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Health

Date	03/07/2025	Deadline	IHI call11 09/10/2025 Topic 4

CONTACT

Organisation	CEA/IRIG	**Department**	BGE
Contact person	Arnaud Millet, Deputy Director of Biomics Lab Xavier Gidrol, Director of Biomics Lab	**Email**	arnaud.millet@cea.fr emily.tubbs@cea.fr haiyet.chebli@cea.fr EU contact
City	Grenoble	**Website**	https://www.bge-lab.fr/en/Pages/Biomics/Presentation.aspx
Country	France		

Organisation type

Research organisation type	☒ Research Organisation ☐ University ☐ Company ☐ Other	**Is your company a Small and Medium Sized Enterprise (SME*)?** **Number of employees:**	☐ YES ☒ NO

Your enterprise is an SME if:
- it is engaged in **economic activity**
- it has **less than 250 employees**
- it has either an **annual turnover not exceeding €50M**, **or an balance sheet total not exceeding €43M**
- it is **autonomous**

For the definition of SMEs, look at: http://ec.europa.eu/growth/smes/business-friendly-environment/sme-definition_en

Short introduction of key areas of institute's research:
The BGE unit aims to contribute to improving human health and the medicine of the future by identifying biomarkers of interest for diagnosis, prognosis, theranostics, and patient monitoring, discovering drug candidates, and developing and producing innovative therapies derived from cell and tissue engineering. To this end, the BGE unit seeks to identify biomarker candidates and therapeutic targets and to understand their pathophysiological functions in the cellular response to developmental signals, its macro- and microenvironment, or pathological contexts related to metabolic diseases, cancers, and rare diseases. Its research is based on the unbiased, large-scale analysis of biological and clinical samples, cell and tissue engineering, particularly using adult stem cells (e.g., tumoroids, organoids), and the use of animal models and complex multicellular models. This work is based on the continuous development of high-throughput, high-content investigation strategies (proteomics, functional genomics, bioinformatics, and molecular screening).

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Former participation in an FP European project?	☒ YES ☐ NO
Project title / Acronym:	H2020 – Orchid (CSA) H2020 – NewDeal
Activities performed:	

Expertise / Commitment offered

Description of your expertise:

BIOMICS (Bioengineering and Microphysiological systems for Pancreatic Diseases)

Scientific context

BIOMICS uses the potential of microphysiological systems and microfluidic to characterize molecular determinants, which control the balance between proliferation and differentiation in the course of development and carcinogenesis in pancreatic diseases. More specifically, we used large scale biology approaches (RNAi-based high content and high throughput screening) on human cells grown in 3D (organoids, tumoroids, spheroids and organoids on chip) to characterize new early diagnostic biomarkers and therapeutic targets in pancreatic cancer as well as new prognostic biomarkers in diabetes.

Highlights

The BIOMICS team has developed an internationally recognized expertise in the generation and characterization of pathological organoids, patient-derived organoids as well as organoids-on-chip. This research has been carried out in close collaboration with technologists (CEA/LETI/DTIS) to optimize the relevance of the microphysiological systems used and to enable a better understanding of molecular mechanism at work in cancer and diabetes. Thus, we demonstrated the importance of incorporating blood vessel organoids (BVO) generated from human induced pluripotent stem cells (iPSC) into a serpentine microfluidic architecture that offers multiple advantages over traditional microvascular network platforms. Using this unique design and readily translatable materials, we were able to grow endothelial networks on-chip, which not only arborized the organoids but, most importantly, also connected them functionally. The device we have developed offers the flexibility to vascularize and perfuse other types of pre-endothelialized organoids, spheroids, tumoroids, or even human tissue explants to create *ex vivo* culture conditions that mimic the *in vivo* state (Biosens Bioelectron. 2022; Nature Comm 2024). We developed self-organized 3D human BVOs from human iPSC, composed of both endothelial and mural cells. BVO recapitulate key features of human microvasculature such as formation of vascular network, vascular lumen and basement membrane, and have been shown to be perfusable. We have

developed a new strategy to construct prevascularized islets of Langerhans by fusion of the islets with iPSC-derived BVOs. We have demonstrated that islets and BVOs in co-culture lead to fusion and improved insulin secretion over time, suggesting a new therapeutic approach for pancreatic islet transplantation and type 1 diabetes modelling.

