AIX-MARSEILLE UNIVERSITE
ECOLE DOCTORALE DES SCIENCES DE LA VIE ET DE LA SANTE – ED62

PROPOSITION SUJET DE THESE

Concours d'attribution des Contrats Doctoraux 2019 – 2022
A renvoyer impérativement **avant le 2 mars 2019** par courriel au format **PDF** à
edsvs-direction@univ-amu.fr

1. Choix du sous-jury (vous ne pouvez cocher qu'une seule case) :

X JURY 2 – Microbiologie – Génomique (Bioinformatique – Biochimie Structurale – Biochimie).

Laboratoire	
Nom et N° :	Centre de Génétique Médicale de Marseille - MMG - U1251
Adresse :	Faculté de Médecine de La Timone
	27 bd Jean Moulin - 13005 Marseille
Directeur :	Nicolas Lévy
Website :	www.marseille-medical-genetics.org
Nom de l'équipe	Differentiation and Proliferation of Neuroendocrine Tissues
Responsable équipe :	Thierry BRUE
Nombre d'HDR dans l'équipe	5
Directeur de Thèse	
Nom :	BARLIER
Prénom :	Anne
Grade :	PU-PH
Courriel :	anne.barlier@univ-amu.fr
Téléphone :	04 91 32 49 31
HDR obtenue le :	2007
Nom du Codirecteur éventuel :	KRAHN Martin
Nom(s) du(es) doctorant(s) en cours d'encadrement :	Arnaud LAGARDE à 50%
Nom et date de soutenance du précédent doctorant encadré :	Pauline ROMANET - soutenue le 10 juillet 2018
Publication du Doctorant : (sont indiquées uniquement celles avec P Romanet, dernier doctorant, en premier auteur)	**P Romanet,** M-F Odou, M-O North, A Saveanu, L Coppin, E Pasmant, A Mohamed, F Boron-Chazot, A Calender, C Béroud, N Lévy, S Giraud, **A Barlier.**. Propositions of adjustement to the ACMG-AMP framework for the interpretation of MEN1 missense variants. Hum Mut accepté avec corrections mineurs * publication en Special article à la demande de l'éditeur **Romanet P**, Philibert P, Fina F, Cuny T, Roche C, Ouafik L, Paris F, Reynaud R, **Barlier A**. Using Digital Droplet Polymerase Chain Reaction to Detect the Mosaic GNAS Mutations in Whole Blood DNA or Circulating Cell-Free DNA in Fibrous Dysplasia and McCune-Albright Syndrome. J Pediatr. 2019 Feb **Romanet P,** Mohamed A, Giraud S, Odou MF, North MO, Pertuit M, Pasmant E, Coppin L, Guien C, Calender A, Borson-Chazot F, Béroud C, Goudet P, **Barlier A.** UMD-MEN1 Database: An Overview of the 370 MEN1 Variants Present in 1676 Patients From the French Population. J Clin Endocrinol Metab. 2019 Mar 1;104(3):753-764. * article sélectionné par l'Endocrine Society pour une publication thématique spéciale : Endocrine Neoplasia and Cancer **Romanet P,** Guerin C, Pedini P, Essamet W, Castinetti F, Sebag F, Roche P, Cascon A, Tischler AS, Pacak K, **Barlier A,** Taïeb D. Pathological and Genetic Characterization of Bilateral Adrenomedullary Hyperplasia in a Patient with Germline MAX Mutation. Endocr Pathol. 2017 Dec;28(4):302-307.

PROJET DE THESE

Optimization of the detection of unconventional mutational events in next-generation sequencing data from patients suffering from genetic diseases.

During the last few years, it has become clear that single nucleotide variants are only a portion of mutational events causing genetic diseases. Many example now show that copy number variants (e.g. Shen et al. Methods Mol Biol 2019, 1908:113-), insertion of transposable elements (Kvikstad et al. BMC Genomics 2018, 19:115), mosaicism (e.g. D'Gama and Walsh, Nat. Neurosci. 2018, 21:1504-p) and balanced chromosomal rearrangements such as small inversions (e.g. Chen et al. Methods Mol Biol. 2018, 1833:107-) are not rare in the genome of patients affected by genetic diseases. However, these mutational events are either not looked after, not efficiently detected, or not simultaneously searched in the same dataset.

Our laboratory has produced hundreds of panel, clinical exome or whole exome sequencing datasets from our patients' cohorts with different types of genetic diseases. These sets were produced in the laboratory of molecular diagnosis at APHM Conception Hospital (Prof. Anne Barlier), the laboratory of molecular genetics of APHM Timone Children's Hospital (Prof. Nicolas Lévy / Prof. Martin Krahn) and in the NGS platform of Marseille Medical Genetics Center (Dr. Valérie Delague / Dr. David Salgado). A large proportion of the data, even when initially produced in a diagnostic setting, includes consent to perform additional research projects. This constitutes a very rich substrate **to test/improve/develop new tools to identify unconventional mutational events** that will be the aim of this project. There is also a strong need to develop new solutions at the interface between biology and informatics for the benefit of affected patients and to ease mining of NGS data by clinical or research specialists.

Supervision of this research project will be ensured by the (director / co-directors) , providing a clinical and molecular expertise for the interpretation of identified variants, and by a dedicated support from the genomics platforms providing bioinformatics support (two bioinformatics engineers will supervise the bioinformatics development by the PhD candidate). Several teams of Marseille Medical Genetics Center producing NGS data will also contribute to the analyzed dataset (this includes neuroendocrine disorders, disorders of neurodevelopment, or neuromuscular diseases).

We believe that the amount of data, availability of clinical cohorts, clinical expertise for the interpretation of identified variants, together with bioinformatics expertise and the various diseases that can be studied, will be a strong asset in order to obtain new (and relevant) results.

The PhD candidate must hold a master degree in bioinformatics with a strong interest in biomedical research and analysis of data from genetic diseases.