DOCTORAT BIOLOGIE BRETAGNE SANTE LOIRE

Year 2023

THESIS TOPIC

Subject N° (to be completed by the ED):	**FUNDING:** X☐ **Requested** ☐ **Acquired**	**Funding origin: Rennes University**
Thesis title: **Study of cocktail effects of endocrine disruptors and chemical carcinogens on DNA alterations in human liver organoids**		3 keywords: **Genotoxicity / Lipid metabolism / Complex co-culture of human hepatocytes in 3D**
Unit / team: **UMR Inserm 1085 IRSET, DYMEC2 Team**		
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Socio-economic and scientific context

Studies on the exposome, which aim to understand the risk induced by the continuous exposure of individuals to low doses of environmental and dietary contaminants, are a public health issue and a priority in environmental health research. These exposures could favor the appearance of metabolic disturbances (obesity, diabetes), the increase of chronic liver diseases (steatosis, fibrosis) and the development of hepatocellular carcinoma (HCC) (3rd cause of cancer mortality; 500,000 new cases/year worldwide). In the context of these multifactorial pathologies, it is crucial to study in the human liver the combined effects of metabolic disturbances and genotoxic damage of mixtures of particularly worrying compounds.

Working hypothesis and aims

The objective of the project is to characterize the effects of carcinogenic contaminants (Aromatic Heterocyclic Amines, AHA) in a context of hepatic metabolic disorder induced by endocrine disruptors (PFAS molecules), two families of environmental contaminants to which humans are exposed daily. Taking into account the inter-species differences, the studies will be performed on an innovative model of human hepatocytes cultured in 3 dimensions in a matrix and organized in organoids in a microfluidic flow optimizing the contacts between cells and with the contaminant mixtures. Moreover, these human hepatocytes will be used alone or in co-culture with other cell types (star cells and endothelial cells) involved in liver physiopathology. This thesis will provide new and relevant insights into the toxicity and mixture/cocktail effect of these compounds of concern for human health and the development of hepatocellular carcinoma.

Main milestones of the thesis

The project is based on the analysis of the toxicity and metabolic disturbances related to PFAS/AHA mixtures. The experiments will be performed after a long treatment and at low dose concentrations comparable to the human exposure to these contaminants. After defining the conditions of the mixtures on human liver organoids in mono and co-culture, cytotoxicity, metabolic perturbation analysis and genotoxicity will be studied. We will focus on the genotoxicity in order to define if there are synergistic, additional or other effects in the combinations of contaminants with respect to DNA alterations. The nature of the interactions between the different compounds will be determined

The mechanisms of action involved will also be studied with a particular focus on interactions with certain nuclear receptors such as PPAR/, PXR, CAR and AhR. The cell cultures will also be integrated in a microfluidic system to promote exchanges and expose the cells with different combinations.

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

The PhD student should have a Master 2 level education in biology, cell physiology, biochemistry and/or toxicology. Experience in cell culture would be appreciate, ideally cell cultures in 3D.

3 publications from the team related to the topic (last 5 years):

ROSE S, EZAN F, CUVELLIER M, BRUYERE A, LEGAGNEUX V, LANGOUËT S AND BAFFET G. Generation of proliferating human adult hepatocytes using optimized 3D culture conditions. Scientific Reports, 2021, 11, 515. doi: 10.1038/s41598-020-80019-4

ROSE S, CUVELLIER M, EZAN F, CARTERET J, BRUYERE A, LEGAGNEUX V, NESSLANY F, BAFFET G and LANGOUET S. DMSO-free highly differentiated HepaRG spheroids for chronic toxicity, liver functions and genotoxicity studies. Arch Toxicol, 2022, 96, 243-258 PMID: **34762139** DOI: 10.1007/s00204-021-03178-x

CUVELLIER M, ROSE S, EZAN F, JARRY U, DE OLIVEIRA H, BRUYÈRE A, DRIEU LA ROCHELLE C, LEGAGNEUX V, LANGOUËT S, BAFFET G. *In vitro*long term differentiation and functionality of three-dimensional bioprinted primary human hepatocytes: application for*in vivo*engraftment. Biofabrication. 2022 Jun 30;14(3). doi: 10.1088/1758-5090/ac7825. PMID: 35696992

National and international collaborations:

UMR Inserm 1124, T3S, Paris, Etienne Blanc, Xavier Coumoul

Université de Minneapolis, Cancer Research Center, Robert Turesky