AAP SIRIC 2018
Recherche translationnelle et SHS en oncologie

Identification du Projet	
Titre	Single cell characterisation of MCL within its immune niches touncover novel therapeutic targets.
Axe thématique du SIRIC	Etude de la résistance tumorale et de ses paramètres
Porteur du projet	David Chiron
Equipe/Service	Equipe 10 « Regulation of Bcl2 and p53 networks in Multiple Myeloma and Mantle Cell Lymphoma"
Laboratoire/Etablissement	CRCINA, INSERM, CNRS, Université d'Angers, Université de Nantes
Co-porteur du projet	Steven Le Gouill
Equipe/Service	Service d'Hématologie Clinique, Unité d'Investigation Clinique
Laboratoire/Etablissement	CHU Nantes

Résumé du Projet

The aggressive clinical behavior of mantle cell lymphoma (MCL) and its short-term response to current treatment 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 within protective niches. Nevertheless, our recent results have shown the critical role of the immune microenvironment in the proliferation, survival and resistance of MCL primary cells.

In the present research program, we propose to deeply analyze 8 MCL bone marrow (BM) samples using a last generation single-cell RNA-seq Chromium 10X genomics system. We aim to investigate the nature and the dynamics of MCL within the BM microenvironment in a setting in which mechanistic insights will directly be applied to therapy, through 4 complementary axes:

(i) To set up the single cell RNA (scRNA-seq) profiling of malignant lymphoma cells.
(ii) To characterize the main immune actors within MCL BM niche at the single cell level.
(iii) To extensively analyze patient samples from the OAsIs study (obinutuzumab, venetoclax, ibrutinib) including BM samples from 3 responders and 3 non-responders.
(iv) To integrate MCL BM scRNA-seq data with relevant ongoing project from the SIRIC ILIAD such as normal and multiple myeloma BM.

Our recent works highlight the fact that the integrated molecular and cellular characterizations of MCL within its microenvironment allow the discovery of novel targets and biomarkers for this pathology. Now we need to decipher the dynamics of neoplastic lymphoma cells in contact to the still unknown key immune components of the tumoral microenvironment *in situ*. We believe that the deep characterization of biologically (mutational profile, drug response *ex vivo*) and clinically (response to targeted therapy *in vivo*) annotated samples at the single cell level will increase our understanding in the role of the microenvironment in tumor expansion and targeted therapy resistance.

Mots clés : Lymphoma, microenvironnement, subclonal composition, single cell, targeted therapy resistance