Qu'est-ce que le dispositif ExposUM Doctoral Nexus ?

Les Doctoral Nexus proposés par l'Institut ExposUM sont des réseaux de 3 à 4 doctorantes et doctorants, issus de disciplines différentes et affiliés à au minimum deux unités de recherche différentes.

Par rapport à une thèse classique, participer à un Doctoral Nexus favorisera la capacité à travailler en équipe et à concevoir des projets de manière transdisciplinaire tout en approfondissant son propre champ d'expertise.

Un programme pédagogique spécifique sera proposé et les doctorant(e)s concerné(e)s auront également l'opportunité d'organiser un séminaire au sein du réseau Nexus.

Les thèses sont financées d'emblée pour 4 années, comprenant le salaire du doctorant ou de la doctorante ainsi qu'une enveloppe d'environnement.

Sujet de thèse

Effect of PFAS on intestinal tumorigenesis

Context - For many cancers, including colorectal cancer (CRC), several aspects of the disease such as the epidemiological features, epigenetic profiles or patient outcomes, are linked to environmental factors and various molecular pathways govern tissue-specific tumorigenicity induced by chronic exposure to endocrine disruptors. Perfluoroalkyl and polyfluoroalkyl substances (PFAS) represent major health concerns and, in a very recent study, it has been reported that very low concentrations of the binary PFOS and PFOA mixture induced synergistic effects on human cancer cell proliferation. In this model, the PFAS mixture also altered cell morphology and promoted cell migration and invasion [1]. Interestingly, in this study, the cellular effects of PFAS were inhibited by sulforaphane suggesting the involvement of the pregnane X receptor (PXR, NR1I2), a member of the nuclear receptor superfamily [2]. PXR is unique amongst the superfamily in that it is activated by a diverse array of xenochemicals that differ greatly in size and chemical structures and can act synergistically [3]. PXR regulates the growth and apoptosis of colon cancer cells [4] and has been suggested to play a role in the development of tumor cell resistance to anticancer drugs. Finally, in addition to targeting directly tumor cell proliferation, PXR may also play a role in CRC by acting on the tumor immune microenvironment [5].

Objective and methods - The overall objective of this research project is to characterize the effects of PFAS on colorectal tumorigenesis using in vitro and in vivo approaches. We will focus on their role as PXR activating-environmental disruptors and will try to define their impact on the tumor immune microenvironment and on the response to chemotherapies.
Our project is organized around 5 major tasks:

Task1. In vitro effect of PFAS on colon cancer cell lines.

We will first evaluate the influence of various concentration of PFAS (single molecules or combinations) on the *in vitro* proliferation of both human and mouse colon cancer cell lines. Depending on the results, we will also use 3D culture to test the effect on intestinal stemness. Other parameters including cell migration and invasion will also be analyzed. Finally, we will perform global analysis on gene expression to define the cellular pathways activated by PFAS.

Task2. Regulation of PXR signaling by PFAS.

Very recently, PFAS have been identified as regulator of PXR signaling in human breast cancer cells. In order to define whether the same regulation exist in CRC cells, the experiments described in Task#1 will be performed in the presence or not of sulphoraphane. We will also use siRNA against PXR to knock-down its expression. In collaboration with the screening platform of IRCM (PCC-Plateforme de Criblage en Cancérologie), we will test the effects of various concentration of PFAS combinations on the transcriptional activity of hPXR et mPXR using stably transfected bioluminescent cell lines [6].

Task3. Impact of PFAS on CRC growth in vivo.

In order to define the effects of PFAS on the in vivo growth of colon cancer cells, mice grafted with human CRC cells will be treated with PFAS alone or in combination. At the end of the protocol, mice will be euthanized. Tumor development will be quantified and analyses using immunohistochemistry (IHC) in collaboration with the RHEM platform (Dr N Pirot). This will allow specifying the qualitative impact of PFAS on intestinal tumor development and progression.

Task4. Impact of PFAS the tumor immune microenvironment.

Several studies suggest a differential role of PXR in tumor growth regulation dependent on tumor microenvironment [5]. To investigate the effect by PFAS on TIME remodeling in colorectal tumorigenesis, tumor infiltration by T and B lymphocytes together with tertiary lymphoid structures (known to be linked with the response to therapies) will be analyzed by IHC. All these stainings have been recently set up through a collaboration with the RHEM platform. In addition, cytokines and genes involved in adaptive or innate immunity will be quantified in samples from the intestinal mucosa of these animals. Depending on the results, the effect of PFAS will be tested on *in vitro* coculture experiments using CRC cells and immune cells.

Task5. Role of PFAS as PXR-activating EDCs on the response to treatments.

Since PXR regulate the drug-inducible expression of specific cytochrome P450 enzymes and transmembrane drug transporter proteins, it might play a role in the development of tumor cell resistance to anticancer drugs used to treat CRC patients (including 5-FU, irinotecan and oxaliplatin). This will first be tested in vitro on the different CRC cell lines. Moreover, to evaluate possible interferences of PFAS with chemotherapy response, we will also test their effects on tumor regression in vivo on xenografted mice receiving a FOLFIRI treatment which reproduce the chemotherapy regimen given to patients.

