SOOC · 2021

The 4th Symposium on Organoids and Organs-on-chips

11th-12th December 2021

PROCEEDINGS

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Welcome to SOOC 2021!

The 4th Symposium on Organoids and Organs-on-Chips will be held in Hainan on Dec. 10th-12th, 2021, cohosted by Southeast University, Hainan University, and Columbia University. Experts, scholars, and entrepreneurs engaged in the research and applications of organs-on-chips, organoids, tissue engineering, biomedical big data, and other related fields are sincerely invited. This symposium aims to provide a platform for the integration of biomedical engineering industry, education, and research among universities, research institutions, and enterprises, so as to jointly promote the research and industrial development of organs-onchips in China to reach a new milestone. So far, past symposiums have invited presentations from renowned experts in the fields of organs-on-chips and tissue engineering such as Prof. David Weitz, Prof. Danilo Tagle, Prof. Kam Leong, Prof. Michael Shuler, Prof. Marcus Textor, Prof. Kaiming Ye, and Prof. Zhongze Gu, among others. Scholars, representatives of relevant enterprises, and graduate students engaged in biomedical engineering research are sincerely welcomed to contribute and participate in this year's symposium. We look forward to seeing you in Haikou, Hainan on Dec. 10th-12th.

Conference Chairs:



Prof. Zhongze Gu Southeast University, China



Prof. Kam W. Leong Columbia University, USA



Prof. Qingming Luo Hainan University, China



Prof. Kaiming Ye SUNY at Binghamton, USA

Keynote Speakers:



Prof. Marcus Textor ETH Zurich, Switzerland



Prof. Kevin E. Healy University of California, Berkeley



Prof. Qingming Luo Hainan University, China



Prof. Kam W. Leong Columbia University, USA



Prof. Zhongze Gu Southeast University, China



Prof. Wei Sun Tsinghua University, China



Prof. Adrian Roth F. Hoffmann-La Roche Ltd., Switzerland



Prof. Yasuyuki SAKAI University of Tokyo, Japan



Prof. Ji anzhong Jeff Xi Peking University, China



Prof. János Vörös ETH Zurich, Switzerland



Prof. Patricia Y.W. Dankers Eindhoven University of Technology, the Netherlands



Prof. Wei Wang Peking University, China



Prof. Danilo Tagle National Institutes of Health, USA



Prof. Gordana Vunjak-Novakovic Columbia University, USA



Prof. Christopher S. Chen Boston University, Harvard University, USA



Prof. Xinhua Lin Fudan University, China



Prof. Kaiming Ye SUNY at Binghamton, USA



Prof. Y. Shrike Zhang Harvard Medical School, USA



Prof. Rio Sugimura University of Hong Kong, China

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Program for the 4th Symposium on Organoids

and Organs-on-Chips

	Friday, Dec. 10, 2021
14:00~22:00	Registration (The 1st floor of International Academic Exchange Center Hainan University)
	Saturday, Dec. 11, 2021 Hexun Hall
8:30~9:00	Opening Ceremony (Zhongze Gu, Kam W. Leong, Qingming Luo, Marcus Textor)
Keynote Speaker	Session Chair: Xinghua Xia (Nanjing University)
9:00~9:30	Kevin E. Healy (University of California, Berkeley, USA) Microphysiological systems as testbeds spanning drug discovery to organ preservation
9:30~10:00	Qingming Luo (Hainan University, China) Optical Imaging for Brain-wide Mesoscopic Connectome
10:00~10:30	Tea Break & Take Photos
Keynote Speaker	Session Chair: Dan Zhu (Huazhong University of Science and Technology)
10:30~11:00	Kam W. Leong (Columbia University, USA) Response of iPSC-derived Midbrain Organoids to Opioid Exposure
11:00~11:30	Zhongze Gu (Southeast University, China)The Fabrication and Measurement of Organ-on-a-Chip for the Substitution of AnimalTests
11:30~12:00	Wei Sun (Tsinghua University, China) Bioprinting Tumoriods and Organ Chips for Drug Testing
11:30~12:00	Lunch (Hexi Hall)
Keynote Speaker	Session Chair: Xingyu Jiang (Southern University of Science and Technology)
14:00~14:30	Adrian Roth (F. Hoffmann-La Roche Ltd., Switzerland)Novel human cell models in drug development:How 3D, Organoids & Organs on Chips can improve and renew current paths - and ourvision for the future
14:30~15:00	Yasuyuki Sakai (University of Tokyo, Japan)Use of an oxygen-permeable membrane in advanced in vitro tissue models both in staticmicroplate and perfused microphysiolgical systems

