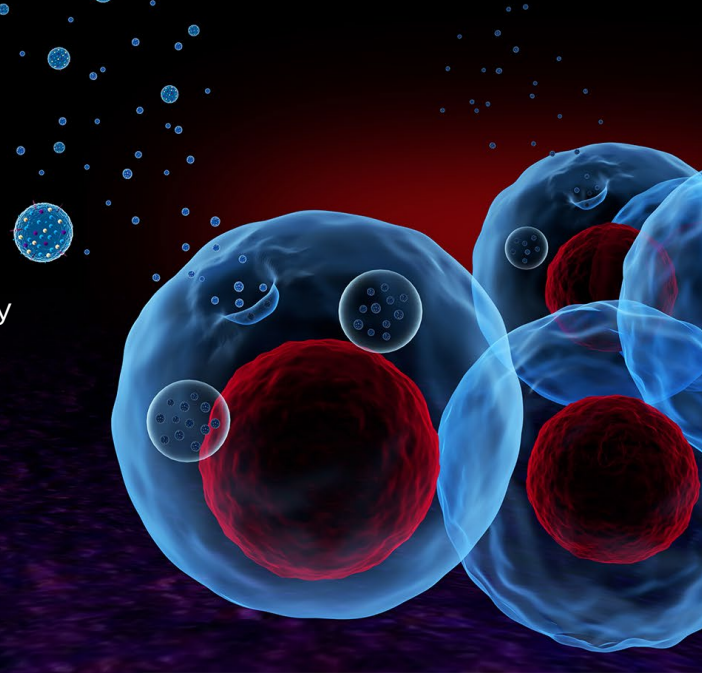
PHOREVER

PHOtonic integrated OCT-enhanced flow cytometry for canceR and cardiovascular diagnostics enabled by Extracellular VEsicles discRimination



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- Institute of Communications and Computer Systems (ICCS) – EL
- LioniX International – NL
- CSEM – CH
- AMC - NL
- PHIX – NL
- LRE – DE
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https://horizon-de-phorever.eu/

Motivation

The development of techniques and instruments that can shed light on the mechanisms of our current two greatest health threats, cancer and cardiovascular disease (CVD), is a constant goal of modern medicine. High-end imaging modalities such as sonography, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) are still the fundamental non-invasive tools for a definitive diagnosis of these diseases, but they are too complicated, expensive, and, at least in the case of the CT and the PET, harmful to use as tools for routine monitoring. Additionally, because they are imaging tools, these modalities can effectively produce images of the symptoms of these diseases, such as the presence of solid tumors or blood clots, but they are unable to provide accurate insight into the molecular mechanisms that underlie the progression, recurrence, or resistance to medical treatment of these diseases. In fact, it is believed that circulating cells, vesicles, and molecules found in human blood provide the majority, if not all, of the information required to understand these systems. To sense and quantify this blood content, however, we need strong imaging technologies that can move us from the macroscopic to the microscopic level of imaging. Extracellular vesicles (EVs), in particular, are membrane-enclosed vesicles that cells secrete and play a crucial function in the process of removing cell waste and in

cell-to-cell communication. Their use as circulating markers can provide insightful info related the physiological and pathological status of their cell of origin, and consequently, regarding the existence and stage of disease. Thus, one of the most disruptive and possibly significant goals in contemporary medicine has been highlighted as the potential to identify EVs in blood samples. The majority of EVs range in size from 50 to 200 nm, hence this potential still presents a significant difficulty. The most promising method for detecting small-size EVs is flow-cytometry (FCM), yet even the most sophisticated FCM devices now available can only identify particles as small as 150–200 nm.

A multi-sensing platform that will enable the first-ever detection of EVs with size down to 80 nm, detection of EVs with disease-specific proteins (biomarkers) as cargo on their membrane surface, and calculation of the corresponding EV concentrations in human blood samples will be developed by PHOREVER using this medical and technological background. Three different sensory modalities will be used to produce this disruptive detection performance:

The optical coherence tomography (OCT) as a secondary sensing modality for the micro-imaging of the sensing area and the application of a coherent gate for drastic noise reduction in the FCM measurements, the fluorescence sensing as a third modality for the detection of the target biomarkers on the surface of the EVs after a proper stain process with fluorescent dye, and the FCM as the main sensing modality for the detection and size classification of particles in blood samples.

