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

**Topic:** Advanced multi-sensing systems (Photonics Partnership) (RIA)  
HORIZON-CL4-2022-DIGITAL-EMERGING-01-03

**Call:** HORIZON-CL4-2022-DIGITAL-EMERGING-01

**Project No:** 101093171

**Start date:** 1 January 2023

**Duration:** 42 Months

**EC contribution:** € 4,973,882.50



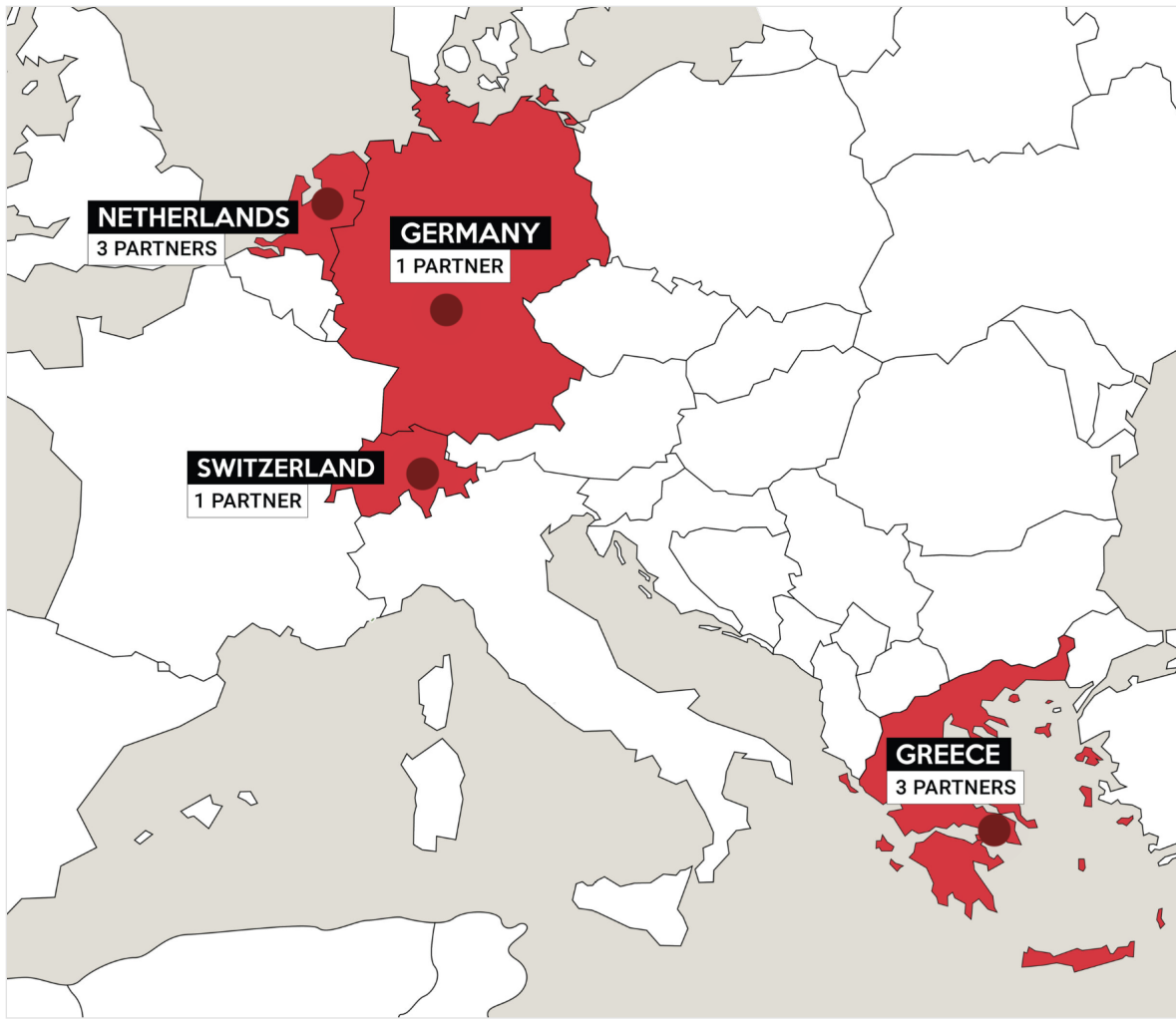
UNIVERSITY OF IOANNINA









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# PHOREVER Consortium



 8 PARTNERS	 4 COUNTRIES
 4 ACADEMIC ORGANISATIONS	 1 INDUSTRY-ORIENTED RESEARCH INSTITUTE
 1 SME	 2 LARGE COMPANIES

# Introduction

- ◆ Next generation **multi-sensing photonic and electronic systems** with increased integration of new functionalities, decreased size and cost-effective manufacturing
- ◆ Supporting a European open strategic autonomy in **key integration** and **packaging technologies** and related manufacturing value chains
- ◆ Sensing devices and components allowing for reaching the new green deal objectives through enabling high levels of **reuse/repair/repurpose, recovery and recycling of waste and materials** or helping to **reduce overall power consumption** of a system
- ◆ **Reinforcing European industrial leadership** in high performance multi-sensing systems and components for sectors such as healthcare and well-being

# PHOREVER main driving ideas

- ◆ Develop a biosensing platform
  - Upgrade the prediction and the treatment of cancer and cardiovascular diseases
- ◆ Develop of the first ever integrated swept laser source for sub-micron operation
- ◆ Develop of an innovative TriPleX PIC (sensing module-1)
  - Combine the fluorescence detection with the Flow-cytometry measurements.
- ◆ Develop of an innovative TriPleX PIC (sensing module-2)