15:00~15:30	Jianzhong Xi (Peking University, China) Mini-Tumour Chip as a Robust Tool for Precision Cancer Therapy
15:30~16:00	Tea Break
Keynote Speaker	Session Chair: Wei Xie (Southeast University)
16:00~16:30	Janos Vörös (ETH Zurich, Switzerland)
	Starting bottom-up neuroscience with small "brains" on a chip
16:30~17:00	Patricia Dankers (Eindhoven University of Technology, the Netherlands)
	Engineering the Dynamics of Cell Adhesion Cues in Supramolecular Hydrogels for
	Facile Control over Cell Encapsulation and Behavior
17:00~17:30	Wei Wang (Peking University, China)
	Flexible filter based liquid biopsy
18:00~20:00	Dinner
	(Hexi Hall)
	Sunday, Dec. 12, 2021
	(Hexun Hall)
Keynote Speaker	Session Chair: Chunxiang Xu (Southeast University)
8:00~8:30	Danilo A. Tagle (National Institutes of Health, USA)
	The NIH Microphyiological Systems program: In Vitro 3D Models for Safety and
	Efficacy Studies
0.20 0.00	Gordana Vunjak-Novakovic (Columbia University, USA)
8:30~9:00	Integrated human multi-organ platforms for modeling systemic pathologies
9:00~9:30	Christopher S. Chen (Boston University, Harvard University, USA)
	Next-Generation Culture Models of Cardiovascular Physiology and Diseas
	Xinhua Lin (Fudan University, China)
9:30~10:00	The Application and Prospect of Organoids in Biological Research and Precision
	Medicine
10:00~10:30	Kaiming Ye (State University of New York at Binghamton, USA)
	Human Islet Organoid Development and Angiopoietin Signaling Pathways
10:30~11:00	Yu Shrike Zhang (Harvard Medical School, USA)
	Integrative Biofabrication Technologies for High-Content Modeling of Human Tissues
	and Diseases in vitro
11:00~11:30	Rio Sugimura (University of Hong Kong, China)
	The application of vascular immune organoids from human pluripotent stem cells in
	cancer immunotherapy and SARS-CoV-2 modeling
12:00~14:00	Lunch
	(Hexi Hall)

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Microphysiological systems as testbeds spanning drug discovery to organ preservation

Professor Kevin E. Healy Department of Bioengineering, Department of Materials Science & Engineering University of California, Berkeley, California, USA

Our work has emphasized creating both healthy and diseased human model organ systems, we call microphysiological systems (**MPS**), or 'organs on chips', to address the costly and inefficient drug discovery process. The average time to develop and launch a new drug is 10-15 years, and costs ~\$3bn USD. The poor efficiency and high failure rates are attributed to the heavy reliance on non-human animal models employed during safety and efficacy testing that poorly reflect human disease states. With the discovery of human induced pluripotent stem cells (**hiPSC**), we can now develop MPS to be used for high content drug screening, disease modelling, and numerous other applications.

By combining the genetic background of hiPSC with microfabrication technologies, we can create MPS with appropriate biophysical tissue architecture and "tissue-like" drug gradients that recapitulate minimal human organoids sufficiently to allow accurate prediction of the toxicity of drugs and environmental toxins. The benefits of our approach include: 1) robust microengineering platforms that control microtissue organization and function; 2) precise delivery of molecules (e.g., drugs) in a computationally predictable manner; 3) ability to model human disease; 4) cost efficient and high content characterization of an integrated multi-organ drug response; and, 5) reduction in use and refinement of animal experiments.

While organ chips are poised to disrupt the drug development process and significantly reduce the cost of bringing a new drug candidate to market, organ chip technology is much more robust and creates a whole new paradigm in how to conduct biological science, and advances medicine in revolutionary ways. This presentation will discuss our progress in developing integrated *in vitro* models of human cardiac and liver tissue based on populations of normal and patient specific hiPSCs differentiated into cardiomyocytes, hepatocytes, and supporting cells for drug screening, including COVID-19 therapeutics. In addition, the presentation will address the emerging use of microphysiological systems as unique testbeds for organ preservation, biomaterials development, and gene editing, and environmental toxicology.



Kevin E. Healy, Ph.D. is the Jan Fandrianto and Selfia Halim Distinguished Professor in Engineering at the University of California at Berkeley in the Departments of Bioengineering, and Materials Science and Engineering. He is a thought leader and innovator working at the interface between stem cells and materials science to develop dynamic engineered systems to explore both fundamental biological phenomena and new applications in translational medicine. His group currently conducts research in the areas of: bioinspired stem cell microenvironments to control stem cell lineage specification and self- organization into microtissues or organoids; bioinspired systems for regenerative medicine; biological interfaces; and, microphysiological systems for drug development, gene editing, and environmental toxicity screening. Professor Healy is an elected Fellow of AIMBE, AAAS, FBSE, BMES, and a recipient of an Alexander von Humboldt Foundation Award. He is a named inventor on numerous issued United States and international patents relating to biomaterials, therapeutics, stem cells, and medical devices, and has founded several companies to develop these systems for applications in biotechnology and regenerative medicine.

