PhD position, FEMTO-ST Institute (Besancon, France) – starting at 01/09/2021

PhD title: High-speed and discriminant morphomechanical analysis of subpopulations of extracellular vesicles trapped on a multiplex chip

Atomic force microscopy (AFM) constitutes a nano-tool perfectly suited to the qualification of biological nanoobjects and under physiological conditions. In addition, if this nanometrological investigation is carried out while these nanoobjects or subpopulations of nanoobjects of interest are captured on a sensitive and selective biodetection surface, this has the advantage of not requiring any preanalytical step. Our approach around AFM, valued through a nanobioanalytical platform (NBA) by coupling to SPR imaging technology, is now recognized (Obeid et al, Biosens Bioelec 2017 & NBM 2019).
A biochip in multiplex format and presenting several ligands is at the heart of this instrumental coupling and allows the selective trapping of the different nanoobjects of interest coexisting in the sample. The nanoobjects of interest are, in particular, extracellular vesicles (EVs), circulating in all our biological fluids, and which can be used either as potential biomarkers for various pathologies, or as therapeutic vectors. Our nanobioanalytical approach allows us to establish a complete profiling of EV populations in a biological fluid, from a phenotypic, metrological and morphomechanical point of view.

This thesis is part of a scientific collaborative program involving the ICB lab (Dijon, France), a Japanese team (in Kwansei) and a company (Horiba company). In this program, the objectives are to increase the analytical throughput in the characterization of these EVs; this requires an evolution of the NBA platform:
- Regarding the biochip, a need for increased multiplexing, miniaturization and design adapted to AFM analysis will lead to the design and production of new generation biochips,
- Concerning the AFM acquisition module, the thesis will consist in setting up a high-speed AFM acquisition module on these SPRi multiplex biochips. A metrological but also morphomechanical characterization of the EVs subpopulations will be carried out.
- Concerning the implementation of an additional module on the analytical platform, the interest relates to obtaining spectral signatures, by infrared and Raman spectroscopy, of the EVs trapped on a multiplex biochip. The AFM / infrared spectroscopy coupling is a technology implemented by the partner at ICB (Dijon). Collaborations with the Japanese team and the Horiba company will enable the TERS (Tip Enhanced Raman spectroscopy) method to be tested and optimized on EVs.

The thesis, in the field of nanoinstrumentation, and whose objective is a high-throughput and discriminating analysis of subpopulations of EVs, will therefore have as milestones: 1 / the realization of nanostructured / nanopatterned biochips -, 2 / the implementation place of high-speed AFM technology on these high spot density biochips, and 3 / the metrological, morphomechanical and spectroscopic analysis of these subpopulations of EVs on biochips.

Multidisciplinary profile: atomic force microscopy, chemistry of biointerfaces, biodetection and spectral analysis of nanoobjects

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Kiyotaka Shiba (Japanese Foundation for Cancer Research) : innovative ligands specific to EVs
Torsten Mueller (Bruker, Berlin), for instrumentation support

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