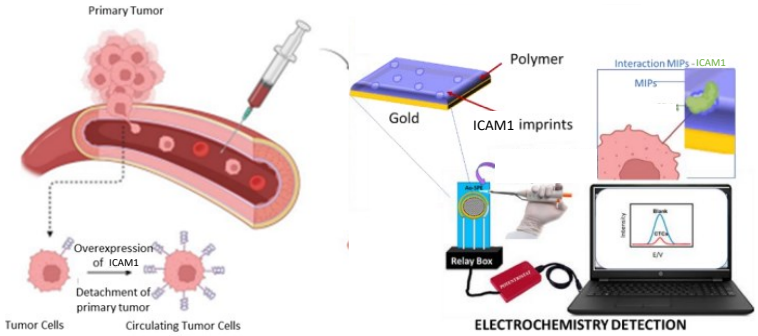
**Context:** Breast cancer is the most common cancer in women, affecting almost one in eight women worldwide, and the second cause of cancer deaths in women. Despite advances in diagnostic and treatment of breast cancer, 4% to 10% of women will present a metastatic disease at the time of diagnosis. Furthermore, up to 30% of patients with early stage tumors will develop distant metastases after primary treatment. Persistence of breast cancer stem-like cells (BCSCs) are considered as a major mechanism for breast cancer progression, metastasis and recurrence [1]. A key characteristic of BCSCs is their tumor-forming ability and innate drug resistance mediated by their relative quiescence within the tumour core. These cells also involve molecular mechanisms enabling them to evade the cytotoxic effects of anti-cancer drugs and to migrate to form metastasis [2]. In the recent years, a better definition of the phenotype of these cells has been proposed allowing their detection both in the primary tumor and the metastasis. However, their identification in the bloodstream (liquid biopsy) would be of great interest as biomarkers for diagnostic, patient monitoring and as potential therapeutic target to limit the apparition of metastasis, which is the main event, correlated with prognostic. Liquid biopsies have been regarded as robust tools for routinely screening and identifying tumors before symptoms appear [3]. Besides the "classical biomarkers" which are routinely used in clinic, new biomarkers are emerging, in particular in liquid biopsies, whereby molecules such as nucleic acids, as well as circulating tumor cells (CTCs) coming directly from the tumor make it possible to obtain molecular information on the tumor itself [4]. The quantification and characterization of CTCs represent major technological challenges in liquid biopsy due to the extremely low concentrations of these cells in blood. Hence, novel CTC sensors need to be developed to detect CTCs from other origins. New biosensors with enrichment and characterization steps have been investigated and may become breakthrough analytical tools in this context [5]. However, the commercial success of biosensors has been partially hindered by the absence of appropriate biological receptors that are expensive to produce and unstable for storage. Molecularly imprinted polymers (MIPs) open the door to sustainable alternatives for solving these problems. **MIP-based sensors have been investigated as promising analytical devices in clinical analysis because they are cheap, portable, give a fast response and they are specific** [6]. In cancer diagnosis, MIP-based sensors exploiting different detection techniques for cancer biomarker sensing have been developed for several years [7]. However, none have considered the detection of CTCs. In this work, **we aim to detect and capture BCSC-CTCs that are supposed to be the metastasis-initiating cells from blood.** The chosen biomarker for BCSC-CTC is ICAM1, a key initiator of metastasis through homophilic ICAM1-ICAM1 interactions that not only promote homotypic CTC cluster formation but also drive tumor-endothelial heterotypic cell adhesion. In addition, ICAM1 signaling sustains the levels of cyclin-dependent kinase 6 (CDK6) and other pathway components related to the cell cycle, stemness, and survival [8].

