Phononic-crystal waveguide biosensor system for BC biomarkers detection

PhD candidate: Francesca Izzo
Supervisors: Hamida Hallil, Florence Poulletier de Gannes

The World Health Organisation (WHO) and the International Agency for Research on Cancer (IARC) predict a growing burden of new cases up to 30.2 million in 2040 in the world. The most frequent type of cancer, with 2.26 million cases in 2020, is breast cancer (BC). In Europe, it is the most diagnosed cancer among women (355,000 women ~ 13.3% of all cases) and the third most frequent cause of deaths among both men and women.

This European doctoral project, funded under the Horizon Europe Marie Skłodowska-Curie Actions Doctoral Network aims to develop a liquid biopsy-based integrated sensing platform for Point-of-Care Breast Cancer assessment. Such a platform would be highly sensitive and specific, involving non-invasive and user-friendly analysis. Further, it envisions a multiplexed detection strategy, which involves the detection of different types of biomarkers: exosomes and miRNAs. This work integrates expertise in biochemistry, nanotechnology, and engineering to address the diagnosis challenge at an early stage when therapeutic intervention is most effective.

In this first year of PhD, to enable the development of portable, reusable, and robust Point of Care devices, Quartz Crystal Microbalance (QCM) sensors have attracted considerable interest due to their capability for real-time, label-free detection with nanoscale mass sensitivity. However, conventional QCM measurement strategies predominantly rely on tracking the resonance frequency shift at the fundamental mode, which limits sensitivity and does not adequately account for viscoelastic effects associated with biological binding events. To this end, this work investigates the effectiveness of a multivariate and multimodal strategy for enhancing the sensitivity of QCM, thanks to impedance analysis. Along with the resonance frequency shift, variations in phase, amplitude, were also analyzed to achieve a comprehensive characterization of the sensing response. First the QCM electrodes were functionalized with specific DNA probes, able to detect our target (miRNA-21) and the detection step was analyzed thanks to a sequential least-squares quadratic programming algorithm. In addition, a gold nanoparticle (AuNP)–assisted sandwich hybridization protocol is employed as a signal amplification approach, due to their favorable physicochemical properties, which contribute to enhanced detection sensitivity . The AuNPs were synthesized and subsequently functionalized with complementary probes targeting the same miRNA of interest. As result, the multivariate multimodal analysis reduced the detection limit from ~10 nM (single-frequency) to 100 pM. AuNP-mediated amplification further increased the effective signal by ~1.5×, yielding a final detection limit of 1 pM, corresponding to a two-order-of-magnitude improvement. Specificity assays with non-target miRNAs (miRNA-145 and miRNA-9) showed minimal cross-reactivity. The efficacy of the proposed approach is demonstrated through the detection of miRNA-21, a biomarker implicated in a wide range of pathological conditions. In BC, miRNA-21 plays a particularly important role and has been reported as a diagnostic, prognostic, and predictive biomarker. In fact, in breast cancer, miRNA-21 is known to promote tumor-induced angiogenesis by targeting multiple tumor suppressor genes involved in proliferation, apoptosis, and invasion.

Moreover, in this second year of PhD the research will focus on the integration of aptamers as novel bioelements for functionalization, targeting extracellular vesicles secreted by BC cells. Preliminary experiments were already conducted during her secondment at the University of Naples. Additionally, alternative acoustic sensing platforms will be investigated, alongside the design and development of microfluidic systems during a secondment at Université Paris-Saclay