Origami Paper-based tecHnology fOr the innovativE aNd sustaInable Organ-on-Chip devices

Organ-on-a-Chip (OoC) technology offers a promising alternative to traditional animal testing in drug development, addressing limitations and ethical concerns. While animal models are crucial for understanding human physiology and disease development, they often fail to represent human responses accurately, leading to uncorrelated results.

Although 2D cell cultures have been valuable in biomedical research for over a century, they cannot replicate in vivo tissue functions or accurately predict biological responses to drug testing, especially in complex diseases with multiple comorbidities. Despite advancements in in vitro biology and toxicology, a high percentage of investigational drugs fail in clinical trials due to issues with toxicity or efficacy, resulting in high drug costs and fewer successful compounds.

OoC models can help fill this gap by mimicking human tissue functions and providing insights into biological mechanisms, which could lead to more effective and personalised medicine. The design and development of OoCs depend on the specific biological questions they aim to answer.

Among the most cutting-edge projects in the OoC field, PHOENIX-OoC (Origami Paper-based tecHnology fOr the innovativE aNd sustaInable Organ-on-Chip devices) aims to revolutionise the way OoCs are developed, introducing paper's unique and versatile features as the main material and employing an origami configuration for cell co-culture simulating organ tissues, integrating (bio)sensors to perform accurate pharmacological studies. The goal is to create more affordable, sustainable and accessible devices while maintaining the effectiveness and precision needed for biomedical research.

The PHOENIX-OoC consortium

PHOENIX-OoC is an international initiative bringing together six partners from five different countries. The consortium includes four universities, one research organisation and one industrial partner, each contributing specific expertise in the fields of microfluidics, biomaterials, tissue engineering, analytical chemistry, paper-based (bio)sensors and modelling. The interdisciplinary approach ensures the development of advanced technology capable of filling the needs of pharmacological research and regenerative medicine.

Figure 1: One of the microfluidic devices developed by the team, based on a non-traditional microfluidic design.

