Milica Radisic

Dr. Milica Radisic is a Professor at the University of Toronto, Canada Research Chair in Functional Cardiovascular Tissue Engineering and a Senior Scientist at the Toronto General Research Institute. She is also the Associate Chair-Research for the Department of Chemical Engineering and Applied Chemistry at the University of Toronto, Director of the NSERC CREATE Training Program in Organ-on-a-Chip Engineering & Entrepreneurship and Director of Ontario-Quebec Center for Organ-on-a-Cho Engineering.

She obtained B.Eng. from McMaster University, and Ph.D. form the Massachusetts Institute of Technology. She is a Fellow of the Royal Society of Canada-Academy of Science, Canadian Academy of Engineering, the American Institute for Medical & Biological Engineering and Tissue Engineering & Regenerative Medicine Society.

She received numerous awards and fellowships, including MIT Technology Review Top 35 Innovators under 35. She was a recipient of the Professional Engineers Ontario-Young Engineer Medal in 2011, Engineers Canada Young Engineer Achievement Award in 2012, Queen Elizabeth II Diamond Jubilee Medal in 2013, NSERC E.W.R Steacie Fellowship in 2014, YWC Toronto Woman of Distinction Award in 2018, and OPEA Research & Development Medal in 2019 to name a few.

Her research focuses on organ-on-a-chip engineering and development of new biomaterials that promote healing and attenuate scarring. She developed new methods to mature iPSC derived cardiac tissues using electrical stimulation. Currently, she holds research funding from CIHR, NSERC, CFI, ORF, NIH, and the Heart and Stroke Foundation. She is an Associate Editor for ACS Biomaterials Science & Engineering, a member of the Editorial Board of Tissue Engineering, Advanced Drug Delivery Reviews, Regenerative Biomaterials, Advanced Biosystems, Journal of Molecular and Cellular Cardiology and eLife. She serves on review panels for Canadian Institutes of Health Research and the National Institutes of Health. She is actively involved with BMES (Cardiovascular Track Chair in 2013 and 2104) and TERMIS-AM (Council member, Chair of the Membership Committee). She was a co-organizer of a 2017 Keystone Symposium, “Engineered Cells and Tissues as Platforms for Discovery and Therapy”. She served on the Board of Directors for Ontario Society of Professional Engineers and currently serves on the Board of Directors of Canadian Biomaterials Society.

Her research findings were presented in over 200 research papers, reviews and book chapters with h-index of 60 and over 12,000 citations. Her publications appear in prestigious journals such as: Cell, Nature Materials, Nature Methods, Nature Protocols, Nature Communications, PNAS etc. In 2014, she co-founded an award winning company TARA Biosystems that uses matured human engineered heart tissues in drug development. TARA currently tests drugs for major pharmaceutical companies. In 2017, she founded Quthero Inc, a company focused on disrupting the skin regeneration and wound healing market through the use of proprietary Q-gel to promote scar-free wound healing.

Recapitulating pancreatic tumor microenvironment through synergistic use of patient organoids and organ-on-a-chip vasculature

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the most common form of pancreatic cancer and has poor survival rates, with an average of 8% in a 5-year survival rate [1]. The poor prognosis of PDAC is due to a notably complex microenvironment that complicates treatment. In this heterogeneous microenvironment, the intercellular interactions between different stromal cells, normal epithelial cells, and neoplastic epithelial cells become disoriented to accommodate reorganization into a tumorigenic niche. This cell cross-talk affects stromal development and tumor progression, and ultimately the heterogeneity impacts drug efflux and efficacy.

Experimental procedure

To mimic this evolving paradigm, we have micro-engineered a three-dimensional (3D) vascularized pancreatic adenocarcinoma tissue in a tri-culture system composed of patient derived pancreatic organoids, primary human fibroblasts and endothelial cells on a perfusable InVADE platform situated in a 96-well plate. Uniquely, through synergistic engineering we combined the benefits of cellular fidelity of patient tumor derived organoids with the addressability of a plastic organ-on-a-chip platform.

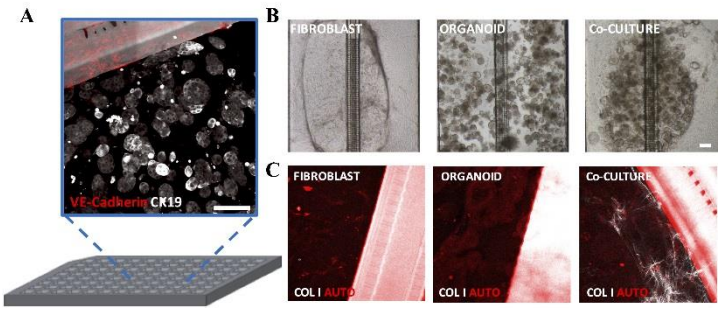

*Figure: **A,** A vascularized 3D pancreatic tumor tissue on a perfusable organ-on-a-chip platform (red, VE-cadherin; white, CK19; scale bar 100µm) **B,** Bright-field images of remodeling tissues on Day 8 (scale bar 200µm). **C,** Second Harmonic Generation images capturing the co-culture of tumor organoids with fibroblasts potentiated pro-fibrotic changes in comparison to monoculture controls (white, new thick fibrillar collagen type I deposited in stromal microenvironment)*

Results and Discussion

Validation of this platform included demonstrating the growth of pancreatic tumor organoids by monitoring the change in metabolic activity of the tissue. Investigation of tumor microenvironmental behavior highlighted the role of fibroblasts in symbiosis with patient organoid cells, resulting in a six-fold increase of collagen deposition, higher level of fibrotic-related cytokine (IL-6) and chemokine (MCP-1) detected in the tumor microenvironment and a corresponding increase in tissue stiffness in

comparison to fibroblast free controls. The value of a perfusable vascular network was evident in drug screening, as perfusion of gemcitabine into a stiffened matrix did not show the dose-dependent effects on tumor viability as those under static conditions.

Conclusion

These findings demonstrate the importance of studying the dynamic synergistic relationship between patient cells with stromal fibroblasts, in a 3D perfused vascular network, to accurately understand and recapitulate the tumor microenvironment.

References

[1] R.L. Siegel, K.D. Miller, A. Jemal, CA Cancer Clinc, **66** (2016).