Optical Imaging for Brain-wide Mesoscopic Connectome

Qingming Luo

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The brain is the most complex and significant organ, but little is known regarding to the mechanisms of its function, which is related to brain anatomy. Conventional anatomical methods based on brain slices fail to reconstruct the neural projection in axial direction at single-cell resolution. To solve the problem, my lab has spent more than ten years developing Brain-wide Positioning System (BPS), a novel solution combining microscopic optical imaging and physical sectioning to obtain the tomographic information of a whole brain with sub-micron voxel resolution. BPS includes several generations such as Micro-Optical Sectioning Tomography (MOST) and several types of fluorescence MOST (fMOST). In this talk, I will introduce the principles of BPS and demonstrate how to locate and visualize the labelled neurons and neuronal networks in the whole brain. The pipeline includes whole-brain sample preparation, whole-brain optical imaging, and massive brain image processing and analyzation. BPS may play a crucial role and usher in a new era of Brainsmatics. Brainsmatics refers to the integrated, systematic approaches of measuring, analyzing, managing, and displaying brain spatial data, including but not limited to the concepts of digital mapping and visualization of the brain neuronal/vascular networks, brain atlas, brain connectome and projectome, brainnetome, neuroinformatics, and neuroimaging. Brainsmatics will provide comprehensive and systematic information to understand the brain, defeat the brain disease, and develop the brain-inspired intelligence.



Dr. Luo's research interests focus on multi-scale optical bioimaging and crosslevel information integration. He forged a new discipline Brainsmatics. His team created "the most detailed three-dimensional map of all the connections between the neurons in a complete mouse brain" and "demonstrated the first long-range tracing of individual axons in the mouse brain" with their homemade Brain-wide Positioning Systems (BPS). He is an elected Member of Chinese Academy of Sciences (CAS), Chinese Academy of Medical Sciences (CAMS), elected Fellow of The International Academy of Medical and Biological Engineering (IAMBE), The American Institute for Medical and

Biological Engineering (AIMBE), The International Society for Optics and Photonics (SPIE), The Institution of Engineering and Technology (IET), The Optical Society (OSA) and Chinese Optical Society (COS). With his leading contributions, the Biomedical Engineering in HUST was rated A+ in the latest 4th round of China Discipline Ranking. Dr. Luo is the elected Chair of Biomedical Engineering Steering Committee for Guidance in Teaching in Higher Educations Institutions 2018-2022 appointed by MoE.

Response of iPSC-derived Midbrain Organoids to Opioid Exposure

Hye Sung Kim, Yang Xiao, Bin Xu¹, and Kam W. Leong*

Kam W Leong Samuel Y Sheng Professor Department of Biomedical Engineering ¹Department of Psychiatry Columbia University, New York, NY 10032 <u>kam.leong@columbia.edu</u>

Understanding the impact of long-term opioid exposure on the embryonic brain is critical due to the surging number of pregnant mothers with opioid dependency, but has been limited by human brain inaccessibility and cross-species differences in animal models. Here we establish a human midbrain model that uses hiPSC-derived midbrain organoids and apply it to assess cell-type-specific responses to acute and chronic fentanyl treatment and fentanyl withdrawal. Single-cell mRNA sequencing indicates that chronic fentanyl treatment arrests neuronal subtype specification during early midbrain development and alters synaptic activity and neuron projection. In contrast, acute fentanyl treatment increases dopamine release but does not significantly alter gene expression related to cell lineage development. These results provide the first examination of the effects of opioid exposure on human midbrain development at the single-cell level.



Kam W. Leong is the Samuel Y. Sheng Professor of Biomedical Engineering at Columbia University. He received his PhD in Chemical Engineering from the University of Pennsylvania. After serving as a faculty in the Department of Biomedical Engineering at The Johns Hopkins School of Medicine and the Duke University for 20 and 8 years, respectively, he moved to Columbia University in 2014, where he focuses on three major research directions: 1) Nonviral gene editing *in vivo*; 2) Biomaterials-assisted modulation of inflammation; 3) Human-

tissue chips for disease modeling and drug screening. He has published ~450 peer-reviewed with an hindex of 126 and holds more than 60 issued patents. He is the Editor-in-Chief of *Biomaterials*, a member of the USA National Academy of Inventors, the USA National Academy of Engineering, and the USA National Academy of Medicine.

The Fabrication and Measurement of Organ-on-a-Chip for the Substitution of Animal Tests

Zhongze Gu^{1,2}

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Organ-on-a-chip (OOC) system, or microphysiological system (MPS), is a new type of biomedical research method that aims to recapitulate organ-level tissue structures and functions for drug evaluation and disease modeling. The MPS can be used to simulate the microstructure, microenvironment, and functional features of human organs, and applied in drug screening and clinical diagnosis and treatment. In previous studies, we have developed multiple organ-on-a-chip systems including biomimetic blood vessels, kidney, liver, heart, etc^[1-2]. Our previous work demonstrated that the miniature organs made with advanced microfabrication, 3D printing, microfluidics and tissue engineering techniques could form tissue-specific structures and could maintain some desirable organ functions for drug screening and disease modeling purposes^[3-7].

In this presentation, we report the development of a two-photon/multi-photon based 3D printing systems for the OOC fabrication and microenvironment formation, and the fabrication of multiple microphysiological systems for disease modeling, and the development of an automated high-content organs-on-a-chip imaging system for automated drug screening together with deep-learning based AI-algorisms for data analysis. The systems that we reported here have been widely applied in drug discovery and toxicity evaluation in collaboration with top-tier pharmaceutical companies in China, and have been used for precision medicine in collaboration with top-tier hospitals. We also report the design and development of a functional Lung-on-a-Chip system for lung bacterial/viral infection, inflammation studies. Lastly, our system and platform have been successfully applied in Covid-19 and other virus infectiousness evaluation, testing of efficacy for drug, neutralizing antibodies (including vaccines from Pfizer, BioNTech, etc.), and other protective measures. In summary, our work demonstrated the usefulness and progressive applications of OOC in multidisciplinary fields in China.