  - Based on the swept laser source, develop an integrated Swept-Source Optical Coherence Tomography (SS-OCT) module
  - Combine the two modules for increasing the precision and the reliability of the FCM measurements
- ◆ Develop a complete microfluidic unit
  - Pre-analytical and analytical treatment of blood samples
  - Co-integration with the photonic circuits
- ◆ Detection of small size EVs
- ◆ Develop of AI algorithms for the correlation of the EV levels with the progression of the pancreatic cancer and the type of the stroke

# PHOREVER overview

## Photonic integrated OCT-enhanced flow cytometry for cancer and cardiovascular diagnostics enabled by Extracellular vesicles discrimination

### Vision - Concept

“Develop of a photonic biosensor for the detection of small-size EVs that can be used as biomarkers for the diagnosis, progression monitoring and treatment assessment of diseases such as the pancreatic cancer and the stroke stand out due to their potential for scientific breakthrough and societal impact”

- ◆ Use of **extracellular vesicles (EVs)** as **biomarkers** for pancreatic cancer and stroke
- ◆ **FCM and fluorescence** sensing for the measurement of **EV concentrations** inside blood samples
- ◆ **Photonic integration** of an optical setup for execution of **FCM** measurements and **fluorescence** sensing
- ◆ **Photonic integration** of an **OCT** setup as a coherent gate for the **validation of FCM measurements**
- ◆ **Physical integration** of the two sensing PICs as **the non-disposable core** of the multi-sensing platform
- ◆ **Multi-functional, low-cost and disposable unit** for automated blood sample analysis
- ◆ **Physical integration** of the flow-cytometer, fluorescence and OCT sensing modules with the microfluidic unit
- ◆ Use of **AI methods** and development of application-specific **data analysis tools**