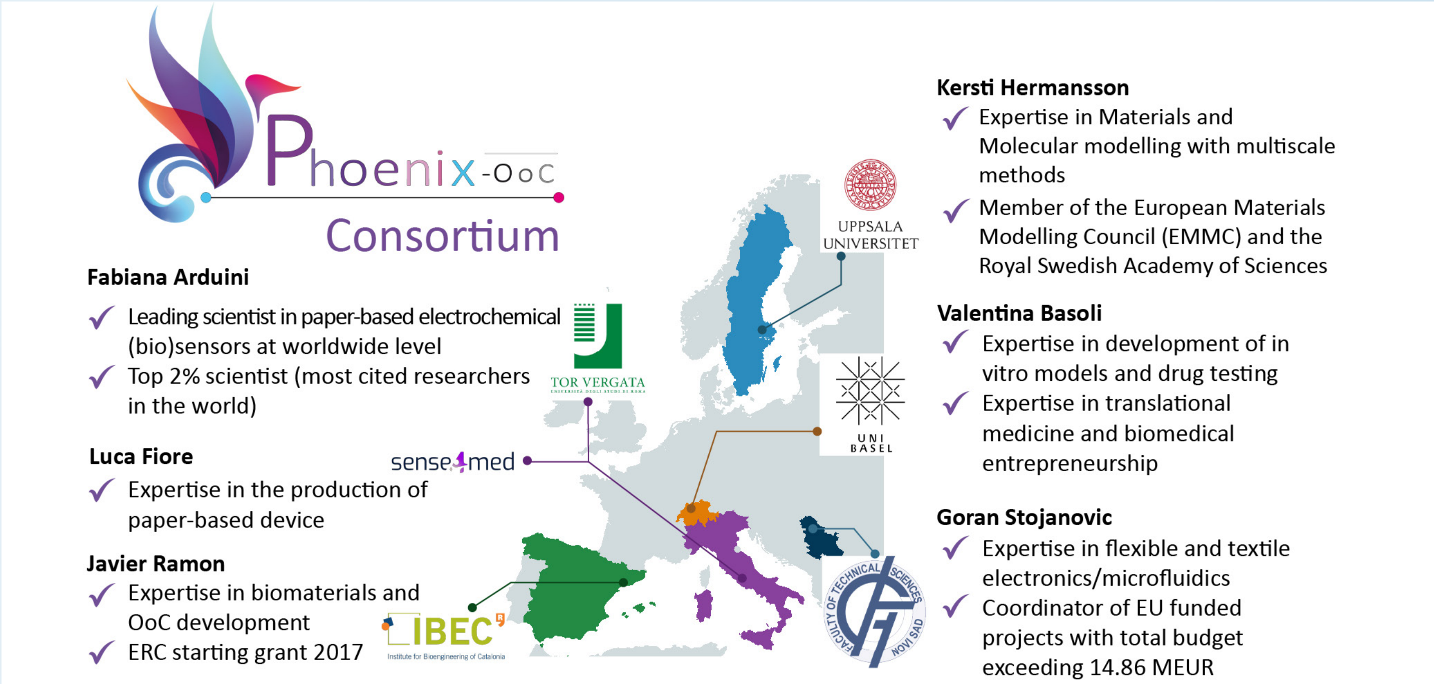

Figure 2: A map showing the details and locations of the PHOENIX-OoC consortium members.

Collaboration

This synergy between academic and industrial partners ensures a comprehensive approach to PHOENIX-OoC device development, from design to clinical trials. This consortium arises from previous collaboration between the partners in international projects, guaranteeing successful coordination. UNITOV and UU were the Italian and Swedish coordinators, respectively, in the INNOCONCRETE project, with an output of one patent and five publications in peer-reviewed journals (Agosta *et al.*, 2024; Colozza *et al.*, 2020, 2021a, 2021b; Sassolini *et al.*, 2019). FTN and UNITOV have collaborated on the Strentex Horizon 2020 project, where FTN was the coordinator. UNITOV was one of the advisory boards with the output of two peer-reviewed publications (Fiore *et al.*, 2023; Mazzaracchio *et al.*, 2022). The article published in Green Analytical Chemistry was one of the most downloaded in 2022, while the one published in Chemical Communications was selected for the cover page. UNITOV and UNIBAS are partners in the CostAction CA21110 – Building an open European Network on OsteoArthritis research (NetwOArk) (2022–2026) with the output of one peer-reviewed publication (Belcastro *et al.*, 2025).

Fabiana Arduini

University of Rome Tor Vergata coordinates the PHOENIX-OoC project with a research team led by Professor Fabiana Arduini, with strong expertise in analytical chemistry, miniaturised electrochemical (bio)sensors and innovative diagnostic technologies. Full Professor Fabiana Arduini, at the University of Rome Tor Vergata, is internationally recognised as one of the leading experts in the development of paper-based electrochemical (bio) sensors. Her scientific influence is demonstrated by her ranking among the top 2% of the most cited researchers in the world, highlighting the significant impact her work has had in the field of (bio)sensors and applied analytical chemistry.

Goran Stojanović

The University of Novi Sad (FTN) is a project partner specialising in unconventional microfluidics, using sustainable materials such as cellulose based substrates, combined with mechanical engineering expertise to support the optimisation of paper-based microfluidic systems. Full Professor Goran Stojanović of the University of Novi Sad, Serbia, leads a multidisciplinary research team, and his research activity focuses on flexible and textile electronics and microfluidics, with a strong emphasis on practical applications. He is the coordinator of several European projects totalling over 14 million euros, demonstrating scientific excellence and exceptional skills in securing funding and managing projects.

Javier Ramon

Institute for Bioengineering of Catalonia, Barcelona (IBEC-CERCA) is a research organisation partner, a centre of excellence for biomaterials and tissue engineering for cell encapsulation. Associate Professor Javier Ramon, of the Institute of Bioengineering of Catalonia in Barcelona, Spain, is the leader of this research group and a central figure in the development of biomaterials and OoC systems. Winner of an ERC Starting Grant in 2017, he is responsible for creating advanced biological models to simulate the activity of human organs in vitro, contributing decisively to progress in personalised medicine and drug experimentation.

Valentina Basoli

The University of Basel is a leading partner in cell biology and pharmaceutical sciences, with renowned expertise in articular joint cells, tissue engineering, OoC technologies, biofabrication, and pathological in vitro models for drug development. Dr Valentina Basoli, Group Leader and Lecturer at the University of Basel, is internationally recognised for her contributions to advancing in vitro models for pharmacological research and translational medicine. Her research focuses on biofabrication and the integration of cellular systems with advanced sensing technologies to drive cartilage and bone bioengineering. Alongside her scientific achievements, she places strong emphasis on fostering entrepreneurship within the biomedical field.

Kersti Hermansson

Uppsala University contributes expertise in computational chemistry modelling. The research team is led by Full Professor Kersti Hermansson of Uppsala University, Sweden, who is an internationally renowned expert in computational modelling and material sciences. Her expertise in multiscale methods for materials chemistry has led to her being selected as a member of the European Modelling Council and the Royal Swedish Academy of Sciences, acknowledging her strong role in the field.

