Development of chitosan based hydrogel for the delivery of drugs.
Développement d'hydrogels à base de chitosane pour la délivrance de medicaments.

The objective of this PhD is to design and develop safe by design biopolymer for the delivery of drugs. The smart biomaterial developed in this work will be based on functionalized chitosan. Chitosan is a polysaccharide recognized for its attractive biological properties including biocompatibility and biodegradability (O. Kapusta *et al., Int. J. Mol. Sci.,* **2023**). The FENNEC team of ILM in collaboration with the team of Pr Laurent David in IMP has already shown that chitosan can be functionalized by chelates like DOTAGA, EDTA or DTPA that lead to zwiterrionic polymer (M. Natuzzi *et al., Sci. Rep.,* **2021**). Interestingly, this new type of polymer can be used in combination with conventional chitosan for the drug delivery of different biomolecules such as peptides or antibodies (T. Gréa *et al., Adv. Mat.,* **2023**) (Figure 1).

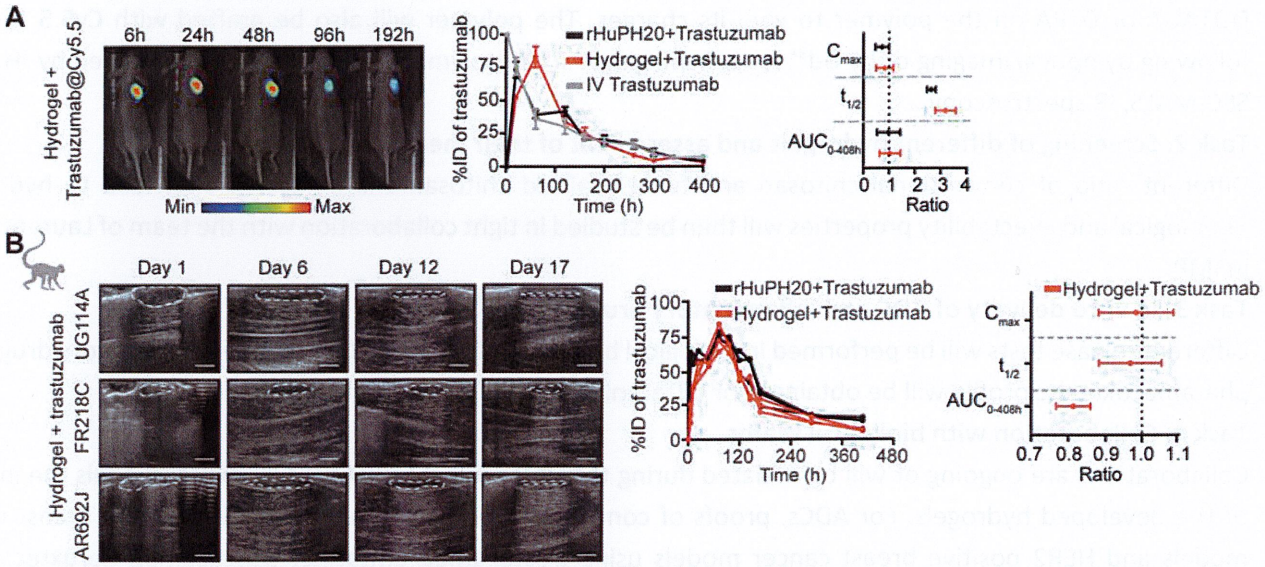

Figure 1: Monoclonal Antibody release profile in mice and non-human primates. *A. Fluorescence imaging confirming the release of labelled trastuzumab. Pharmacokinetics profiles and parameters were compared to intravenous formulation and clinical subcutaneous formulation. B. Following by ultrasound imaging of the gel in non-human primate.*

The proposed PhD will contribute to continue the development of this new platform for biodelivery by adapting it to two new systems already used in clinic: Antibody drug conjugates (ADCs) for oncology and nanocrystals of anti-inflammatory drugs.

