

PhD proposal between Sanofi and Institut Pasteur (CIFRE grant)

Title: Structural characterization of the *in vivo* biotransformation products of next-generation biotherapeutics by high-resolution mass spectrometry

Description: In past years, the pharmaceutical industry has largely turned to biological molecules for which the therapeutic interest is now well established. These biotherapeutics (BTx), which include antibodies (mAb), "nanobodies" (Nbs), fusion proteins (mAb/Nbs) and immunoconjugates (ADC) allow extending the arsenal of novel therapies for patients in cancer, autoimmune and chronic inflammatory diseases. Once administered, BTx are most often catabolized leading to small peptides or amino acids that can be recycled by the body. But in many cases BTx are only partially degraded into smaller entities. The study of these biotransformation processes is decisive for the optimization of drug candidates to limit any premature loss of efficacy and any risk of toxicity. Indeed, biotransformations generate truncated proteins that can circulate and be active, inactive or in some cases toxic.

The main objective of this PhD project is to develop a combination of high-resolution mass spectrometry (HRMS) approaches (bottom-up, middle-down, top-down proteomics) allowing the characterization of BTx biotransformations at the molecular level. This characterization is an essential step to better understand the biotransformation mechanisms and further develop optimized BTx scaffolds less prone to degradation.

HRMS approaches will be developed on state-of-the-art Orbitrap instrumentation including the recently modified Q-Exactive HF mass spectrometer equipped with an Omnitrap.

Context of the PhD: The proposed project is a collaboration between Sanofi and Institut Pasteur. The PhD candidate will therefore share his time between the Metabolism team, DMPK France (Sanofi), located primarily at Chilly-Mazarin (91) and then at Vitry sur Seine (94), and the Mass Spectrometry for Biology Unit (Institut Pasteur, Paris) for a period of 3 years.

Starting date: October 2023

Candidate: The candidate should hold a master's degree in analytical chemistry or proteomics with a first practical experience in mass spectrometry, ideally for the analysis of peptides or proteins. Knowledge in Orbitrap MS and in bioinformatics for proteomics would be a plus. He/she should be highly motivated and interested to evolve in an international scientific environment. He/she should have good oral and written communication skills in English (and ideally also in French) and excellent interpersonal skills.

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