello A., Savoia C., Garbi C., Annunziato L., and Feliciello A. Control of PKA stability and signalling by RING ligase Praja2. Nat. Cell. Biol. 2011 Apr;13(4):412-22.