Current project in relation to IHI

Islet transplantation represents one of the recent therapeutic breakthroughs in type 1 diabetes (T1D). However, there is a clear clinical need to improve the survival of transplanted islets and to anticipate potential immune rejection. Moreover, hiPSC-derived Langheranoids offer new perspectives in this context.
We currently developthe following projects:

- Studying the physiological determinants that impact survival and function of pancreatic islet after transplantation

The current understanding of acute islet graft failure involves pretransplantation storage conditions, inflammatory processes and hypoxia. Oxygen culture conditions is one of them. We currently study the involvement of circulating monocytes in the instant blood mediated inflammatory reaction (IBMIR). Indeed, we have revealed recently an underestimated link between oxygen environment and monocyte inflammatory response. We want to benefit from this link to transfer oxygen to monocytes to dampen their inflammatory response. This strategy is based on the use of oxygen bubble stabilization using a polymeric shell (patent 2025 EP25305027.2). After the acute phase of potential failure, the main problem is the development of alloreactivity against the graft. This immune rejection is difficult to predict before destruction of the graft and makes immunosuppressive treatment adjustment difficult to anticipate. We currently use islet on chip, from frozen islets before transplantation, to test the alloreactivity of patients at different time points to demonstrate the possibility to detect reactive T lymphocytes before rejection and initiate immune treatment adaptation in a timely course. The involvement of the innate immune system in this process is part of our analysis scope.

- Developing strategies to increase maturation and survival of pancreatic islets

The demonstration that vascularization of organoids is capable of restoring physiological conditions (Nat Comm 2024) offers the possibility of exploiting this state to optimize islet survival *in vitro*. Another area of interest for the team is the development of hiPSC-derived Langerhanoids capable of restoring the complexity of real islets as a promising source of potential autologous grafts. The study of the vascularization of a Langerhanoid on chip and its impact on their maturation is under scrutiny.

- Role of innate immune cells in pancreatic islet organization

The two previous goals raise the question of the role of surrounding cells in the survival and maturation of hiPSC-derived pancreatic islets or mature islets from donors. We currently investigate the role of macrophages in the maturation and vascularization of these organoids and study how modulation of the macrophage state of activation could influence the resulting development of the islet. In

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	this part, we will explore the possibility to use iPSC-derived monocytes and macrophages to decipher the molecular determinants (using CRISPR-Cas9 strategies) involved in macrophage-mediated maturation of pancreatic islets. References Quintard C, et al. A microfluidic platform integrating functional vascularized organoids-on-chip. Nat Commun. 2024 Feb 16;15(1):1452. doi: 10.1038/s41467-024-45710-4. Quintard CC, et al. Microfluidic device integrating a network of hyper-elastic valves for automated glucose stimulation and insulin secretion collection from a single pancreatic islet. Biosens Bioelectron. 2022 Apr 15;202:113967. doi: 10.1016/j.bios.2022.113967
Keywords specifying your expertise:	Pancreatic islet maturation iPSC-derived pancreatic islet Organ and organoid on chip Innate immunity Inflammation Targeted therapies

Commitment offered:

☒ Research ☐ Demonstration ☐ Training
☐ Technology ☐ Dissemination ☐ Other:

Interested in participation in project types:

☒ Research & Innovation Action	☐ Innovation Action	☐ SME Instrument

Work Programme research areas: indicate your interest

We are interested in the Horizon-JU-IHI-2025-11-04 two stages "Leveraging Europe'sExerptise to accelerate cell therapy for T1D" and particularly in the objective related to enhancing graft survival and immune tolerance

Call topic(s): Topic 4 : **Leveraging Europe's Exerptise to accelerate cell therapy for T1D**

Do you have other partners for this topic (which partners/country)?

Current partners on this topic:
Françoise Carlotti (Leyden University Medical Center).
Raphael Scharfmann (Cochin Institute Paris, France).
Cédric Chauvierre (LVTS, Paris, France).

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HNN 2.0
HEALTH-NCP-NET

Profile of partner sought

Role	☒ technology development	☒ research	☐ training
	☐ dissemination	☐ demonstration	☐ other _____
Country /region	☐		
Expertise required	We are open to join a consortium needing our expertise.		

I agree with the publication of this document and my contact data: ☒ YES ☐ NO