PhD position

Advanced in vitro Ear-Nose-Throat (ENT) respiratory models: development of cellularized anatomical models for cell culture air-liquid exposure to enhance in vitro-in vivo correlation of intranasal drugs.

Host laboratory:

Ecole Nationale Supérieure des Mines de Saint-Etienne is one of the top 10 French graduate schools for science and technology dedicated to the training of highly qualified engineers. Its mission is to support the economy by: 1) Educating highly qualified managers with strong technical and scientific skills; 2) Developing applied research to meet the needs of industry; and 3) Contributing to companies' innovation, creation & competitiveness worldwide. Our academic standing is committed to excellence, wealth of subject fields, and we desire to offer each student a curriculum tailored to his or her goals. Partnerships are and always will be important to us. The Center for Biomedical and Healthcare Engineering which aims at improving health through science and engineering is located in brand new buildings in the Campus Santé Innovations, near the University Hospital, fostering collaborations with physicians for an applied and translational research. It is a unique position in France. The host laboratory has been integrated into the UMR INSERM U1059 since 2016. The research team for the project is composed of an interdisciplinary group of engineers, aerosol experts and biologists from Mines de Saint-Etienne but also clinical experts of pharmacokinetics from CHU de Saint-Etienne.

Scientific context:

In vitro respiratory 3D replicas serve as invaluable tools for investigating aerosol transport and deposition of intranasal drugs. By providing precise control over experimental conditions, these replicas enable detailed analysis of aerosol deposition patterns. However, limitations exist in terms of anatomical complexity and physiological relevance. Establishing a robust correlation between in vitro and in vivo (IVIVC) results is crucial for the development of novel inhaled drug delivery systems. The complexity of the respiratory tract, inter-individual variability, and challenges in measuring local aerosol deposition have hindered the establishment of such correlations. The project will identify and compare the key parameters that influence the deposition and absorption of drugs delivered into the nasal cavity by intranasal spray technologies. Through a multidisciplinary translational approach, this project aims to evaluate and compare the performance of a range of spray technologies in terms of (i) aerosol physical properties (droplet size, delivered dose and spray geometry), (ii) deposition zone in segmented nasal casts as a function of insertion angle and depth and drug formulation, (iii) in situ absorption of drugs on innovative cellularized nasal casts. Then, in vitro data will be used to build a predictive pharmacokinetic model, which will be further refined by integrating in vivo pharmacokinetic data from a clinical trial.

Work plan:

The project is divided into work packages (WP) requiring a wide range of complementary expertise in the field of aerosol metrology, industrial design, pharmacokinetics, in silico predictive model and nasal aerosol deposition.

WP1 - Development of dismountable segmented nasal casts: Nasal casts will be 3D-printed from CT scans of patients representing two population groups: infants and adults. The nasal impressions are segmented to cover all regions of drug deposition (nasal vestibule, nasal valve, turbinates (inferior, middle and superior) and posterior nasopharynx). The nasal casts will be

dismountable to allow full access to the region and the future development of cellularized nasal casts.

WP2 - Regional aerosol deposition in segmented nasal casts: The intranasal regional deposition of the aerosol generated with selected nasal sprays will be assessed in segmented nasal casts (developed in WP1) using multiple markers (fluorimetric and drug dosage after washing of selected anatomical regions) according to different insertion angle and depth.

WP3 - Development of cellularized nasal cast and In situ pharmacokinetics (PK) of intranasal drugs: Segmented nasal casts are modified to incorporate docking areas determined from deposition data WP2 into the plug culture insert containing epithelial cells cultured at the air-liquid interface. Nasal sprays that have achieved optimal deposition in the selected anatomical regions according to the insertion parameters determined in WP2 are used to generate aerosols.

WP4 - Building a predictive Physiologically Based PharmacoKinetic (PBPK) model: A PBPK model will be built and parameterized to predict the systemic absorption of nasally administered drugs. The model is first parameterized with data available in the literature and then refined with empirical data generated from WP3.

