PHD GRANT

One PhD position is available in CBMN CNRS laboratory at the University of Bordeaux in France (CNRS UMR 5248, CBMN "Institute of Chemistry & Biology of Membranes & Nano-objects"), as part of the ANR young researcher project MultiRaMaS.

PHD SUBJECT

Title:
Multimodal Imaging combining Raman and Mass Spectrometry applied to Tuberculosis.

Scientific context and objectives:
In public health contexts, where results of conventional imaging methodologies are often limited, molecular multimodal imaging is within a realm of possibility. Various imaging techniques are informative for functional groups, molecular weights, or special recognition sites, but no individual technique provides optimal answers to all questions. Thus, combining information from two or more measurement platforms is highly attractive. Such an approach is required to elucidate the complex spatial distribution of biomolecules in tissues, opening the way for a qualitative and quantitative multi-omics overview, both targeted and unbiased, of lipids, proteins, peptides, antibiotics, nucleic acids as well as glycans. Herein, we propose to combine vibrational spectroscopy, namely Raman Scattering (RS) and Mass Spectrometry Imaging (MSI) in a single workflow. Strengths and weaknesses of these technologies make them highly complementary. Key objectives of MultiRaMaS are both methodological and biological. On the one hand, as an emerging and challenging strategy multimodal imaging combining RS and Matrix-Assisted Laser Desorption/Ionization (MALDI) MSI needs further improvements: 1) optimization of a stringent and common sample preparation including cryo-sectioning and accurate identification of anatomical structures, 2) optimization of settings for fast multi-omics screening by RS imaging, 3) optimisation of settings to access the high chemical specificities and structure details by MALDI-MSI, 4) quantification of biomolecules of interest by MALDI-MSI, and 5) data processing including visualization, quantification, co-registration as well as fusion of hyperspectral imaging data. On the other hand, this original and remarkable approach, not fully explored, will be applied throughout a single tissue section and methodological outputs will be applied for the first time to the characterization of tuberculosis (TB), an infectious disease which affects each year 10 million humans and causes 1.7 million deaths. *Mycobacterium tuberculosis* (*Mtb*), the etiological agent of TB, establishes a durable lung infection in complex lesions where it is found intracellularly in various immune cell types and extracellularly in the central necrotic core of these lesions. Our current efforts are focused on increasing spatial resolution to visualize and identify the structures of molecules of interest at the cellular and subcellular level, *i.e.* lifting a scientific barrier. Of particular interest is the mapping and quantification of anti-TB drugs and biomarkers in the phagolysosome of macrophages where *M. tuberculosis* bacilli reside. Thus, the major biological objectives are: 1) to decipher the architecture and the microenvironment of tuberculous lesions, 2) to map, identify and quantify anti-TB drugs and biomarkers in the phagolysosome of macrophages, and finally 3) to evaluate the effect on *Mtb* of anti-TB drug concentration and duration of treatment. As an ultimate objective, all imaging data will be used to apply artificial intelligence and machine learning to facilitate the automation of the superimposition of imaging data onto digitized and fully annotated histological images. To meet the strategic objectives, MultiRaMaS is organized into 5 tasks. MALDI-MSI experiments shall rely on a highly performant combination of a source with high spatial resolution and high resolution mass spectrometer

combining high accuracy and efficient MS/MS capability. This project gathers the complementary expertise of the project coordinator and his renowned collaborators to ensure the development of a multimodal imaging workflow to investigate tuberculosis. Complementary resources and expertise are assembled to ensure the feasibility of the proposed scientific program. This multidisciplinary and interdisciplinary project is original because of the technologies implemented which have rarely been combined, as well as by its applications to investigate tuberculosis.

Keywords: Multimodal imaging, Mass spectrometry imaging, Raman imaging, Tuberculosis, Multi-omics, Technology for healthcare.

WORKING CONDITIONS

Laboratory: CNRS CBMN UMR 5248, Allée Geoffroy Saint-Hilaire, Bât. B14, 33600 Pessac.

Website: http://www.cbmn.u-bordeaux.fr/

PhD Director: Nicolas Desbenoit.

Location: Bordeaux, France.

Start: November 1st 2019.

Tenure: 3 years.

HOST LABORATORY PROFILE

The host laboratory has a long-standing and respected expertise in the field of analytical chemistry applied to biological systems and offers the expertise, technical skill and technological means to develop this priority research area.

All resources are available on site at CNRS CBMN UMR 5248 and Proteome Platform: Confocal Raman Microscopy (WITec), AP-SMALDI-Orbitrap QExactive (TransMIT, ThermoFisher), Home-built sprayer, Sublimation chamber, NanoLC-MS/MS (ThermoFisher), Microscope (Leica), FT-IR (Bruker). Purchase planned in 2019: Cryo-microtome.

INTERNATIONAL COLLABORATION

The project is in collaboration with Prof. Véronique Dartois from Center for Discovery and Innovation, Hackensack Meridian Health (USA). In addition, the PhD supervisor is in collaboration with Prof. Dr. Andreas Römpp (University of Bayreuth, Germany) throughout an International Project for Scientific Cooperation (PICS).

REQUIRED COMPETENCES

Essential skills and experience include:

- Master or engineer in bioanalysis, biochemistry, (bio) analytical chemistry or in a related field.
- Demonstrated knowledge of analytical chemistry, in particular mass spectrometry applied to the analysis of biomolecules (theoretical and experimental).

- Knowledge of, and demonstrated experience in designing, implementing, as well as optimizing: (i) analytical chemistry methods for drugs, lipids and peptide/protein characterizations, (ii) biochemical methodologies for sample preparation for drugs, lipids, peptide/protein analysis.
- Demonstrated experience in interpretation and analysis of MS and MS/MS data.
- Knowledge of vibrational spectroscopies (FT-IR, Raman) would be an advantageous, but by no means a prerequisite.
- To speak English is mandatory.
- Writing and communication skills, autonomy, integrity, rigor, taste for team work and interest in multidisciplinary approaches are essential qualities to apply to this project.
- Ability to comfortably work in a high interdisciplinary environment with colleagues with different scientific backgrounds.
- Expertise in bioinformatics and statistical analysis of large molecular datasets is a valued plus.

REQUIRED DOCUMENTS

The candidates will have to provide the following documents:

- CV,
- Cover letter,
- Master marks and ranking,
- Letter of recommendation,
- Other information to consider,
- Contact details for 2 referees.

The required documents have to be sent by e-mail to Dr. Nicolas Desbenoit (supervisor of the PhD): n.desbenoit@cbmn.u-bordeaux.fr.

AGENDA AND DEADLINE FOR APPLICATION

Submission deadline: September 30th 2019.
Results of candidate selection and skype interview: October 4th 2019.
PhD starting: November 1st 2019.