There is currently a specific challenge to deliver ADCs by the subcutaneous pathway to mirror the success achieved by different formulations with monoclonal antibodies. ADCs are emerging has an important treatment for a large number of cancer indications. They are composed of (i) a mAb (monoclonal antibody), (ii) a linker and (iii) a drug payload. Currently 13 ADCs are on the market and more than 100 are in different phases of clinical trials (C. Dumontet *et al., Nature Rev. Drug Discover.,* **2023**). Developing a nontoxic formulation of ADCs that can be delivered subcutaneously has the potential to increase the quality of life for patients by reducing the administration time and by spacing out the number of visit to the hospital.

The second application is connected to an indication in rheumatology and aims at designing a hydrogel for the delivery of anti-inflammatory drugs against arthritis. To do so, the hydrogels will be loaded with nanocrystals

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made of the anti-inflammatory drugs for a long term drug delivery. Osteoarthritis (OA) represents the most prevalent joint disease worldwide (16%) and is considered to cause the largest disability. Rheumatoid arthritis (RA) with 1% prevalence. RA is characterized by a local (joint) and a systemic inflammation, while OA is associated with cartilage damages also inducing inflammation and pain in joints and bones. From the clinical point of view, because local inflammation may persist in some cases, in a single or few joints, and is only temporarily alleviated by current anti-inflammatory strategies such as corticosteroid intra-articular injections, there is a need for drug delivery systems providing longer-term, sustained and controlled release of anti-inflammatory drugs.

The work during the PhD can be separated roughly in 4 tasks.

Task 1. Functionalization of chitosan.

It will consist to functionalize the chitosan by changing the acetylation ration and adapting the ration of DTPA, DOTAGA or DTPA on the polymer to vary its charges. The polymer will also be grafted with Cy5.5 for easy following by optical imaging or by Gd^{3+} for MR imaging. All the polymers will be fully characteirized by ^{1}H NMR, SEC-MALS, IR spectroscopy...

Task 2. Screening of different hydrogels and assessment of their mechanical properties.

Different ratio of conventional chitosan and functionalized chitosan will be tested that lead to hydrogels. Rheological and injectability properties will then be studied in tight collaboration with the team of Laurent David in IMP.

Task 3. In vitro delivery of ADC and inflammatory drugs.

Different release tests will be performed in biological buffers like PBS for ADCs and anti-inflammatory drugs. The pharamacokinetic profile will be obtained for different loading of drugs in the hydrogel.

Task 4. Collaboration with biological teams.

Collaborations are ongoing or will be initiated during the PhD project to validate in animal models the interest of the developed hydrogels. For ADCs, proofs of concept will be performed on triple negative breast cancer models and HER2 positive breast cancer models using trastuzumab emtasine, trastuzumab deruxtecan and sacitruzumab govitecan. For arthritis, nanocrystals of prednisolone will be tested first and the animal models selected are high grade and chronic low grade joint inflammation in mice. The PhD student will be in direct contact with the research teams of collaborators and depending of the biological results, the formulations designed in task 1 and 2 will be changed accordingly.

Collaborations.

This work is a highly collaborative work. The network of collaboration is composed of:

- Pr. Laurent David, IMP, Lyon. Characterization of mechanical properties of polymers.
- Dr Eloïse Thomas, LAGEPP, Lyon. Fluorescence *in vivo* imaging.
- Pr Alexandre Detappe, ICANS, Strabourg. ADC delivery and study of breast cancer models.
- Pr Yohann Corvis, UTCBS, Paris. Development of nanocrystals.
- Pr Christelle Nguyen, Cohin Hospital, Paris. Speciality in osteoarthritis.
- Dr Bich Thuy Doan, ENSCP, Paris. MRI.

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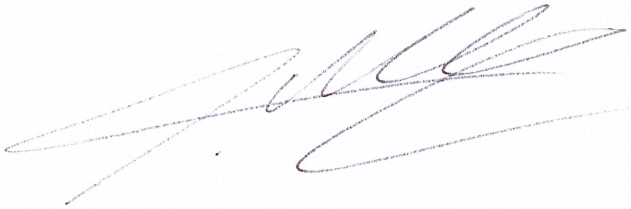
The competences required for the PhD are basic skills in chemistry, in organic functionalization and characterization of materials. Interest and skills in biology are not mandatory but will be appreciated.



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