References:

[1] Zheng F, Fu F, Cheng Y, et al. Organ-on-a-Chip Systems: microengineering to biomimic living systems. *Small*, 2016, 12(17): 2253-2282.

[2] Zheng F, Cheng Y, Wang J, et al. Aptamer-Functionalized Barcode Particles for the Capture and Detection of Multiple Types of Circulating Tumor Cells. *Advanced materials*, 2014, 26(43): 7333-7338.

[3] Chen Z, Ma N, Sun X, et al. Automated evaluation of tumor spheroid behavior in 3D culture using deep learning-based recognition. *Biomaterials*, 2021, 272: 120770.

[4] Zhang J, Chen Z, Zhang Y, et al. Construction of a high fidelity epidermis-on-a-chip for scalable in vitro irritation evaluation. *Lab on a Chip*, 2021, 21(19): 3804-3818.

[5] Liu X, Gu H, Wang M, et al. 3D printing of bioinspired liquid superrepellent structures. *Advanced Materials*, 2018, 30(22): 1800103.

[6] Zhao Z, Wang H, Shang L, et al. Bioinspired heterogeneous structural color stripes from capillaries. *Advanced Materials*, 2017, 29(46): 1704569.

[7] Sun L, Gu H, Liu X, et al. 3D-printed cellular tips for tuning fork atomic force microscopy in shear mode. *Nature communications*, 2020, 11(1): 1-12.



Zhongze Gu is a Changjiang Scholar, a winner of the National Science Fund for Distinguished Young Scholars, an elected fellow of American Institute for Medical and Biological Engineering (AIMBE) and Royal Chemical Society (RSC), an honorary professor of East Anglia University (UK), a guest professor of Tokyo University of Science. He received his B.S. degree and M.S. degree from the Department of Biomedical Engineering of Southeast University. He obtained Ph.D. from the Department of Applied Chemistry of The University of Tokyo in 1998 and returned to southeast University as a professor in 2002.

He is currently the dean of the School of Biological Science and Medical Engineering of Southeast University, and the director of the Institute of Biomaterials and Medical Devices of JITRI. He used to be a researcher of Kanagawa Institute of Science and Technology in Japan, and the director of State Key Laboratory of Bioelectronics. He is also the vice director of the National Advisory Committee on Biomedical Engineering Programs, Ministry of Education of China, a member of the Evaluation Committee of Biomedical Engineering, Academic Degrees Committee of the State Council of China, and a member of experts group of the National Science and Technology Major Project of China. His current research focuses on the development of human organ-on-a-chip. He has published over 300 papers with more than 15,000 citations. He was awarded the First Prize of Natural Science Award by the Ministry of Education of China and the First Prize of Science and Technology Award of Jiangsu Province. He leads multiple projects such as the Key Scientific Issues of Transformative Technologies in the National Key R&D Program of China, the National High-tech R&D Program (863 Program) of China, and the Major Program of the National Natural Science Foundation of China.

Bioprinting Tumoriods and Organ Chips for Drug Testing

Yuan Peng¹, Rui Yao¹, Ting Zhang¹, Zhuo Xiong¹, Yu Song¹, Shengli Mi², Wei Sun^{,1,3,*} ¹Departments of Mechanical Engineering, Tsinghua University, Beijing, China ²Tsinghua Graduate School – Shenzhen, Shenzhenm China ³Department of Mechanical Engineering and Mechanics, Drexel University, USA

Bioprinting uses living cells as building blocks to construct *in vitro* biological models. The printed models can be applied for regenerative medicine, disease study and drug testing. This presentation will report our preliminary work at Tsinghua Biomanufacturing Center on bioprinting cells as in vitro biological models, tumoriods and organ-on-a-chip for drug testing. Topics of presentation will cover: an overview of the field of 3D bioprinting and printing techniques, printing neural network models for studying DNQX influence, printing patient-derived cells and heterogeneous tumor assembloids as in vitro tumoroids for drug testing for cervical tumor, breast tumor, liver tumor, cholangiocarcinoma tumor and lung tumor. Some personal experience on cell printing, its challenges and lessons to learn will also be shared.



Dr. Wei Sun is a Professor and Director of Biomanufacturing Research Center, Department of Mechanical Engineering, Tsinghua University, China, and Albert Soffa Chair Professor of Mechanical Engineering, Drexel University, USA. Dr. Sun's research is on Biofabrication, 3D Bio-Printing, Computer-Aided Tissue Engineering, CAD/CAM, and Additive Manufacturing. Dr. Sun is the Founding President for International Society of Biofabrication (2010-2014), and the Founding Editor-in-Chief for Biofabrication (2009-present). Dr. Sun has published over 180+ SCI journal papers with 13,000+ SCI citations, and 48 granted patents. Dr. Sun

received Distinguished Visiting Fellow Award from the Royal Academy of Engineering in UK (2018), Visiting Professorship from Nanyang Technological University (2018-2020), the inaugural Senior Investigator Award from International Society of Biofabrication (2017), the MII / Fralin Visiting Scholar Award from Virginia Tech (2015), Outstanding Research Award, College of Engineering, Drexel University (2009), and William Mong Fellow Award, the University of Hong Kong (2008).