# Innovations (I)

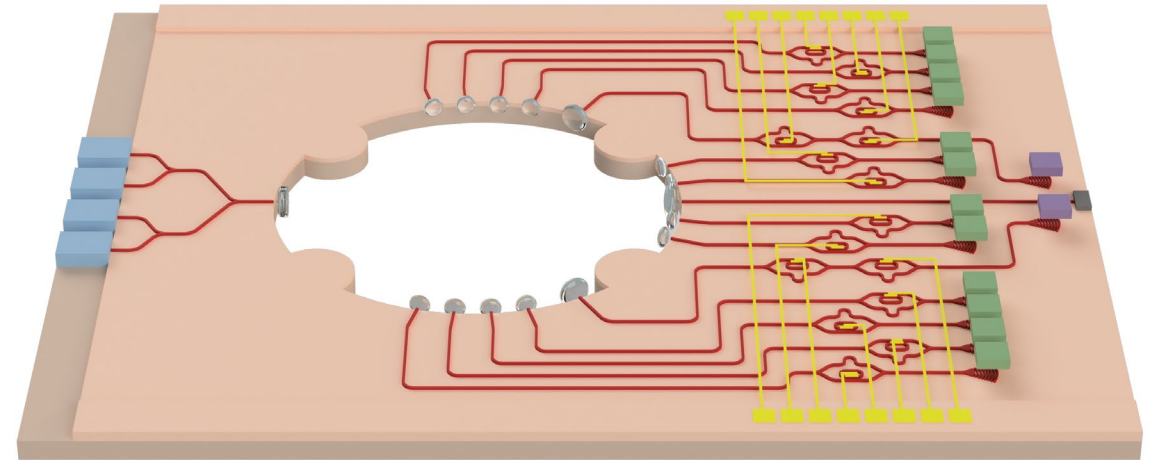
**Develop a TriPleX PIC for flow-cytometry (FCM) and fluorescence sensing and use it as a dual sensing tool for detection of EVs in blood samples and detection of biomarkers on the surface of these EVs**

## **FCM sensing modality**

- Multi-wavelength operation (405, 488, 633, 785 nm)
- Multiple collection waveguides (12) with hybrid lenses
- Large collection angle ( $10^\circ$  for each waveguide)

## **Fluorescence sensing modality**

- Wavelength operation at 488 nm
- 2 collection waveguides with hybrid lenses
- Even larger collection angle ( $30^\circ$  for each waveguide)



## Previous experience

FCM in TriPleX platform with fixed flow channel and single illumination wavelength. No micro-lenses were used. External laser and photodetectors



# Innovations (II)

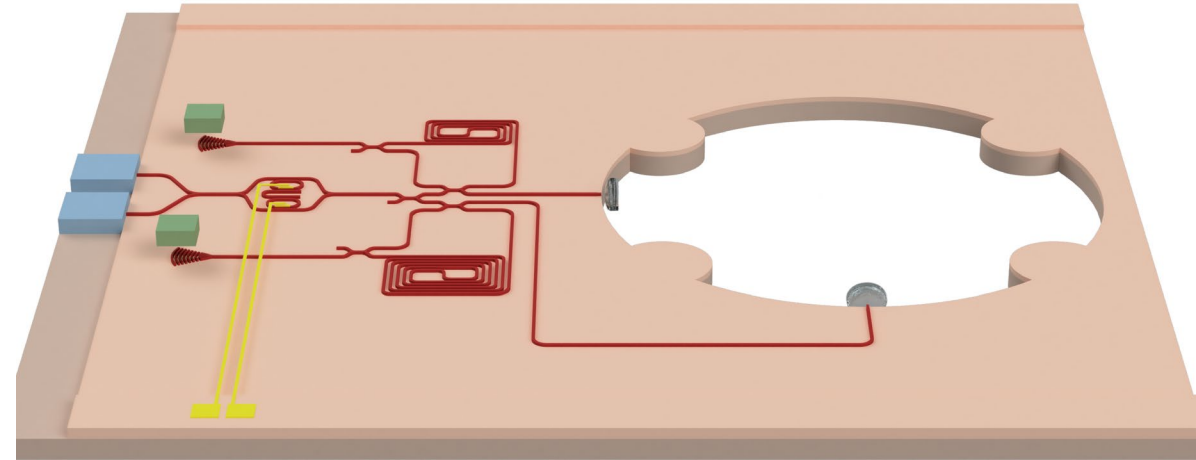
Develop a TriPlEx PIC with a dual-channel swept-source optical coherence tomography (SS-OCT) unit on-chip and use it as a coherent gate for the processing of the FCM measurement data

## Photonic integrated wavelength swept laser source

- Sweeping span: 100 nm (700-800 nm)
- Sweeping step: 1 nm
- Sweeping rate: 100 kHz
- Output optical power: >50 mW

## SS-OCT sensing modality

- 2 perpendicular channel operation (2x 1D image slices)
- Axial resolution: 2.5  $\mu\text{m}$
- Imaging depth: 1.4 mm
- Illumination waveguides with hybrid lenses



