Profile N° (à remplir par VAS) **FUNDING Planned**

Obtained

Sheet abstract of thesis 2017 **Disciplinary Fields Autres et Autres**

Thesis Title : (1-2 lines)
Predictive approach to assess the genotoxicity of environmental contaminants during liver fibrosis

3 keywords : (1 line) **ACRONYME** Genopredict
Systems toxicology-Biology / Xenobiotics metabolism / Modelling

Unit/Team of supervising : (1-2 lines)
UMR Inserm 1085 IRSET

Name of the scientific director and co-director : (1 line)

LANGOUET Sophie

Contact : (1 line)
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Socio-economic and scientific context : (10 lines)

Many contaminants in the environment and food are procarcinogens, ie they need to be metabolized to be activated. This bioactivation involves many metabolic pathways that are species-specific (animal / man) and specific for each compound. They depend in particular on their chemical structures, the enzymes present in the target tissue and the polymorphism of the latter. While the team has, for several years, characterized metabolic activation and DNA adducts derived from certain environmental contaminants in the human liver, it now seems essential to develop predictive methods for large-scale study of l The impact of these contaminants during hepatic fibrosis in humans.

Assumptions and questions (8 lines)
The objective of the project is to establish an innovative multidisciplinary strategy to establish the causality between the pathways of environmental contaminant activation and their genotoxicity during human hepatic fibrosis.
By combining approaches of integrative biology, from systems biology to experimental approaches, the project aims to establish predictions as to the ability of molecules to alter DNA. The identification of metabolites and DNA adducts is essential for the development of exposure markers necessary to accurately estimate the exposure of individuals to environmental contaminants.

The main steps of the thesis and demarche (10-12 lines)

Methodological and technical approaches considered (4-6 lines)
This project will consist in generating predictive models which will then be validated experimentally using multidimensional mass spectrometry data obtained in collaboration with the laboratory of Dr R Turesky (University of Minnesota, Minneapolis). We will first validate the data obtained for aromatic heterocyclic amines (AHA), contaminants of particular concern in the development of liver cancer in industrialized countries and for which we have recognized expertise (Nauwlaers et al, Chem Res Toxicol, 2015, Tath et al, J Biol Chem, 2015, Nauwelaers et al, Chem Res Toxicol, 2013, Wang et al., Chem Res Toxicol, 2015, Bellamri et al. Mut, 2016, Bellamri et al., Chem Res Toxicol, 2017).
Computational approaches will be developed in collaboration with Anne Siegel's team (Dyliss, IRISA). The difficulty will be to take into account in the automatic analysis process the information relating to the chemical structure of the molecules. This will be done through the knowledge of the large databases being standardized to develop automatic systems for predicting molecular transformation pathways. These metabolic maps will then be confronted with expression data (transcriptomes of patients) to be filtered and refined. Finally, the filtered maps will be confronted with mass spectrometry data to identify peaks relevant to the AHA issue and

allow their identification.

Scientific and technical skills required by the candidate (2 lines)

This subject is addressed to a bioinformatician. Theoretical knowledge in cellular and molecular biology (eventualy toxicology) would be an advantage