Luca Fiore

Sense4Med is an industrial partner (SME) that specialises in designing and developing electrochemical sensors for biomedical applications. Luca Fiore, principal investigator at Sense4Med, contributes his expertise in developing and fabricating paper-based sensors.

Project objectives

The PHOENIX-OoC project is organised around six main objectives, each focused on harnessing the properties of paper to create innovative Organ-on-a-Chip devices:

1. Isolation and immobilisation of joint cells for creating a physiologically relevant cellular model for mimicking the joint structure and functionality within the OoC device, immobilising the cells in paper-based microporous scaffolds with an anisotropic microstructure.
2. Development of a paper-based model of osteoarthritic (OA) tissue for creating a reliable OA model for pharmacological testing, marking a significant milestone in research on degenerative diseases.
3. Design of paper-based microfluidic pattern for mimicking blood flow and cellular dynamics within the PHOENIX-OoC device, disrupting the traditional microfluidic methods for OoCs.
4. Integration of electrochemical paper-based (bio)sensor array within the PHOENIX-OoC device, for the detection of physiologically relevant biomarkers for real-time monitoring of cell status and response to stimuli.
5. Computational modelling for drug and water adsorption on paper, a new interesting platform to study drug uptake and release, improving understanding of molecular interactions and diffusion dynamics in tissues.
6. Development of the PHOENIX-OoC device and pharmacological tests by creating the working prototype, then applicating in drug screening tests.

Innovation in the use of paper

The distinctive element of PHOENIX-OoC is the use of paper as a structural and functional material for the construction of Organ-on-a-Chip devices. Unlike traditional, rigid polymers used for OoCs, paper offers significant advantages:

1. **Flexibility:** thanks to the possibility of being folded and shaped into complex three-dimensional structures.
2. **Porosity:** which allows the transport of liquids and gases in a controlled manner.
3. **Biodegradability:** reducing the environmental impact compared to traditional plastic materials.
4. **Low cost:** making the technology accessible even to laboratories with limited resources.

The use of origami in the design of OoC devices allows for compact, versatile and easily transportable structures, with a configuration that can be adapted to the specific needs of each experiment.

Economic, environmental and social implications

One of the most revolutionary aspects of the project is its potential economic and environmental impact. Traditional devices for in vitro studies are often expensive and made from non-recyclable materials. The use of the paper may: *(i)* reduce production costs by improving access to technology, *(ii)* decrease laboratory waste since paper is biodegradable and easily disposable, and *(iii)* promote more inclusive research allowing even institutions with limited budgets to access advanced tools for biomedical experimentation.

Applications in the pharmaceutical and biotechnology industries

PHOENIX-OoC is proposed as an innovative solution for pharmaceutical and biotechnology companies that need reliable platforms for the evaluation of drug toxicity and efficacy. This will be achieved by offering high-thoughput screening and real-time monitoring thanks to the ability to test multiple compounds simultaneously with the paper-based sensor array—an alternative to animal models and testing. PHOENIX-OoC will contribute to the reduction of the use of animals in preclining testing.

Conclusions and prospects

PHOENIX-OoC represents a step forward in Organ-on-a-Chip device research, combining sustainability, efficiency and accessibility. The use of paper and origami microfluidics opens new perspectives for the study of human pathologies and the development of drugs, contributing to a more ethical and environmentally friendly science. With the advancement of international research and collaborations, it is possible that this technology will find large-scale application, revolutionising the biomedical sector in the coming years.

References click here

PROJECT SUMMARY

PHOENIX-OoC develops sustainable, origami-inspired paper-based Organ-on-a-Chip devices integrating (bio)sensors for real-time monitoring of cellular responses. It aims to make drug testing more accessible, cost-effective and accurate, reducing reliance on animal models. Through interdisciplinary collaboration among six European partners, the project advances biomedical research and personalised medicine.

PROJECT PARTNERS

The consortium includes four universities, namely University of Rome Tor Vergata (UNITOV), Uppsala University (UU), University of Novi Sad, Faculty of Technical Sciences (FTN), and University of Basel (UNIBAS); one research organisation, Insitut de Bioenginyeria de Catalunys (IBEC-CERCA), and one industrial partner, Sense4Med (SENSE), merging expertise in analytical and computational chemistry, microfluidics, cell biology and bioengineering.

PROJECT LEAD PROFILE

Professor Fabiana Arduini, full professor at UNITOV, is the coordinator of PHOENIX-OoC. Expert in printed electrochemical (bio)sensors, she has published over 150 peer-reviewed papers, holds ten patents, and leads several national and international projects. She is among the world's top 2% of scientists and actively contributes to science policy and editorial leadership.

PROJECT CONTACTS

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