## Previous experience

Efforts for the development of OCT-PIC have been made by LioniX



# Innovations (III)

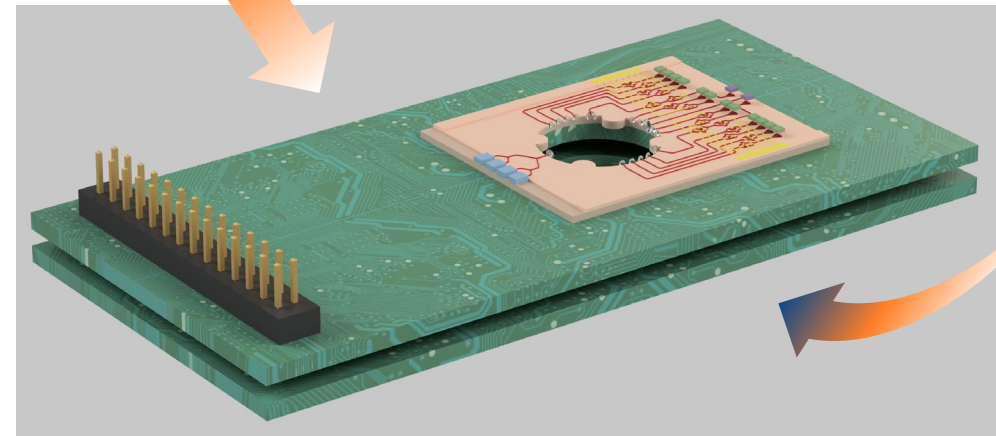
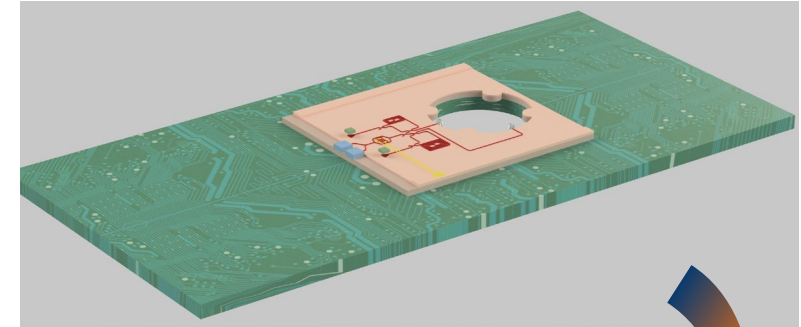
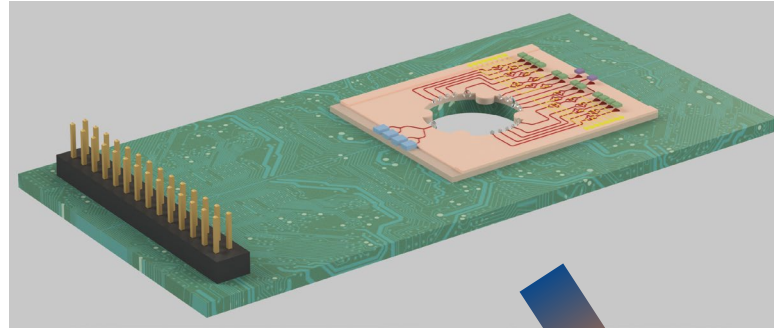
Develop a photonic-electronic stack comprising the two sensing PICs and their companion interposers as the non-disposable part of the multi-sensing platform

## 4-layer photonic-electronic stack

- Each PIC will be mounted on an interposer PCB
- Routing of electrical lines for the PIC operation
- B2B mounting of the two subassemblies
- Aligned through holes

