AAP SIRIC 2018
Recherche translationnelle et SHS en oncologie

Identification du Projet	
Titre	Defining chemotherapy resistance molecular signature of osteosarcoma in PDX models
Axe thématique du SIRIC	Etude de la résistance tumorale et de ses paramètres
Porteur du projet	Francoise REDINI
Equipe/Service	Equipe 1 - Micro environnement des tumeurs osseuses primitives : signalisation et ciblage thérapeutique
Laboratoire/Etablissement	UMR1238 – Sarcomes Osseux et Remodelage des Tissus Calcifiés - Nantes
Co-porteur du projet	Estelle THEBAUD
Equipe/Service	Service d'oncologie-hématologie et immunologie pédiatrique
Laboratoire/Etablissement	CHU Nantes

Résumé du Projet

Osteosarcoma (OS), the most primary malignant bone tumors affecting children and young adults remains one of the pediatric tumors more resistant to conventional treatments. This underscores the urgent need for further research on the molecular mechanisms driving OS initiation, progression and resistance to chemotherapy treatment.

During the last years, our research unit identified several molecular mechanisms responsible for either chemoresistance or tumor development to the critical metastatic stage. We specifically demonstrated that HSP, TGF-or RANK/RANK/OPG cascades, and epigenetic process play crucial roles in metastatic dissemination and resistance to chemotherapy by targeting tumor cells and/or their microenvironment such as bone or immune cells. Based on our data, we hypothesize that these molecular signatures could allow to differentiate good and bad responders to current chemotherapy, and disease progression (metastatic dissemination).

Our project aims to confirm that this identified molecular signature is associated with resistance to chemotherapy and metastasis occurrence using osteosarcoma PDX models. For that, we will develop PDX models from primary bone tumors biopsies isolated from good or bad responders to chemotherapy, and from patients with or without lung metastasis at diagnosis.Specifically, we will evaluate the identified molecular signatures (HSP, TGF- and mi-RNA, RANKL/RANK/OPG) in PDX models using high throughput approaches (RNAseq, RPPA), immunohistochemistry and in vitro functional analyses. Recruitment for PDX establishment is already ongoing and there is an efficient coordination between pediatric oncology (Dr THEBAUD, Nantes), orthopedic surgery (Dr CRENN, Nantes) and translational research (UMR1238).

To resume, this translational research project focuses on both a fundamental approach to the study of molecular mechanisms involved in resistance to current treatments of OS and a clinical collaboration (pediatric oncology and orthopedic departments) through the use of original and relevant animal PDX

models from human biopsies and to develop diagnostic, predictive or therapeutic applications for OS.

Keywords : Patient-Derived Xenografts, osteosarcoma, chemotherapy, resistance