frontiers | Frontiers in Chemical Engineering

TYPE Editorial
PUBLISHED 09 February 2024
DOI 10.3389/fceng.2024.1376921

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OPEN ACCESS

EDITED AND REVIEWED BY
Shang-Tian Yang,
The Ohio State University, United States

*CORRESPONDENCE
Federica Michielin,
f.michielin@ucl.ac.uk
Luca Urbani,
luca.urbani@researchinliver.org.uk
Camilla Luni,
camilla.luni@unibo.it
Onelia Gagliano,
onelia.gagliano@unipd.it

RECEIVED 26 January 2024
ACCEPTED 31 January 2024
PUBLISHED 09 February 2024

CITATION
Michielin F, Urbani L, Luni C and Gagliano O (2024), Editorial: 3D-engineered organoids for modelling tissue development and precision medicine.
Front. Chem. Eng. 6:1376921.
doi: 10.3389/fceng.2024.1376921

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Editorial: 3D-engineered organoids for modelling tissue development and precision medicine

Federica Michielin[1]*, Luca Urbani[2,3]*, Camilla Luni[4]* and Onelia Gagliano[5,6]*

[1]Great Ormond Street Institute of Child Health, University College London, London, United Kingdom, [2]Roger Williams Institute of Hepatology, Foundation for Liver Research, London, United Kingdom, [3]Faculty of Life Sciences and Medicine, King's College London, London, United Kingdom, [4]Department of Civil, Chemical, Environmental and Materials Engineering (DICAM), University of Bologna, Bologna, Italy, [5]Department of Industrial Engineering (DII), University of Padova, Padova, Italy, [6]Venetian Institute of Molecular Medicine (VIMM), Padua, Italy

KEYWORDS

engineered organoids, 3D tissue modeling, microtechnologies, engineered scaffolds, stem cells

Editorial on the Research Topic
3D-engineered organoids for modelling tissue development and precision medicine

Organoids are small, self-organized three-dimensional (3D) tissue cultures that reproduce organ structure and function, allowing to mimic physiological and pathological conditions and critical functions of organs. These features enable establishing a simplified, scalable, and accessible approach to address the human tissue availability constraints and the gap between animal models and patients.

For this reason, organoid research has dramatically increased over the past decade, to create suitable microscale 3D tissue models that can be used for modelling human development, study disease pathophysiology and for personalized medicine.

In vitro tissue engineering enables the creation of 3D organoid-based models with even more advanced properties and structures, and with various degrees of complexity. This can be achieved, for example, by integrating different cell or organoid types (assembloids), or by using extracellular matrix (ECM) extracts for improving organoid culturing and enhancing microenvironment properties, or engineered ECM-mimicking hydrogels and scaffolds to generate tissue engineered miniaturized constructs.

By recreating many of the cell-cell and cell-matrix interactions found in native tissues, as well as by providing the proper biophysical and biochemical stimuli to cells mimicking the *in vivo* microenvironment, these complex 3D cultures provide more physiologically accurate models than traditional 2D, monolayer or spheroid cultures, making them an attractive replacement for or addition to animal models in drug development and testing by pharmaceutical companies.

The goal of this Research Topic titled "*3D-Engineered Organoids for Modelling Tissue Development and Precision Medicine*" is to disseminate critical review on the state-of-the art

and original research articles on emerging approaches to develop innovative 3D-engineered organoid models.

Lampart et al. provide a comprehensive review on the advancement of organoid models starting from the most common 3D systems to cover more complex, multilayered 3D structures, such as assembloids, gastruloids and ETiX embryoids. Authors highlight the potential of these complex 3D systems for disease modelling, particularly in the context of cancer, by using both patient-derived cells or genetic manipulation tools to recapitulate tumorigenesis *in vitro*.

They also highlight developments in high-throughput organoid culturing systems and analysis tools to take full advantage or organoid accessible model, providing examples of culture alternatives to make them compatible with liquid-handling robots, and high-content screening, through the development of automated pipelines for image-based and omic-based analyses. They also summarize the potential of machine learning and computational modelling to process large multidimensional datasets obtained from the high-content screening, including the automated processing of imaging data.

The two other reviews presented next cover more specific aspects on lung organoids and organoids of the gastrointestinal tract.

The lung is a complex organ exposed to significant mechanical loads since fetal development. Recapitulating these stimuli *in vitro* is key to fully understand disease pathogenesis and identify therapeutical targets for lung regeneration. In this context, Shao et al. showcase the potential of lung organoids as a platform to investigate the underappreciated impact of biophysical and biomechanical properties in enhancing lung organoid complexity and functionality, and ultimately provide new insight into embryonic lung development and pulmonary distal disease pathogenesis. Technological solutions to improve functionality include the use of microfluidics, and scaffolds derived from decellularized lungs of animal or human origin that maintain the *in vivo* architecture of the lung ECM, which is significantly altered in many chronic lung diseases.

Along the same line, Benedetti et al. provide a review on the progresses in human organoid engineering applied to the gastrointestinal tract (esophagus, stomach, and intestine). They present an overview of the advances of tissue engineering in animal systems, concerning novel materials and scaffolds to be combined with a variety of cell types to reconstitute a viable surrogate for implantation, while providing biophysical and biochemical stimuli relevant to these organs. Specifically, they discuss the engineering details for developing esophagus, stomach, and intestine organoids and tissue-engineered constructs. They cover aspects related to cell genetic engineering, niche modifications, which span from medium composition to ECM composition, and microarchitecture bioprinting, as well as the advancements made in microfluidic devices and organ-on-a-chip systems.

Lastly, in an original research article, Decoene et al. report the development of an engineered model of bone-forming callus organoids amenable to industrial scale-up and automation, which also facilitates the implementation of non-invasive imaging and the use of quality control parameters based on secreted biomarkers. They perform an in-depth comparison of transcriptional changes during *in vitro* differentiation of human periosteum–derived cell (hPDCs) aggregates into cartilaginous microtissues cultured in a standard medium *versus* a xeno-free equivalent medium. They highlight an increased microtissue homogeneity with no uncontrolled fusion of microtissues, that might affect the diffusion of oxygen, nutrients, and growth factors leading to a reduced quality profile of the implant as an end tissue product. In addition, they assessed the bone-forming potential of these microtissues assembled into larger meso-tissues structures ectopically *in vivo*.

In summary, this Research Topic comprises both novel research and review articles relating to the most recent advances in human physiopathologically-relevant *in vitro* modelling systems. A common factor highlighted in the contributed works is the complementarity between the cell culture system itself and the supportive technologies around it, both experimental and computational.

Author contributions

FM: Writing–original draft. LU: Writing–review and editing. CL: Writing–review and editing. OG: Writing–review and editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

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