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Nantes Université

Postdoctoral position
INSERM_U1307 CNRS_U60751 Nantes Université
Centre de Recherches en Cancérologie et Immunologie Intégrée Nantes Angers (CRCI²NA)

A one-year (renewable) postdoctoral position is available in the Team reMOVE-B "MOlecular Vulnerabilities of tumor Escape in mature B-cell malignancies" of the Cancer Research in Cancerology and Integrated Immunology of Nantes Angers (www.crci2na.org**).** This position will be part of the topic **"microenvironment of mature B cells malignancies"**.

This project aims to characterize microenvironment-dependent molecular regulations involved in resistance/escape of cancer cells to death. The candidate will benefit from the expertise of the team in the fields of B-cell lymphoma ecosystems and Bcl2-family/TP53 networks. In addition, the candidate will have access to pre-established models (*ex vivo coculture model*, *PDX*) and cutting edge technologies (*multispectral IF, scRNA-seq*) (see detailed abstract).

The commitment of both academic (CRCINA, INSERM, CNRS) and clinical actors (CHU de Nantes) in our structured consortium "L'Héma-NExt" (I-SITE labeled cluster), which is dedicated to hematology, provide a strong research environment and ensure the rapid translation of bench discoveries into clinical studies. In addition, our team also belongs to several networks gathering experts in hematology (Calym Carnot Institute www.experts-recherche-lymphome.org/calym/) and microenvironment (GDR3697 MicroNit) and is part of the SIRIC ILIAD (www.siric-iliad.com), an INCa-certified multidisciplinary research project.

The position is open
The application should be sent to Dr. David Chiron david.chiron@univ-nantes.fr and Dr. Catherine Pellat-Deceunynck Catherine.pellat-deceunynck@univ-nantes.fr and should include a CV, a cover letter including a statement of motivation and 2 contacts information for recommendation.

We seek for a motivated and autonomous postdoctoral fellow with a strong expertise in cell biology (including flow cytometry and primary cell culture) and molecular biology. Teamwork skills as well as excellent oral and written communication skills are mandatory (French/English). Candidates with skills in bioinformatics (including R) and/or in vivo models will be prioritized.

Evidence of expertise supported by first-author publications in peer-reviewed journals is essential.

The salary is based on experience (INSERM ref): 0-2 years 2569,96 euros (Gross income)
2-4 years 2948,59 euros (Gross income)

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Project abstract: Cellular and molecular integration of MCL immune niches for novel rational therapeutic strategies.

Despite recent progress[1,2], the aggressive clinical behavior of mantle cell lymphoma (MCL) and systematic relapses to current treatments highlight a great need for better rational therapy. In contrast to other B-cell malignancies, there is relatively little information regarding the nature of MCL microenvironments and the resulting molecular regulations that occur in protective niches. Nevertheless, our recent data has shown the critical role of the immune microenvironment in the proliferation, survival and resistance of MCL primary cells[3-6]. We demonstrated that the Bcl2-family, major regulator of apoptosis, is deeply regulated within protective niches, leading to a pro/anti-apoptotic imbalance and a consequent tumor survival/escape[4,7]. We now seek to understand the molecular mechanisms involved in these microenvironment-dependent modulations (cellular dialogs, signaling pathways, epigenetic dysregulation, …) and aim to develop novel strategies to restore the Bcl2-family balance and consequently counteract protection acquired in immune niches.

Our project, which includes both phenotypic and functional strategies, is based on relevant *ex vivo* primary cocultures and original *in vivo* models, integrating the key role of the microenvironment in tumor expansion and drug resistance. These models will represent unique tools for evaluating the regulation of the central actors of MCL-microenvironment multiple dialogs and consequently testing the efficacy of the novel (immuno)therapeutic agents selectively directed against them. In addition, we are developing novel strategies to characterize MCL niches *in situ* at the cellular (multispectral IHC) and transcriptomic (scRNA-seq) levels.

As well as increasing our fundamental knowledge of the critical molecular dialogs that take place within the protective niches, our study aims to build a strong biological rationale directed towards the clinic. The characterization of the dynamics of tumor niches should also open up new targeted and innovative therapeutic perspectives in other hematological malignancies whose resistance also involves similar microenvironment.

1. *Le Gouill S, Thieblemont C, Oberic L, et al. Rituximab after autologous stem-cell transplantation in mantle-cell lymphoma. New England Journal of Medicine. 2017;377(13):1250-1260.*
2. *Le Gouill S, Morschhauser F, Chiron D, et al. Ibrutinib, Obinutuzumab And Venetoclax In Relapsed and Untreated Patients with Mantle-Cell Lymphoma, a phase I/II trial. Blood. 2020.*
3. *Chiron D, Di Liberto M, Martin P, et al. Cell-cycle reprogramming for PI3K inhibition overrides a relapse-specific C481S BTK mutation revealed by longitudinal functional genomics in mantle cell lymphoma. Cancer Discov. 2014;4(9):1022-1035.*
4. *Chiron D, Bellanger C, Papin A, et al. Rational targeted therapies to overcome microenvironment-dependent expansion of mantle cell lymphoma. Blood. 2016;128(24):2808-2818.*
5. *Papin A, Tessoulin B, Bellanger C, et al. CSF1R and BTK inhibitions as novel strategies to disrupt the dialog between mantle cell lymphoma and macrophages. Leukemia. 2019;33(10):2442-2453.*
6. *Decombis S, Papin A, Bellanger C, et al. The IL32/BAFF axis supports prosurvival dialogs in the lymphoma ecosystem and is disrupted by NIK inhibition. Haematologica. 2022.*
7. *Tessoulin B, Papin A, Gomez-Bougie P, et al. BCL2-Family Dysregulation in B-Cell Malignancies: From Gene Expression Regulation to a Targeted Therapy Biomarker. Front Oncol. 2018;8:645.*

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