Open PhD position

"A vessel on-chip model to assess nano-object pharmacokinetic"

General information

Workplace: Nancy, France
Type of contract: PhD contract
Contract period: 36 months
Expected date of employment: October 2022
Proportion of work: Full time
Desired level of education: Master's degree in biomaterials, bioengineering,

Missions / Activities

Numerous studies evaluate pharmacokinetic properties of nano-objects, but very few established correlations between physico-chemical design, toxicity and therapeutic efficiency of nanoparticles (NPs) in human[1]. Indeed, **when injected in the body, NPs face rapid covering by various proteins (so-called protein corona, PC)**[2], which modify NPs surface properties (energy, chemistry, size), and biological responses (cell uptake, toxicity). This can either completely contradict or enhance NPs therapeutic efficiency demonstrated either in 2D or 3D *in-vitro* models[3]. This discrepancy results from the huge influence of dynamic flow imposed by human bloodstream, tuning the PC formation compared to static conditions. The dynamic flow creates shear stress (tangential force of the flowing blood), which stimulates the endothelial surface of blood vessels and provides a continual source of biomolecules[4]. **To establish new outcomes** about the role of PC on the biodistribution and circulation, dynamic studies considering blood composition and blood dynamic constraints (shear, circumferential, longitudinal stresses…) applied to NP and the vessel wall must be conducted. To the best of our knowledge, only two studies were conducted in dynamic media those last two years[5,6], but were restricted to coated PDMS-based microfluidic systems with one fixed shear stress. Those systems are of course interesting, but the crucial influences of the bio-fluid dynamic depending on blood vessel type as well as the interaction with the vessel wall are missing. Indeed, the interaction between the shear stress imposed by blood flow to the vessel wall, NPs and the endothelial layer in direct contact with the flow cannot be monitored. On the other hand, different attempts were developed very recently for the characterization of PC covering NPs such as NIR-FCS[7], asymmetrical flow field-flow fractionation (AF4)[8], cryo-TEM[9] to establish PC fingerprint and to link this signature to the behavior of cells in contact with NPs. Those crucial and recent technological developments can be transposed within the project to the study of functional NPs injected in biomimetic vessels. **Indeed, all those current studies referred to NPs in a static environment whereas by using a biomimetic system, where the shear stress can be tuned by controlling the fluid dynamic, this project will be able to provide new insight on PC formation in a model of capillaries, which represent the smallest vessels from which NPs are distributed to tissues.**

To the best of our knowledge, nothing is known about PC formation under dynamic condition, which has a major influence on NP pharmacokinetics and pharmacodynamics. This PhD project aims to develop a vessel-on-chip model in order to determine parameters (NP surface, biofluid flow velocity, composition…) influencing PC formation around NPs under physiological condition of dynamic flow. To achieve this aim, **a microfluidic system composed of channels covered by a layer of endothelial cells mimicking capillaries** will be developed. This microfluidic system models the arrival of nanomedicines to the targeted tissue to highlight the influence of dynamic shear stress on NPs covering by proteins. To consider shear stress influence, NPs will be tested and deeply characterized after their injection in the vessel-on-chip model. The PhD project will then enable the study of NP surface interaction at the nanoscale in robust vessel models by combining the know-how, *i.e.* vessel mechanic and physiology, and material sciences of CITHEFOR and IJL, respectively.

References

1) Shi, J.; *et al.* Cancer Nanomedicine: Progress, Challenges and Opportunities. *Nat Rev Cancer* **2017**, *17* (1), 20–37.
(2) Mahmoudi, M.; *et al.* Protein−Nanoparticle Interactions: Opportunities and Challenges. *Chem. Rev.* **2011**, *111* (9), 5610–5637.
(3) Ke, P. C. *et al.* A Decade of the Protein Corona. *ACS Nano* **2017**, *11* (12), 11773–11776.
(4) Caracciolo, G. *et al.* Identity of Nanoparticles In Vivo : Clinical Implications of the Protein Corona. *Trends in Biotechnology* **2017**, *35* (3), 257–264.
(5) Ho, Y. T. *et al.* Quantifying Vascular Distribution and Adhesion of Nanoparticles with Protein Corona in Microflow. *Langmuir* **2018**, *34* (12), 3731–3741.
(6) Lee, T.-R. *et al.* On the Near-Wall Accumulation of Injectable Particles in the Microcirculation: Smaller Is Not Better. *Sci Rep* **2013**, *3* (1), 2079.
(7) Negwer, I. *et al.* Monitoring Drug Nanocarriers in Human Blood by Near-Infrared Fluorescence Correlation Spectroscopy. *Nat Commun* **2018**, *9* (1), 5306.
(8) Alberg, I. *et al*. Polymeric Nanoparticles with Neglectable Protein Corona. *Small* **2020**, *16* (18), 1907574.
(9) Sheibani, S. *et al.* Nanoscale Characterization of the Biomolecular Corona by Cryo-Electron Microscopy, Cryo-Electron Tomography, and Image Simulation. *Nat Commun* **2021**, *12* (1), 573.

Keywords:
vessel; vessel on chip; protein-corona

Work context

The PhD student will work under the supervision of Dr. Halima Alem and Dr Caroline Gaucher in collaboration between **IJL**, Institut Jean Lamour (UMR 7198 CNRS UL) and **CITHEFOR** (Cibles thérapeutiques, formulation et expertise préclinique du médicament, EA3452)

Skills

Good knowledge of bioengineering, experience in cell culture and microfabrication will be highly appreciated.
Knowledge of English (oral and written) is important and knowledge of French would be an advantage.
As an enthusiastic researcher you like team work, and have a flexible approach to collaborating between different laboratories.
Taste in both experimental and theoretical work.

Constraints and risks

The position you are applying for is located in a sector relating to the protection of scientific and technical potential. It therefore requires, in accordance with the regulations, that your arrival be authorized by the competent authority of the Ministry of Higher Education, Research and Innovation.

About Institut Jean Lamour

The Institute Jean Lamour (IJL) is a joint research unit of CNRS and Université de Lorraine.
Focused on materials and processes science and engineering, it covers: materials, metallurgy, plasmas, surfaces, nanomaterials and electronics.
It regroups 183 researchers/lecturers, 91 engineers/technicians/administrative staff, 150 doctoral students and 25 post-doctoral fellows.
Partnerships exist with 150 companies and our research groups collaborate with more than 30 countries throughout the world.
Its exceptional instrumental platforms are spread over 4 sites; the main one is located on Artem campus in Nancy.

Application

Applicants are invited to send a CV and cover letter together with diploma copies and associated quote, and Master 2 internship supervisor(s) reference letter before **May 8th**:
Halima Alem : halima.alem@univ-lorraine.fr
Caroline Gaucher : caroline.gaucher@ univ-lorraine.fr