Novel human cell models in drug development: How 3D, Organoids & Organs on Chips can improve and renew current paths - and our vision for the future

Adrian Roth, Principal Scientific Director, PHC Safety Interface, Product Development Safety, F. Hoffmann-La Roche Ltd, CH-4070 Basel, adrian_b.roth@roche.com

Using human-relevant, translational in vitro models has been widely considered to reduce attrition during drug discovery and development. Over the past decade a considerable hype emerged regarding the transformative potential of microphysiological systems for pharmaceutical research; yet - while it is agreed that such models could bring value currently, mostly proof-of-concept studies are available and widespread application is still Thus, while acknowledging the opportunity and value such human relevant cell lacking. systems could provide, the adoption by pharma companies is moderate. Realizing the full potential of these models will need more clear use-cases demonstrating clinical translation, improvements on technical ease of use and greater collaboration between stakeholders. Furthermore, it is proposed that refining existing platforms for specific contexts of use where significant gaps exist in drug development will help broader application, rather than unrealistic claims that microphysiological systems can right away replace the complete drug discovery engine at once. Key advantages of such tissue systems over traditional pre-clinical models, e.g. the ability to mimick human-specific biology such as immunology or defined contexts of rare diseases should be further exploited to establish more use cases that demonstrate true added value. Modeling & analytics can help with back- and forward translation using real world data. Furthermore, the ability to generate patient-derived tissue models will allow personalization of treatments and support precision medicine approaches in clinical trials.



Adrian is a molecular biologist by training and since August 2020 is Principal Scientific Director of Personalized Healthcare within Roche's Clinical development organization. The focus is on bringing innovative new scientific approaches, including microphysiological systems, genetics & genomics into clinical testing with a focus on personalized, patient-centric solutions that aim to optimize the benefit/risk ratio. Before assuming this role, Adrian has been the Global Head of Roche's Investigative Safety Department within Roche's Early Research & Development organization overseeing all cell based preclinical safety support in ADME & Toxicology. He also holds a Professorship at the University of Basel, Switzerland and has authored numerous publications.

His team provided support to all therapeutic areas across all modalities using cellular tools addressing key questions in DMPK & Safety. The focus has been prioritization of drug candidates early on to allow candidate selection, de-risking of findings by mechanistic understanding in later stages, Entry-into-human enabling and providing regulatory compliant packages.

A key area of focus and strong interest of Adrian is and has been the establishment of modern human cell models such as 'Organs on Chips', Organoids or Microphysiological Systems which his team has introduced for pre-clinical safety assessment at Roche and now are planned to support also programs at the clinical stage to better understand individual safety risks, to predict outcomes and to stratify patient subgroups at risk.

Use of an oxygen-permeable membrane in advanced in vitro tissue models both in static microplate and perfused microphysiolgical systems

Yasuyuki SAKAI^{1, 2, *}, Kosuke INAMURA¹, Mathieu DANOY¹, Benedikt SCHEIDECKER¹, Hiroshi KIMURA³, Masaki NISHIKAWA¹ ¹Department of Chemical System Engineering, ²Department of Bioengineering, Graduate School of Engineering, University of Tokyo, Tokyo 113-8566, Japan ³Department of Mechanical Engineering, School of Engineering, Micro/Nano Technology Center, Tokai University, Hiratsuka 259-1292, Japan *sakaiyasu@chemsys.t.u-tokyo.ac.jp

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Toward in vitro organization of physiologically-relevant cultured tissue models, we need to integrate various pericellular microenvironments using latest technologies and knowledge; they are concerning stem cell-derived mature organ cells, 3D hierarchical organization of organ parenchymal cell, nonparenchymal cells and extracellular matrices, good oxygen/nutrient supply, wastes removal, physiological culture medium, and mechanical stimulations etc. With such fundamental problem consciousness toward ultimatly-physiological in vitro tissue models, we would like to introduce our latest investigations such as 1) new static heterogenic liver tissue culture and 2) microphysiological system (MPS) comprising liver and small intestine tissues supported by the MPS Project of Japanese Agency of Medical Research and Development (AMED). Those are both based on direct oxygenation of the cells using oxygen-permeable membranes to completely solve the unphysiological insuffient oxygen supply, which has been a historical, forgotton but still unsolved problem in current cell culture formats. Use of oxygen-permeable membrane easily resolves the problem and allows cell to show their unprecedented spontaneous oreganization, high functinality or enhanced organ-to-prgan crosstalks through in vivo-like aerobic respiration and in vivo-mimicking hierarchical 3D coculture. In paticular, 3D heterogenic multilayered tissue formed on oxygen-permeable membranes can be called as "Flat Organoid" and are better compatible with MPS perfused formats. In addition, we would like to discuss about the contributions of such advanced in vitro cell culture models towatrd understanding the systemc responses of humans.



