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SURFACE PLASMON EARLY DETECTION OF CIRCULATING HEAT SHOCK PROTEINS & TUMOR CELLS

Context and Objectives

Cancer has become the leading cause of death in the world and costs more in productivity and life lost than any other illness, according to the American Cancer Society report presented at the 2010 World Cancer Congress. Although the risk of dying from cancer has been decreasing since the early 1990s, the rate of new cancers remains stable. The treatment of cancer is therefore progressively improving but the disease remains devastating. In this "war" against cancer, one main strategy, complementary with the improvement of treatments, aims at detecting the disease at an earlier stage. In practice, the higher the sensitivity of the detection is, the earlier the cancer can be identified and treated. Such higher sensitivity is though not available today neither in clinical nor point of care environment, but also at the level of oncology research institutes. Indeed, today diagnosis still relies mainly on microscopic (but not molecular) cues, when the tumor is already composed of several millions of cancer cells. Alternatively, tracking cancer at the molecular level by monitoring the presence of cancer markers in the patient's body would enable to better anticipate the development of the disease. In this context, the SPEDOC project is a multidisciplinary European initiative that joins forces of photonics experts and oncologists to develop a novel ultrasensitive cancer-marker sensing platform for early detection and accurate treatment monitoring.

Prior research studies have demonstrated that for patients affected by cancer, HSP70 (Heat Shock Protein 70) is over-expressed at the surface of cancer cells and in the peripheral blood. Therefore, HSP70 is an interesting target to be tracked in the organism of a patient for at least 2 reasons: Firstly, HSP70 over- expression is associated with many cancers. Secondly, since HSP70 is expressed on the outer membrane of cancer cells but not normal cells, it may also be possible to detect circulating tumor cells in serum. While conventional ELISA (Enzyme-Linked ImmunoSorbent Assay) tests have been recently used to detect circulating HSP70 proteins, the maximum sensitivity remains limited to a few ng/ml and requires labels that may denature the protein compromising the target affinity for the receptor and extend and complicate the assay. Beyond the sensitivity issues, there is not, to date, any technique, which enables detecting HSP70 directly at the cell membrane surface in serum, which would provide much higher reliability in diagnosis.

Independently, latest advances in nanotechnologies have led to new ultrasensitive sensing schemes able to detect low concentration of specific target molecules. Among the most promising approaches, metallic nanostructures, supporting the so-called surface plasmons resonances, combine (i) a high sensitivity to tiny changes of their surrounding refractive index as induced by the binding of molecules with (ii) intense optical fields suitable for enhanced Raman scattering and enhanced optical trapping.

The SPEDOC project aims at developing a novel integrated optical sensing platform based on surface plasmons (SP) for early diagnosis, treatment monitoring and follow-up of cancer at the level of oncology research institutes. By using the latest advances of surface plasmon nano-photonics, we investigate different configurations of compact and ultra-sensitive sensors able to detect HSP70 proteins both in the peripheral blood and at the surface of cells of a mice model, using resonance perturbation, scattering imaging and Surface Enhanced Raman Scattering (SERS), respectively. The developed sensors will be implemented in an advanced microfluidics chip to increase reproducibility, reduce the volume of analyte involved and enable parallel detection experiments on a single chip.

The three main objectives of the project read:

- Objective1: Increasing the reliability and sensitivity of HSP70 tracking by using ultra-specific detection schemes (coupling highly specific receptors with state of the art plasmonic platforms) able to monitor the concentration of over-expressed biomarkers both circulating in serum and accumulated at tumour cells membrane. This would facilitate cancer detection in an earlier developmental stage for a more efficient population pre-screening and follow-up.

- Objective2: Increasing the detection throughput: The combination of microfluidics and plasmonic nanosensors will facilitate the implementation into a clinical setting due to faster and parallel assays with fewer steps and lesser sample

- Objective3: Integration of optical transduction and plasmonic tweezers into a compact platform able to operate in a biology or oncology laboratory setting. Such device should be understood as a precursor of a future portable device enabling point of care (POC) diagnostics in a medical environment.