Expected results

The completion of this research project will definitely lead to a better understanding of the putative tumorigenic effects of PFAS, in particular through PXR. More precisely, this project may identify environmental effects and molecular pathways controlling the reshaping of the CRC immune ecosystem and the tumor response to therapies. It could lead ultimately to a substantial valorization through the identification of key modulators of anti-tumor response present in the environment.

Feasibility

The feasibility of this project is based both on the expertise of the host laboratory and the network of valuable national collaborations already in place. In addition, this project benefits from the technical and scientific support of the team. All the facilities necessary for the implementation of the project and genetically modified mouse models are already available within the IRCM.

Bibliography

1 Pierozan P, Kosnik M, Karlsson O. High-content analysis shows synergistic effects of low perfluorooctanoic acid (PFOS) and perfluorooctane sulfonic acid (PFOA) mixture concentrations on human breast epithelial cell carcinogenesis. Environ Int. 2023;172:107746.

2 Skandalaki A, Sarantis P, Theocharis S. Pregnane X Receptor (PXR) Polymorphisms and Cancer Treatment. Biomolecules. 2021;11(8):1142.

3 Delfosse V, Dendele B, Huet T, Grimaldi M, Boulahtouf A, Gerbal-Chaloin S, et al. Synergistic activation of human pregnane X receptor by binary cocktails of pharmaceutical and environmental compounds. Nat Commun. 2015;6:8089.

4 Wang H, Venkatesh M, Li H, Goetz R, Mukherjee S, Biswas A, et al. Pregnane X receptor activation induces FGF19-dependent tumor aggressiveness in humans and mice. J Clin Invest. 2011;121(8):3220–3232.

5 Sun L, Sun Z, Wang Q, Zhang Y, Jia Z. Role of nuclear receptor PXR in immune cells and inflammatory diseases. Front Immunol. 2022;13:969399.

6 Mnif W, Dagnino S, Escande A, Pillon A, Fenet H, Gomez E, et al. Biological analysis of endocrine-disrupting compounds in Tunisian sewage treatment plants. Arch Environ Contam Toxicol. 2010;59(1):1–12.

Modalités de candidature

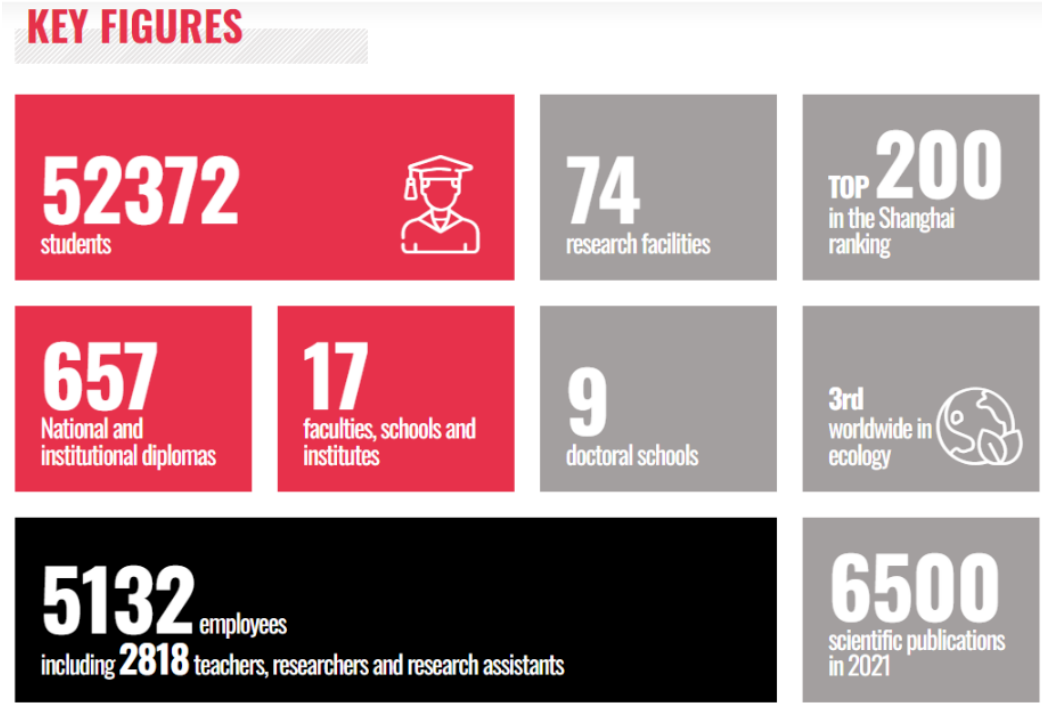
La candidature doit être composée des éléments suivants :

- Un CV
- Une lettre de motivation
- De la copie du diplôme permettant l'inscription
- Des éléments spécifiques demandés par l'école doctorale CBS2 (lien CBS2)

Si vous souhaitez postuler sur ce sujet, adressez au plus vite un mail à vincent.cavailles@inserm.fr en mettant en copie julie.mendret@umontpellier.fr et exposum-aap@umontpellier.fr afin de les informer de votre intérêt.

Avant le dimanche 21 avril, 20h CET

The University of Montpellier



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