Previous experience

Integration of electrical PCBs with PICs in various research projects





# Innovations (IV)

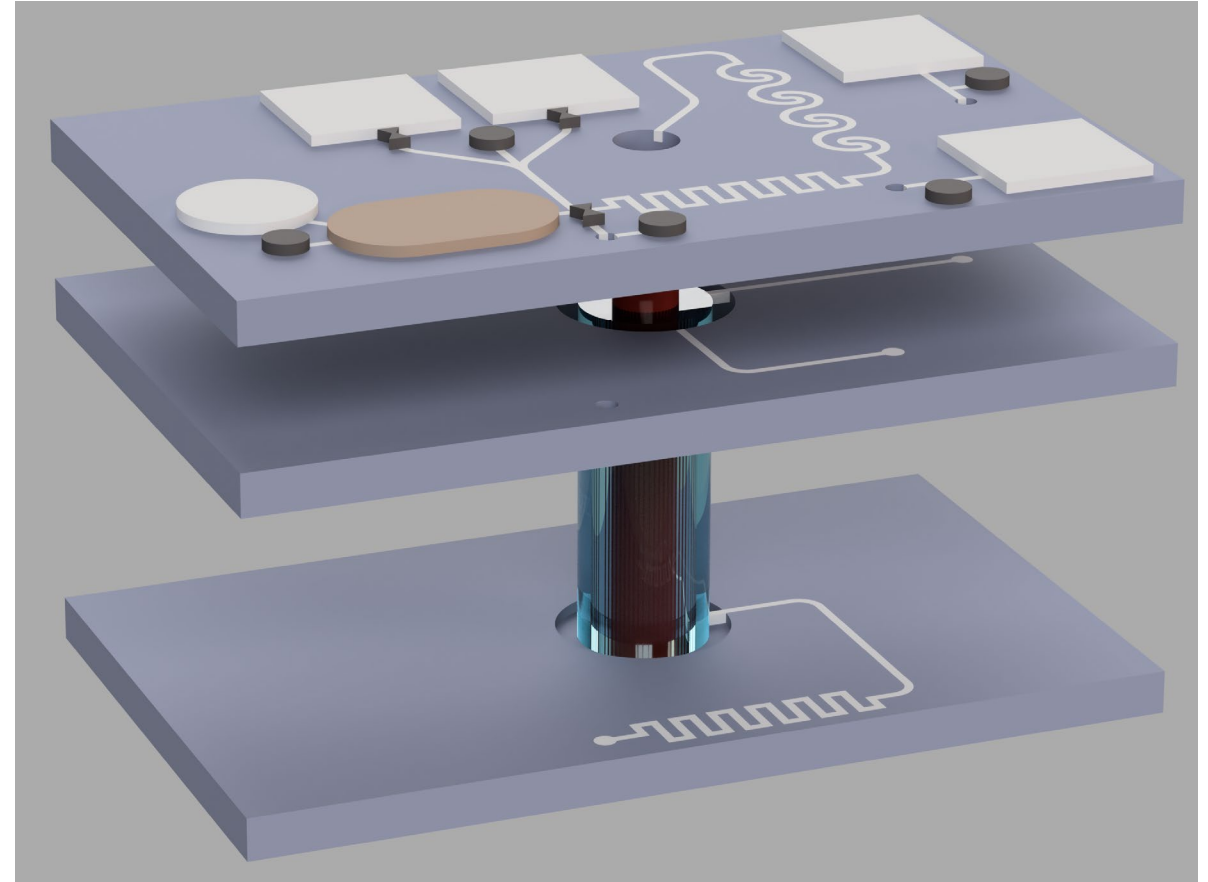
Develop a microfluidic unit for the pre-analytical and analytical handling of blood samples as the disposable part of the multi-sensing PHOREVER platform

## Fluidic cartridge

- Pre-analytical stage
- Analytical stage
- Sample treatment and preparation for measurement by the FCM/fluorescence and OCT PIC
- Disposable

## Previous experience

Development of microfluidic chips for sample preparation in previous EU-projects (ICT-BIOFOS, ICT-BIOCDx)



# Innovations (V)

**Develop the control electronics of the sensing platform and the algorithms for the execution of the measurements and the processing of the measurement data from the two sensing PICs**

## Control electronics and smart algorithms

- For the operation of the microfluidic elements
- For the operation of the PMTs
- For the implementation of the TDM scheme of the operation of the 4 LDs
- Tuning of phase sections of the ECL
- Excursion of the sweeping process



Previous experience

In various EU research projects (ICT-BIOFOS, ICT-BIOCDx, 3PEAT)