<u>Objective and supervision</u>:
The objective of this doctoral thesis is to achieve the WP of the project. Besides these tasks, the PhD researcher will have opportunity to participate in national and international conferences, summer schools and seminars on electrochemistry and gas sensors to present the research outputs and network with other researchers. The researcher is expected to write report, perform data analysis and prepare publications. Tasks may change depending on the needs of the department and Mines Saint-Etienne. This 3-year position will be co-supervised by Pr Jérémie Pourchez, PhD, senior researcher at Ecole des Mines de Saint Etienne, expert in biomedical engineering and aerosol science, Pr Valerie Forest, PhD, senior researcher and expert in nanotoxicology and Dr Clément Mercier, PhD, expert in in vitro air-liquid respiratory cell models. In addition, this project will lead to local cooperation with the University Hospital of Saint Etienne and the pharmacology team working on the topic. The team has over 10 years of international expertise in ENT respiratory models (Figure 1) and master aerosol characterization and deposition (Figure 2).

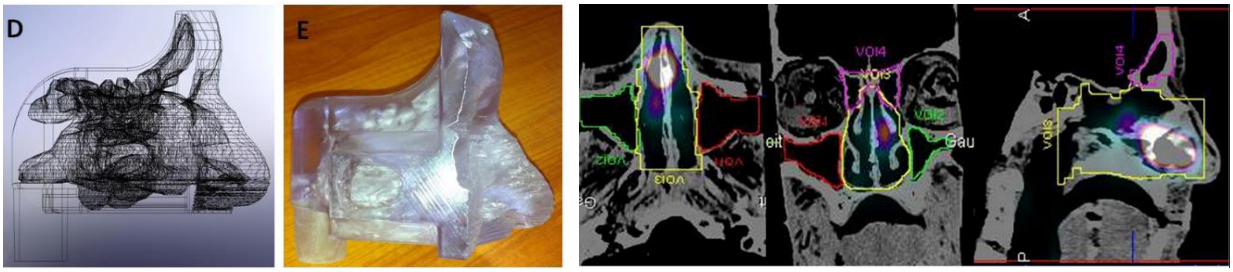

Figure 1 and 2 : 3D-printed ENT model (left) and CT-scan imaging of radiolabelled aerosol in ENT model (right).

<u>Candidate's profile</u>:
The candidate must hold a Master 2 degree in biological sciences, chemistry or pharmacology. He/she must be proficient in cell culture techniques. An autonomous candidate with a strong attraction for the experimental side and a sharp scientific curiosity is preferred. Knowledge of chemistry/CAD/aerosol characterization will be appreciated. The trained PhD student at the end of his/her thesis will have a highly attractive and sought-after multidisciplinary profile. Equal

consideration will be given to candidates regardless of gender, origin and nationality. Annual net salary is around 22k € a year (about 1900€/month).

Application:
Please contact clement.mercier@emse.fr and pourchez@emse.fr with a cover letter indicating your motivation, experience, and research interests. Join a CV, an up to-date master graduate transcript, at least one support/recommendation letter, and past communications if applicable (contribution to a scientific article, review, poster…).
Application deadline: 04/2025

Keywords: anatomical model, aerosol therapy, respiratory physiology, pharmacology.

References:

Leclerc et al. Impact of acoustic airflow on intrasinus drug deposition: New insights into the vibrating mode and the optimal acoustic frequency to enhance the delivery of nebulized antibiotic. (DOI: 10.1016/j.ijpharm.2015.08.025).

Leclerc et al. Assessing sinus aerosol deposition: benefits of SPECT-CT imaging. (DOI: 10.1016/j.ijpharm.2013.12.032)

Le Guellec et al. In vitro – in vivo correlation of intranasal drug deposition. (DOI: 10.1016/j.addr.2020.09.002)