Development of innovative high resolution mass spectrometry workflows for the quantification of biotherapeutics in tissues to support pharmacokinetics/pharmacodynamics and safety assessments.

Project description. In the last two decades, there has been a significant explosion of biological modalities, serving as novel therapies for patients in cancer, autoimmune and chronic inflammatory diseases. Among them, protein-based biotherapeutic drugs such as monoclonal antibodies (mAb) and their derivatives represent an essential class of medicines that have transformed the clinical pipelines of the pharmaceutical industry. The development of new bioanalytical methods for biotherapeutics has become more and more challenging, demanding dedicated quantification methods in support of *in vivo* preclinical studies. In particular, biodistribution of biotherapeutics in tissues is today increasingly required to specifically address pharmacokinetics/pharmacodynamics (PK/PD) questions. However, tissue sample analysis of biologics still needs improvements because of the low *in vivo* concentrations, the binding to target, the inconstant extraction recovery of the multiple forms of the biologics (metabolites, free, bound forms, …) and the lack of standardization protocols for absolute quantification, among others.

In this PhD research proposal, we offer a great opportunity to work within two high-level labs on the set-up of innovative bioanalytical approaches for the analysis of protein therapeutics in tissue samples using liquid chromatography coupled to high-resolution mass spectrometry (LC-HRMS) methods.
Main tasks of the project will focus on the:

- Development, optimization, and evaluation of relevant sample homogenization strategies suitable for diverse tissue samples.
- Set up of quantitative methods using cutting-edge targeted and untargeted LC-HRMS approaches for the sensitive quantitation of biotherapeutics and all the associated forms (metabolites, free, bound forms, …).
- Set-up of “real” *in vivo* model samples to assess the method performances, particularly the recovery of the biotherapeutics from tissue samples and the quantitative accuracy.

Conditions of the thesis: The thesis will take place both at Sanofi R&D, Bioanalysis & Immunogenicity, DMPK France, located primarily at Chilly-Mazarin (91) then at Vitry (94), and at the Commissariat à l'Energie Atomique (CEA), Laboratory Innovations in mass spectrometry for health and life sciences (LI-MS), located at Saclay (91) for a period of 3 years (starting October 2023). The PhD student will divide his/her time between the two labs and will benefit from the support of highly trained staff in LC-MS and state-of-the-art HRMS instrumentations.

Candidate: The ideal candidate should be dynamic, agile, highly motivated by the challenging PhD project proposed and interested to evolve in applied research environments. He/she should have good oral and written communication skills, in French and ideally also in English.

He/she should have a strong background in analytical chemistry and mass spectrometry. Master in Analytical Chemistry with a major in mass spectrometry or proteomics or Engineering Schools is required. A first practical experience in LC-HRMS would be desirable (internship considered).

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