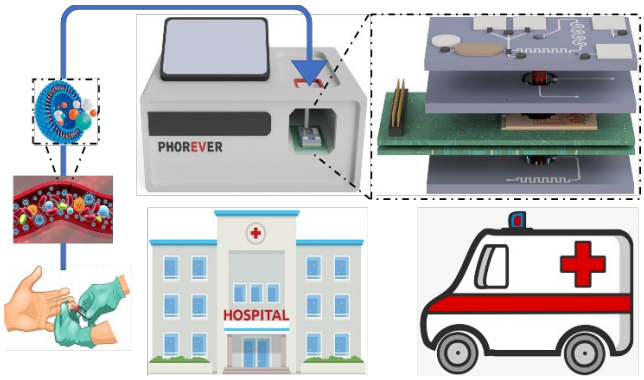

Figure 1. Concept diagram of PHOREVER motivation, concept and objectives: PHOREVER will develop a multi-sensing platform in the form of a point-of-care (POC) device

that can be used for the detection of extracellular vesicles (EVs) in the blood with ultra-small size down to 80 nm as potential biomarkers for the fast diagnosis, progression stage monitoring and treatment response assessment in the case of the pancreatic cancer and the stroke. Its detection performance will be empowered by two photonic integrated circuits and three micro-fluidic chips that will support the combination of three sensing modalities: Flow-cytometry, fluorescence sensing and OCT. Data analysis tools empowered by artificial intelligence algorithms will be responsible for the association of the measurement data to the medical use cases of the project.

Concept and objectives

PHOREVER will demonstrate its potential via the development of:

1) a TriPleX PIC for flow-cytometry (FCM) and fluorescence sensing and use it as a dual sensing tool for detection of EVs in blood samples and detection of biomarkers on the surface of these EVs,

2) a TriPleX PIC with a dual-channel swept-source optical coherence tomography (SS-OCT) unit on-chip and use it as a coherent gate for the processing of the FCM measurement data,

3) a microfluidic unit for the pre-analytical and analytical handling of blood samples as the disposable part of the multi-sensing PHOREVER platform, and

4) development of a comprehensive data analysis tool empowered by AI algorithms for use in the medical cases of the pancreatic cancer and the stroke.

Exploitation and expected impact

This multi-sensing platform has enormous promise for medical applications, but the actual effects will vary depending on the specifics of each medical use case. The project will look into two particular use cases. The first will be a pancreatic cancer case with a focus on tracking the disease's stage of progression, estimating the risk of metastasis, and assessing the effectiveness of treatment. The second example will involve a stroke, with an emphasis on quick stroke event diagnosis and quick stroke type identification using the multi-sensing platform of PHOREVER as a POC device before the patient actually arrives at the

hospital. The focus of the project will be on the association between the total EV concentration in the blood samples and the actual medical information of the patient because, in the case of pancreatic cancer, the medical community is still working to find a protein as a vulgate biomarker. The emphasis within the project will be on the detection of the corresponding subclass of EVs and the correlation of their concentration to the stroke incident parameters, however, as the corresponding efforts in the stroke case have already led to the identification of effective biomarkers that can be carried as cargo by EVs. In either scenario, a set of data analysis tools driven by AI algorithms will be employed to process the readings from the multi-sensing platform and to correlate them with the relevant medical data.

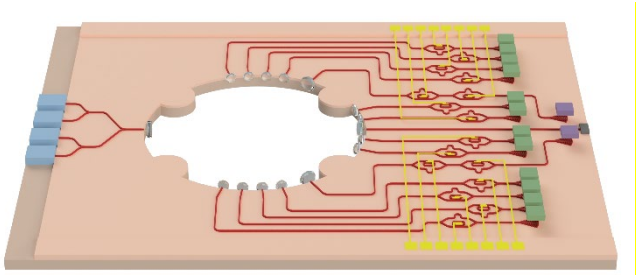

Figure 2. Artistic layout of the first sensing PIC of PHOREVER platform for the execution of FCM measurements and fluorescence sensing

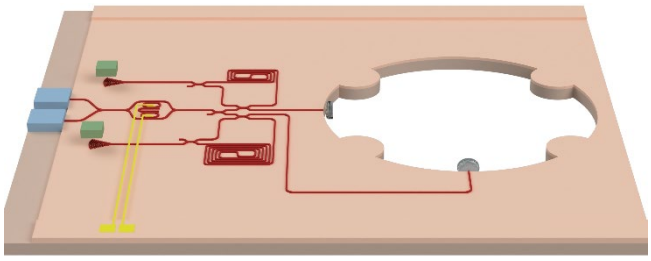

Figure 3. Artistic layout of the second sensing PIC of PHOREVER platform for the execution of the dual-channel OCT imaging of the sensing area