**Objectives:** We aim to develop an emerging promising method for CTC detection based on MIPs. MIPs are synthetic materials that exhibit excellent binding properties with affinities and selectivities comparable to those of antibodies [9,10]. The imprinting process consists in the polymerization of a functional monomer in the presence of a molecule of interest with a cross-linking agent. After the extraction of the molecule, the polymer matrix contains tailor-made binding sites, perfectly complementary to the extracted molecule. These materials are quick and less expensive to synthesize and combine many advantages over antibodies. **The project described here proposes to capture ICAM1+ CTCs from blood using MIP and to detect reactive cells using an organic field-effect transistor (OFET) integrated with an extended-gate gold (Au) electrode as presented in Scheme 1.** The OFET possesses an inherent amplification ability, which enables sensitive chemical sensing in combination with appropriate recognition materials [11]. In this proposal, we employ an extended-gate structure that consists of a device operation unit (i.e., OFET) and a sensing unit made of an Au electrode, allowing electrical detection of the target cells based on surface changes in the extended-gate Au electrode functionalized with MIP [12]. With sensors using MIP, it is possible to detect any cancer cells on condition that using the good protein imprint, and after the detection step and cells extraction from the MIP, the sensor can be used for another cycle of detection. Moreover, with MIPs it is possible to detect several targets in addition of ICAM1.

**Scheme 1.** Representation of the project.




**The project is based on two complementary expertise of the project leaders, namely the development of molecularly imprinted polymer developed in the PHENIX laboratory and the biological study of cancer in the Cancer Biology and Therapeutics team of the CRSA in France (Partner 1) and the development of the MIP-OFET sensor in Tokyo University (Partner 2).**

**Methodology:**

5 interconnected Workpackages (WP) are envisaged during the 36 months of the project. Before developing the MIP-OFET sensor, MIP nanoparticles will be synthesized to determine the perfect conditions needed to target the ICAM1+ CTCs (monomers mixture, ICAM1 epitopes). Then the nanoparticles will be tested in blood. Finaly, the good conditions used for the nanoparticles will be adpated to the MIP-OFET sensor development.

*1. The MIP nanoparticle engineering:* Partner 1 and 2
*2. Targeting tests.* Partner 1
*3. Spicking assay into whole blood:* Partner 1
*4. Development of the MIP-OFET sensor:* Partner 2
*5. Test on patients:* Partner 1 and 2

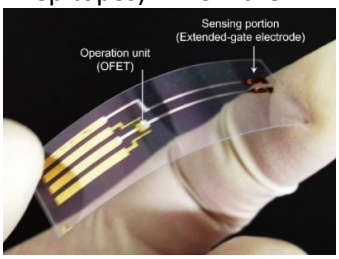



**Figure 1.** The OFET device

**Impacts and outreach**: Currently, counting and isolating CTCs remains questionable because they are mainly identified by epithelial markers such as EpCAM [13]. We now know that circulating tumor cells able to persist in the blood during treatment and able to metastasize exhibit heterogeneous phenotypes including the expression of mesenchymal markers [14] and stem cell markers [15]. Moreover, the use of sub-optimal antibodies for enrichment and detection of sub-population of CTC may be also a bottleneck for the full medical exploitation of the potential of these cells. We proposed here to use the MIPs technology in order to generate a specific material specifically manufactured at molecular level for high degrees of CTCs capture. In our project, we chose the ICAM1 markers, which is clearly an emergent metastatic marker in BC. The development of a technological platform allowing the capture, detection and study of particularly aggressive CTC subpopulations is of major interest to society for both the management and monitoring of patients and for the development of antimetastatic therapeutic strategy which are still largely missing despite recent advances in combinations of targeted therapies and immunotherapies. Thus, the MIP-based sensors that we will develop, **could revolutionize the use of MIP sensors in cancer diagnostics and management.**

**Added-value of the international cooperation** Until now, N. Griffete's team was mostly interested in the development of MIP for cancer therapy. This collaboration is the opportunity to work on another aspect of cancer which is the diagnostic. After the meeting in Tokyo with Minami's team in November 2023, both suggested to collaborate on MIP for cancer which is the speciality of N. Griffete's team and on sensor which is the speciality of Minami's team. N. Griffete is going to deposit an ERC consolidator (november 2024 in LS07) and will put a part dedicated to the development of MIP sensor for CTC detection in collaboration with Minami's team. This will be a good opportunity to show that we started this novel project together, initiated thanks to Sorbonne Université, before the deposition of the ERC.

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