Dr. Sakai is a professor at Department of Chemical System Engineering and Departmenmt of Bioengineering, Graduate School of Engineering, University of Tokyo (UTokyo), Japan. He received Ph.D. in chemical engineering from UTokyo in 1993 and stated his work at Institute of Industrial Science (IIS), UTokyo. In 1997-1998, he stayed in University of Rochester as a visiting scientist. In 2003-2008, he worked as an associate professor at Graduate School of Medicine, UTokyo. He returned to IIS as a professor and then moved to the current position in 2015. During his research carrier, he published more than 180 scientific article and also got several scientific awards such as young investigator award of Society of Chemical Engineers, Japan, publication awards of Society for Bioscience

and Bioengineering, Japan and Japanese Society for Alternatives to Animal Experiments. He is an AIMBE fellow from 2012 based on such activities. He is also working as the president of Japanese Siciety for Alternatives to Animal Experiments (JSAAE) for 2017-2021. His current research topics are large-scale propagation/differentiation of human iPS cells toward pancreatic β an hepatic lineages and engineering of 3D tissues/organs both for clinical applications and advanced cell-based assays such as MPS in comibation with comprehensive omics analyses and numerial simulations.

Mini-Tumour Chip as a Robust Tool for Precision Cancer Therapy

Jianzhong Jeff Xi, Professor, College of Future Technology Peking University, China, 100871 xi@coe.pku.edu.cn

Gastric and colorectal cancers are among the most frequent cancer types around the world, and clinicians often feel struggled to make treatment decisions from a dozen of available chemotherapies. Only ~30% of patients respond positively to their first assigned therapy, and clinicians can't predict correctly whether patients will benefit from the therapy. A large proportion of patients have to receive multiple expensive but ineffective treatments. More severely, those patients could lose the best treatment window in this painful trial-and-failure process. Recently, patient-derived organoids (PDOs) and xenografts (PDX) have demonstrated potential for recapitulating patient responses in clinic and are being implemented in personalized medicine programs. However, these approaches have limited value in patient management because they are not available within a time frame that is appropriate in clinical practice. Here, we report a novel personalized drug testing platform named patient-derived tumor-like cell clusters (PTCs) chip or mini-tumour chip. I will make comparision of mini-tumour chip with 3D cultures and organoids.



Jianzhong Jeff Xi received his B.S. degree in Chemical Engineering at Beijing Institute of Technology in 1996, M.S degree in Cell biology at Tsinghua University in 2000, Ph.D. degree in Biomedical Engineering at UCLA in 2004. He was the first distinguished scholar recruited with the "Plans to Introduce Young Talents" at Peking University in 2005, and he gained a number of awards and prizes, such as "New Century Excellent Talents in University" (2009), "National Science Foundation for Distinguished Young Scholars" (2013), and "Distinguished Professor of Yangtze River Scholar" (2020). Currently, he is the Vice Dean of the College of Future Technology at Peking

University. Dr. Xi is also an Associate Editor in Journal of Cellular and Molecular Medicine, and serve in five scientific societies, including vice director of Gene Diagnosis Branch of China Medicinal. From 2005 to now, Dr. Xi supervises the Laboratory of Large-scale Nucleic Acids Technologies. His research interests include precision medicine, genome editing, cell microarray, and large-scale screening. Up to now, he already published over 50 peer-reviewed SCI papers in top journals, including *Nature, Nature cell biology, etc.*. More than 10 patents were already filled, and several of them were licensed for commercialization. Dr. Xi have also received 17 grants, including 1 grant from the National Outstanding Young Investigator Award (equivalent to PECASE in USA), 2 grants from the National Science Foundation of China key project, and 1 grant from Ministry of Science and Technology 973 (co-PI). In 2018, Dr. Xi got a National Key Project entitled "The Development of 3D Stem Cell-Differentiated Organoid Chip and Their Applications" as a Chief Scientist. In 2021, project "*Mini-Tumour (PTC) Based Investigation of the Molecular Mechanisms of Tumour Heterogeneity*" led by Dr. Xi was awarded NFSC Original Exploratory Program Grant.

Starting bottom-up neuroscience with small "brains" on a chip

Janos Vörös

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The traditional way of addressing questions related to the function of the brain involves studying the nervous system of various organism with the argument: "nature optimized these through millions of years of evolution so we should learn how they function by studying the real system". However, this at the same time means to study something that is highly complex and largely unknown. In addition, although the tools of neuroscience are becoming more and more advanced, due to the complexity of these systems, it is very difficult to address fundamental questions. Probably this is the reason for the lack of consensus in the field even on seemingly basic questions such as "what is information" and "how is information stored and processed" in the brain.

Besides this top-down approach there is also a substantial community (including us) that follows the bottom-up approach1, i.e. trying to learn from small networks of neurons with the advantage that the position and connections of the neurons can be precisely defined and the cells have a good accessibility for recording tools: such as patch clamp2, microelectrode3 or CMOS arrays4, or fluorescence microscopy5.

