Microphysiological systems for modelling microvasculature and multicellular-vascular interactions using microfluidic technology

Microphysiological systems for modelling microvasculature and multicellular-vascular interactions using microfluidic technology

Marco Campisi[1,2], Tatsuya Osaki[3,4], Sarah Shelton[2,5], Shriram Sundararaman[2,6], Sharon Wei Ling Lee[7,8], Clara Mattu[1], Giulia Adriani[9], Claudia Voena[10], Ines Mota[11], Enrico Patrucco[12], Shunsuke Kitajima[2,13], Roberto Chiarle[11,12], David A. Barbie[2], Roger D. Kamm[3], Valeria Chiono[1]

[1] Department of Mechanical and Aerospace Engineering, Politecnico di Torino, Turin, Italy

[2] Department of Medical Oncology, Dana–Farber Cancer Institute, Boston, MA, United States

[3] Department of Mechanical Engineering, Massachusetts Institute of Technology, Cambridge, MA, United States

[4] Institute of Industrial Science, The University of Tokyo, Tokyo, Japan

[5] Department of Biological Engineering, Massachusetts Institute of Technology, Cambridge, MA, United States

[6] University of Virginia School of Medicine, University of Virginia, Charlottesville, VA, United States

[7] Singapore-MIT Alliance for Research & Technology, BioSystems and Micromechanics, Singapore, Singapore

[8] Department of Microbiology and Immunology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore

[9] Department of Biomedical Engineering, Faculty of Engineering, National University of Singapore

[10] Department of Molecular Biotechnology and Health Sciences, University of Turin

11 Boston Children's Hospital - Harvard Medical School

[12] Dept. Biomedical Sciences and Human Oncology University of Turin

[13] Department of Cell Biology, Cancer Institute, Japanese Foundation for Cancer Research, Tokyo, Japan

[14] Belfer Center for Applied Cancer Science, Dana-Farber Cancer Institute, Boston, MA, United States

The recent application of microfluidic technologies in bioengineering has driven considerable progress in the design of 3D tissues on chips, which offer the possibility to improve preclinical experimentation with respect to traditional 2D culture systems, in agreement with the 3Rs principle. Commonly referred to as microphysiological systems, such biomimetic *in vitro* models replicate the *in vivo* tissue-specific microenvironments making use of human induced pluripotent stem cells (iPS) or primary cells embedded in extracellular matrix (ECM)-like hydrogel.

Here, we introduce the design of bio-inspired 3D microphysiological models of the human Blood-Brain barrier, KRAS/LKB1 lung tumor microenvironment and ALK-positive Anaplastic Large Cell Lymphoma (ALCL) as models of multicellular-vascular interactions in a microfluidic device. These models have in common an advanced perfusable microvasculature, developed by different strategies, self-assembled vasculogenesis, or cell culture in 3D macrovessel, and supported by cell-cell dynamic contact interactions and continuous secretion of signaling factors. The BBB model, which used iPS-derived cells, showed increased maturation toward BBB-like structures with vascular permeability lower than conventional *in vitro* systems, and it was used to test transport of innovative carriers, such as polymer nanoparticles. With the advent of immunotherapies, the lung tumor-microvascular model was critical to understand the biology of immune cell recruitment and exclusion to the lung microenvironment. The ALCL model was exploited to unveil a molecular mechanism of tumor drug resistance. These robust and physiologically-relevant models have the potential to revolutionize prognosis and therapy, predict more reliable therapeutic vulnerabilities and study the transport of drugs across barriers, thereby accelerating drug discovery, and improving understanding of several currently incurable diseases.