Supercritical technology applied to the development of innovative intravitreal sustained-release drug delivery systems

- **PhD funding:** CIFRE grant

- **Affiliated research Laboratories:**

- Laboratoire de Mécanique, Modélisation & Procédés Propres – M2P2 – UMR 7340, Aix Marseille Université, CNRS, Centrale Marseille, Technopôle de l'Arbois, Aix en Provence, 13545 Aix-en-Provence

- Aix Marseille Univ, CNRS, INT, Inst Neurosci Timone, Marseille, France

- Centre Paradis Monticelli, 433 bis rue Paradis, 13008, Marseille

- A French pharmaceutical group

- **Doctoral research subject**:

The development of intravitreal sustained-release drug delivery systems of anti-vascular endothelial growth factor (anti-VEGF) antibodies is a challenging issue in the treatment of macular degeneration and diabetic macular edema. Indeed, even if the introduction of anti-VEGF therapy through intravitreal injection has revolutionized the corresponding treatments, they remain limited by the necessity of monthly injections which limits the patient observance and increases complication risks (retinal detachment, endophthalmitis, and cataracts). Such drawbacks can be overcome by the development of sustained release anti-VEGF delivery systems that maintain a therapeutically relevant concentration of protein drug for extended periods of time [1]. Nevertheless, processing therapeutic antibodies through conventional technologies can be hindered by their thermolability, their sensitivity to organic solvents and to shear stresses. All those drawbacks can be avoided using supercritical CO_2 processes.

The originality of this research project is to develop innovative intravitreal sustained-release medical devices while encapsulating anti-VEGF antibodies with biocompatible excipients using the environment-friendly CO_2 supercritical technology.

This technology is now recognized as a real alternative of conventional techniques of drug processes using liquid organic solvents and has been applied to drug formulation for the past 30 years. One of the most interesting properties of supercritical CO_2, is related notably to its moderate critical temperature (Tc = 31°C) and easily accessible critical pressure (Pc= 7.38 MPa), which allows the processing of thermosensitive molecules. Being gaseous at ambient conditions, CO_2 separation from the end-products is spontaneous upon depressurization. There is no need for the several stages of separation as in conventional processes, which are costly and detrimental to thermosensitive molecules (as antibodies). The resulting products from a single-step process exhibit more homogeneous properties.

Furthermore, supercritical fluids are characterized by specific properties, intermediate between those of liquids and gases allowing to reduce, or even to avoid the use of organic solvents. Those properties can be also modulated by varying the pressure and temperature conditions. As a result, supercritical fluid-based processes are characterized by favored transfer phenomena and performances that cannot always be obtained by conventional pharmaceutical formulation processes.

Even if the supercritical technology has been successfully applied to a hundred active pharmaceutical ingredients, several excipients as well as to the development of composite formulations, few studies and processes are applied to the encapsulation of antibodies, which supports the innovative aspect of this research project.

This project is a part of a collaboration between the research team "Processes and Supercritical fluids" of the laboratory M2P2 (UMR CNRS 7340, Aix Marseille University), expert on pharmaceutical formulation processes using supercritical fluids [2-7] and Pr. Matonti, expert in the retina complications and diseases, affiliated to the Neuroscience Institute of La Timône and to the Paradis Monticelli Center of Ophthalmology and supported by a French pharmaceutical group. The complementary skills and competences of involved partners, as well as their geographical proximity, are all assets.

The objective of this Ph.D. work will be to implement a new solvent-free process so as to form innovative intravitreal sustained-release drug delivery systems.

- **Key words:**

Chemical Engineering, Supercritical fluids, Drug delivery systems, Encapsulation

- **Doctoral research subject:**

We are seeking for an outstanding and motivated candidate with an Engineer/Master's degree in Chemical Engineering / Biomedical Engineering / Industrial pharmacy.

The candidate would demonstrate motivation, scientific curiosity and rigor. He/she should present good experimental skills, autonomy and investment.

Experiences in supercritical fluid processes, galenic formulations and encapsulation processes are valuable.

A good command of English language (written and spoken) is required.

- **Application:**

A covering letter, a detailed curriculum vitae, contact details of at least two references and transcript of at least the two last years of studies should be sent to:

yasmine.masmoudi@univ-amu.fr

elisabeth.badens@univ-amu.fr

References:

[1] D.A. Eichenbaum, C. Buznego, C.Y. Weng, D.S. Dhoot, C.C. Wykoff, V.S. Sheth, When and How to Incorporate Steroids for Persistent Diabetic Macular Edema: A Discussion of Real-World Treatment Optimization Strategies, Ophthalmic Surg Lasers Imaging Retina, 49(7), S5-S15, **2018**.
[2] E. Badens, Y. Masmoudi, A. Mouahid, C. Crampon, Current situation and perspectives in drug formulation by using supercritical fluid technology, The Journal of Supercritical Fluids, 134, 274-283, **2018**.
[3] J.M. Silva, S. Akkache, A. C. Araújo, Y. Masmoudi, R. L. Reis, E. Badens, A.R.C. Duarte, Development of innovative medical devices by dispersing fatty acid eutectic blend on gauzes using supercritical particle generation processes, Materials Science and Engineering C, 99, 599-610, **2019**.
[4] A. Bouledjouidja, Y. Masmoudi, Y. Li, W. He, E. Badens, Supercritical impregnation and optical characterization of loaded foldable intraocular lenses using supercritical fluids, Journal of Cataract & Refractive Surgery, 43, 1343-1349, **2017.**
[5] A. Bouledjouidja, Y. Masmoudi, M. Sergent, E. Badens, Effect of operational conditions on the supercritical carbon dioxide impregnation of anti-inflammatory and antibiotic drugs in rigid commercial intraocular lenses, The Journal of Supercritical Fluids, 130, 63–75, **2017**.
[6] R. Djerafi, A. Swanpaul, P. Labuschagne, M.L. Kalombo, E. Badens, C. Crampon, Y. Masmoudi, Supercritical antisolvent co-precipitation of Rifampicin and Ethyl cellulose, The European Journal of Pharmaceutical Sciences, 102, 161-171, **2017**.
[7] J-M. Andre, E. Badens, O. Forzano, Y. Masmoudi, Treatment process for producing implants or prostheses of polymers for controlled release of active ingredients, Patent WO/2014/037651, **2014**.