This talk will introduce new tools that we developed to create and to interact with well-defined neuronal networks. For example, asymmetric PDMS microchannels can be used to guide the axonal growth in the desired direction on top of microelectrode arrays.3-6 This allows studying fundamental neuroscience paradigms and enables the creation of network architectures with real neurons, including human iPSC-derived cells6, that resemble current computational neural networks.

Overall, the tools presented in this talk are the first necessary step for bottom-up neuroscience, a new approach to study neurons and their networks.

References:

- 1. "Brains on a chip": Towards engineered neural networks. Aebersold, M. et al.; *Trends in Analytical Chemistry*; 2016, 78, 60-69.
- 2. Force-Controlled Patch Clamp of Beating Cardiac Cells. Ossola, D.et al.; *Nano Letters*, 2015.
- 3. An experimental paradigm to investigate stimulation dependent activity in topologically constrained neuronal networks; S.J. Ihle, et al.; *Biosensors and Bioelectronics*, 2021, submitted.
- 4. Engineered biological neural networks on high density CMOS based microelectrode arrays; J. Duru, et al.; *Frontiers in Neuroscience*, 2021, submitted.
- 5. Modular microstructure design to build neural structures with defined functional connectivity; C. Forró, et al.; *Biosensors & Bioelectronics*, 2018.
- Topologically controlled circuits of human iPSC-derived neurons for electrophysiological recordings;
 Girardin, et al.; *Lab-on-a-chip*, 2021, submitted.



János Vörös is a Professor in the Institute for Biomedical Engineering of the University and ETH Zurich (Department for Information Technology and Electrical Engineering) heading the Laboratory for Biosensors and Bioelectronics since 2006.

He has studied Physics at the Eötvös Loránd University in Budapest. After receiving a diploma in Physics in 1995, he was a doctoral student at the Department of Biological Physics of the Eötvös University (in collaboration with Microvacuum Ltd.) where he received his PhD in Biophysics in 2000. Since 1998 he was a member of the BioInterface group in the Laboratory for Surface Science

and Technology at the Department of Materials of ETH Zurich as visiting scientist, postdoc, and from 2004 as group leader of the Dynamic BioInterfaces group until 2006.

Prof. Vörös is interested in research and teaching in the areas of bioelectronics, biosensors, and neuroscience. His group focuses on the development of novel biosensor techniques for diagnostics and single molecule sequencing; on bottom-up neuroscience; as well as on stretchable biohybrid electronic devices.

Engineering the Dynamics of Cell Adhesion Cues in Supramolecular Hydrogels for Facile Control over Cell Encapsulation and Behavior

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The extracellular matrix (ECM) forms through hierarchical assembly of small and larger polymeric molecules into a transient, hydrogel-like fibrous network that provides mechanical support and biochemical cues to cells. Synthetic, fibrous supramolecular networks formed via non-covalent assembly of various molecules are therefore potential candidates as synthetic mimics of the natural ECM, provided that functionalization with biochemical cues is effective. Here, combinations of slow and fast exchanging molecules that self-assemble into supramolecular fibers are employed to form transient hydrogel networks with tunable dynamic behavior. Obtained results prove that modulating the ratio between these molecules dictates the extent of dynamic behavior of the hydrogels at both the molecular and the network level, which is proposed to enable effective incorporation of cell-adhesive functionalities in these materials. Excitingly, the dynamic nature of the supramolecular components in this system can be conveniently employed to formulate multicomponent supramolecular hydrogels for easy culturing and encapsulation of single cells, spheroids, and organoids. Importantly, these findings highlight the significance of molecular design and exchange dynamics for the application of supramolecular hydrogels as synthetic ECM mimics.

> Patricia Y.W. Dankers, PhD, PhD, is full professor in Biomedical Materials and Chemistry in the Institute for Complex Molecular Systems (ICMS) and the Department of Biomedical Engineering, in the Laboratory of Chemical Biology and the Laboratory for Cell and Tissue Engineering, at the Eindhoven University of Technology (TU/e).

She studied chemistry at the Radboud University of Nijmegen, the Netherlands, where she majored in biochemistry and organic chemistry. During her PhD in natural sciences/chemistry at the Eindhoven University of Technology in the group

of prof.dr. E.W. (Bert) Meijer, she combined her fascination for biochemistry and supramolecular chemistry. She developed and studied supramolecular bioactive biomaterials by introducing a modular approach. Here, she laid the foundation for the supramolecular polymers nowadays used by Xeltis in their RestoreXTM technology to treat patients with cardiovascular pathologies.

She is a Veni and Vidi laureate (2008 and 2017) and received an ERC starting grant (2012). She has been awarded various (EU) grants and awards, such as the DSM Science & Technology award, the Pauline van Wachem award for the best thesis in biomaterials research and tissue engineering and the Journal of Polymer Science Innovation award at the ACS (2019). From 2011-2013 she has been a member of the first Jonge Gezondheidsraad (JongGR). She has been a member and board member of De Jonge Akademie (DJA) of the KNAW (2015-2020). She has been the president of the Netherlands Society of Biomaterials and Tissue Engineering (NBTE) for a few years. She founded and is currently leading the Eindhoven Young Academy of Engineering (EYAE) at TU/e. Since 2019, she is the chair of the Chemistry Round Table of NWO. This table is the voice of the chemical research community to

the NWO Science Domain. Additionally, she considers the promulgation of science to society a very important topic.