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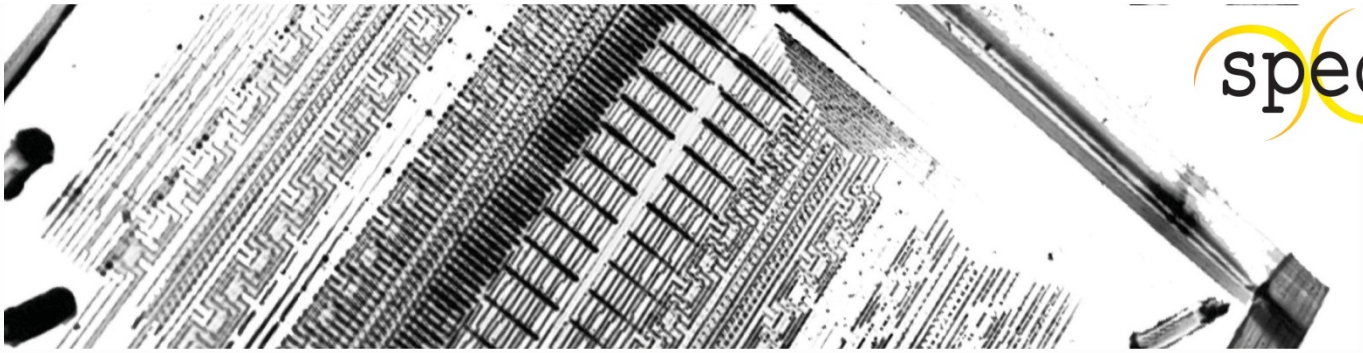

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Description of the work performed and Main research achieved so far

Joint efforts and multidisciplinary interactions within SPEDOC have led to several important advances in the development of several novel analytical tools for early cancer diagnosis.

The main research achievements of the project can be organized into the two main directions, namely the detection of circulating protein cancer markers in serum and the screening of tumor cells based on the overexpression of membrane protein markers.

□ Development of several plasmon-based sensing schemes to monitor low concentrations of circulating protein markers in serum

- Development of a LSPR (Localized Surface Plasmon Resonance) sensing platform for label-free detection of low concentrations of protein markers in serum. The platform enables multiplexed sensing (over several tens of assays) in about 1 hour with a sensitivity of 1ng/ml. This configuration led to a stand-alone and automatic prototype aimed at assisting biology and oncology researchers.

- Development of new statistical approaches to enhance the sensitivity of SPRi (Surface Plasmon Resonance Imaging) and SERS (Surface Enhance Raman Scattering). These approaches were successfully applied to high sensitivity detection of protein markers in serum.

- Development of a high-throughput immunoassay platform capable of screening several protein markers in serum through more than 1000 parallel assays. The device reaches sensitivities similar to ELISA (<1ng/ml), the current gold standard in protein detection, but at a cost that is two orders of magnitude cheaper.

□ Plasmon-based screening of circulating tumor cells

- Development of two new plasmon-based strategies towards the fast discrimination of circulating tumor cells. Alternative to standard flow cytometry, these approaches could

Potential impact

We foresee the technologies developed within SPEDOC will help biologists and oncologists to advance early diagnosis and treatment monitoring of cancer, making them more sensitive and reliable. Beyond the applications to cancer research, the knowhow generated in SPEDOC is expected to contribute to benefit other fields. In particular, most of the developed technologies could be extended to the detection of other diseases as well as to environmental monitoring and food control.
For more details, please visit our webpage: www.spedoc.eu

A multidisciplinary Consortium

ICFO (coordinator) brings its expertise in the fields of advanced optical microscopy and spectroscopy on nanostructures, nanofabrication and optical trapping. **INSERM** is the expert in Heat Shock Proteins and will bring all the know how to enable biochemistry, providing serum of model mice and the necessary background to guide cells manipulation with optical tweezers towards pertinent results. Located in the same city as **INSERM**, **UB** will ensure the optimal interface between partners featuring expertise in nanotechnologies and the biologists of **INSERM**. Moreover, **UB** brings its full support to the consortium in the design and nanofabrication plasmonic devices, near-field optical measurements, surface functionalization and biostatistics. **EPFL** provides to the consortium strong expertise in both numerical simulations (Martin's group) and advanced microfluidics (Maerkl's group). Finally, **COSINGO** is specialized in the integration of optical devices. **COSINGO**'s skills and experience in optical engineering will enable the development of a compact Detection Platform. As the industrial partner of the consortium, **COSINGO** plans to exploit the outcome of the project to offer a new generation of sensing devices for biology research laboratories.

Prof. Romain Quidant
Scientific Coordinator
ICFO
The Institute of Photonic Sciences

Prof. Alain Dereux
Principal Investigator **UB**
Université de Bourgogne

Dr. Carmen Garrigo
Principal Investigator
INSERM U866

Rafael Porcar Principal
Investigator **COSINGO**
Imagine Optic Spain SL

Prof. Olivier Martin
Principal Investigator **EPFL**
Ecole Polytechnique Federale de Lausanne

Prof. Sebastian
Maerkl Principal
Investigator
EPFL
Ecole Polytechnique Federale de Lausanne

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