Title of the PhD project: IntesTox (Do pollutants exert metabolic disturbances through their impact on intestinal health?)

Disciplines: Physiology, Metabolism, Pollutants

Laboratory: CARMeN Laboratory, Lyon; Director: Hubert Vidal (http://carmen.univ-lyon1.fr/team-1-nutritional-adaptations-environnement-and-diabetes/?lang=en)

Host Institution: University Lyon1/INSERM /INRA;

Doctoral school: Interdisciplinary Doctoral program in health-sciences (EDISS) - ED 205

Description

Scientific background and rationale: If industrialization fostered societal progress improving life expectancy, it also led to the presence of thousands of anthropic molecules in the different environmental compartments (air, soil, water). Hence, chronic exposure to pollutants contaminating the food chain has become a key issue and a challenge in terms of Public Health. Indeed several epidemiological studies have established a significant correlation between metabolic syndrome or diabetes and the presence of pollutants or their metabolites in blood and urine. Using a mouse model of lifelong exposure to a mixture of widespread food pollutants at very low doses, we could evidence a cocktail effect (as no adverse effect was expected based on the pollutant dosage) and demonstrate age, diet and sex-specific metabolic disturbances such as reduced estrogen signaling in the liver of exposed females and alteration of cholesterol and bile salt metabolism in males. Inflammation was also a target of pollutants. Eventually, using ovariectomized females, we could demonstrate that the pollutants had estrogeno-mimetic properties consistent with previous reports categorizing them as endocrine disruptors.

Aim: To go a step further in the understanding of the impact of pollutants on metabolic health, we will focus on the intestine for its pivotal role in both drug metabolism and lipid and bile acid homeostasis and explore how the necessary detoxification procedure could divert the xenosensors and in particular PXR from their role on lipid and bile acid homeostasis but also on intestinal permeability and associated inflammation.

Description of the project methodology: We will both lead in vivo and in vitro experimental studies. In vivo, we have developed an experimental model in which mice are exposed lifelong to a mixture of low-dosed pollutants. Using this model, the different segments of the intestine will be explored to define if lipid absorption, bile salts biosynthesis and transport are impacted and by which mechanisms. In vitro, use will be made of the human CACO2 or the murine STC-1 cell line exposed to the various pollutants (alone, in mixture) and genes of interest may be invalidated/ restored (SiRNA/adenovirus) for further identification of mechanisms beyond. Other methods to be used include Elisa assays for hormone measurements (insulin, leptin, adiponectin); cholesterol and triglyceride plasma measurements; RT-qPCR and western blotting analysis as well as histological analysis on the intestine (duodenum, jejunum, ileum, colon).

Genes of interest are related to drug metabolism, inflammation and lipid metabolism.

Expected results: Identification of novel biomarkers of exposure to pollutants and a better knowledge of the impact of wide spread pollutants at low dosage and their impact on metabolic disturbances and intestinal health

Perspectives: basis for developing new strategies to restore metabolic health; more evidences to put weight on political decisions for a better legislation on pollutants endowed with endocrine disrupting activities to which everyone is exposed passively all lifelong

Skills required: A highly motivated candidate with a significant knowledge in metabolism and mouse studies and skills in molecular biology and biochemistry


Key-words: endocrine disruptors, gut, inflammation, microbiota, obesity, diabetes

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Application should include: CV, application letter, Names and addresses of two references. The application file should be sent before May 14, 2017 to: email of the supervisor.

The open competitive recruitment process is in two steps: 1. Internal laboratory procedure. 2. Interdisciplinary jury of EDISS.