**Validation of the detection potential of the multi-sensing platform using reference EV materials, and development of a comprehensive data analysis tool empowered by AI algorithms for use in the medical cases of the pancreatic cancer and the stroke**

## Development of a data analysis tool

- Development of AI algorithms
- Validation of the sensing modules using spiked samples
- Correlation of the EV concentration in blood to the medical use cases



Previous experience

Use reference materials that are clinically relevant (METVES project)



Medical informatics, bio-signal and medical images processing

# Innovations (VI)

## Demonstrate the use of the multi-sensing platform (PHOREVER platform) for the clinical analysis of EVs in blood samples in relation to pancreatic cancer

### System tests at vendor

- Experimentally definition and validation of the process flow for the collection, handling, and storage of blood plasma
- Investigation and demonstration of the PHOREVER platform for the detection of EVs in blood samples from patients with pancreatic adenocarcinoma



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### Previous experience

Day to day work with patients with pancreatic cancer, and use of FMC devices

## Demonstrate the use of the multi-sensing platform (PHOREVER platform) for the clinical analysis of EVs in blood samples in relation to stroke

### System tests at vendor

- Experimentally definition and validation of the process flow for the collection, handling, and storage of blood plasma
- Investigation and demonstration of the PHOREVER platform for the detection of EVs in blood samples from hemorrhagic, ischemic and stroke mimic patients

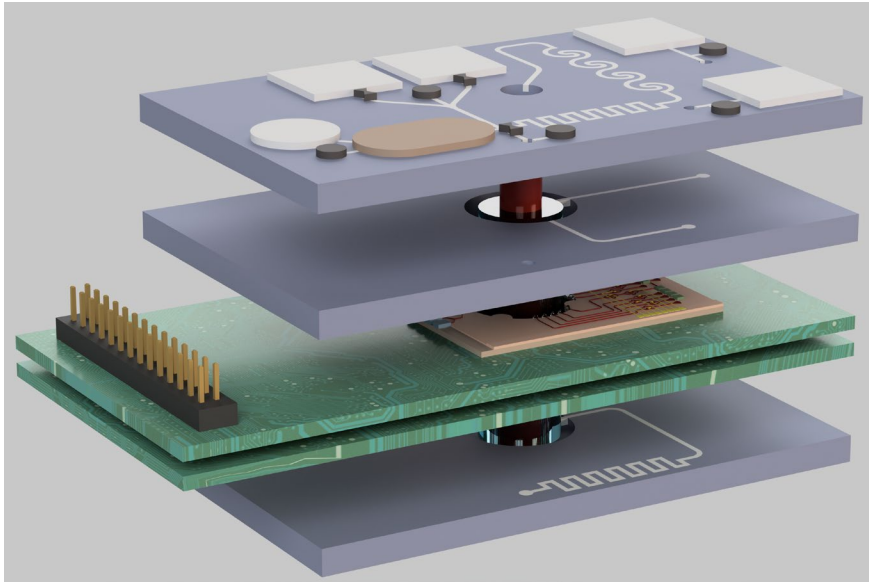


### Previous experience

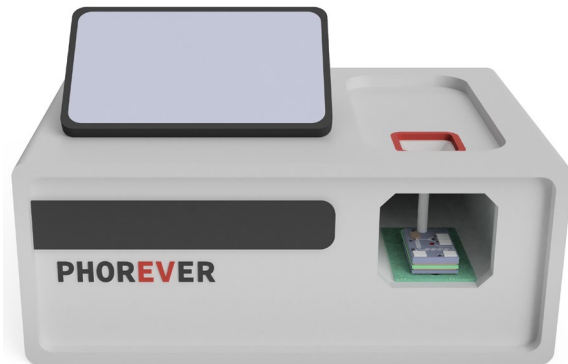
Day to day work with stroke patients, and use of FMC and OCT devices

# PHOREVER demonstrator

## PHOREVER multi-sensing platform



- 4-layer stack with the PICs (FCM/fluorescence and OCT) on the corresponding interposers
- Fluidic cartridge
- Connector as the interface with the rest of the control and driving electronics
- Housing
- Communication components
- Suitable user interface



# Contact

For more info, visit PHOREVER website  
<https://horizon-de-phorever.eu/>

## Project Coordination

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