Flexible filter based liquid biopsy

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A precise, efficient, rapid, flexible, easy-operated, controllable, thin filter, shorted as PERFECT filter, was developed based on the Parylene microelectromechanical system (MEMS) technique. Large (>20 mm×20 mm) filtration membranes containing a 2.5dimensional (2.5D) micropore array with an ultra-high porosity (up to 91.37% with designed pore diameter/space of 100 μ m/4 μ m) were prepared by a Parylene molding process. The notation 2.5D indicates that the large area and the relatively small thickness (approximately 10µm) of the fabricated membranes represent 2D properties, while the large thickness-to-width ratio (10 μ m/<4 μ m) of the spaces between the adjacent pores corresponds to a local 3D feature. The large area and high porosity of the micropore array achieved filtration with high throughputs up to 180 mL/min for PBS solution and 17 mL/min for whole blood simply driven by gravity. Meanwhile, the high mechanical strength, benefiting from the 2.5D structure of the micropore array, ensured a negligible pore size variation during the high-throughput filtration, thereby enabling high size resolution separation, which was proven by single-layer and multilayer filtrations for particle separation. Tumor cells from bronchoalveolar lavage fluid, sputum, pleural fluid, etc were also tested and indicated that the present PERFECT filter holds promising future in clinical diagnosis.



Prof. Wei Wang is the vice director of Institute Microelectronics, Peking University and the director of the National Key Laboratory of Science and Technology on Micro/ Nano Fabrication. He received his B.S. in Thermal engineering from University of Shanghai for Science and Technology (USST, 1999) and the Ph.D. in Thermal Engineering from Tsinghua University (2005). He was a Visiting Professor in UC Davis (with Prof. Tingrui Pan) from 2007-2008 and Caltech (with Prof. YC Tai) from 2014-2015. His research focus is Parylene MEMS, clinical micro/nanosystem, and thermal management of 3D microsystem. He has published over 100 peer-reviewed articles, over 50 presentations with over

15 invited presentations, and 15 patents pending or granted. He is the Associated Editor of Microfluidics and Nanofluidics, and has served/ is serving on organizing committees for several international conferences, including IEEE MEMS'2015 and '2016, Transducers'2019, and 2021 etc.

The NIH Microphyiological Systems program: In Vitro 3D Models for Safety and Efficacy Studies

Danilo A. Tagle, Director, Office of Special Initiatives, National Center for Advancing Translational Sciences, National Institutes of Health 6701 Democracy Blvd., Room 940 Bethesda, MD 20892 USA

Aproximatley 30% of drugs have failed in human clinical trials due to adverse reactions despite promising pre-clinical studies, and another 60% fail due to lack of efficacy. A number of these failures can be attributed to poor predictability of human response from animal and 2D in vitro models currently being used in drug development. To address this challenges in drug development, the NIH Tissue Chips or Microphysiological Systems program is developing alternative innovative approaches for more predictive readouts of toxicity or efficacy of candidate drugs. Tissue chips are bioengineered 3D microfluidic platforms utilizing chip technology and human-derived cells and tissues that are intended to mimic tissue cytoarchitecture and functional units of human organs and systems. In addition toxicity studies in drug development, these microfabricated devices are also being used to model various human diseases for assessment of efficacy of candidate therapeutics. A more recent program is the development of "clinical trials on chips" to inform clinical trial design and implementation, and for studies in precision medicine. Presentation will provide a program update and also elaborate in the development and utility of microphysiologicals sytems and in the partnerships with various stakeholders for its implementation.



Dr. Danilo Tagle is director for special initiatives at NCATS. He also recently served as acting deputy director of NCATS, and has previously served as acting director of the NCATS Office of Grants Management and Scientific Review and as executive secretary to the NCATS Advisory Council and Cures Acceleration Network Review Board. Prior to joining NCATS, Tagle was a program director for neurogenetics at the National Institute of Neurological Disorders and Stroke (NINDS), where he was involved in developing programs concerning genomics-based approaches for basic and translational research in inherited brain disorders.

Prior to joining NINDS in 2001, Tagle was an investigator and section head of molecular neurogenetics at the National Human Genome Research Institute and has been involved in the highly collaborative effort toward the positional cloning of genes for Huntington's disease, ataxia-telangiectasia and Niemann-Pick disease type C. He has served on numerous committees and advisory boards, including the editorial boards of the journals *Gene* and the *International Journal of Biotechnology*.

Tagle obtained his Ph.D. in molecular biology and genetics from Wayne State University School of Medicine in 1990. He was an NIH National Research Service Award postdoctoral fellow in human genetics in the laboratory of Francis S. Collins, M.D., Ph.D., at the University of Michigan. Tagle has authored more than 150 scientific publications and has garnered numerous awards and patents.

Integrated human multi-organ platforms for modeling systemic pathologies

Gordana Vunjak-Novakovic Columbia University New York NY, USA

Bioengineered "organs on a chip" platforms are evolving into a new paradigm for modeling human pathophysiology, with utility in both biological and preclinical studies. Establishing physiological communication between different tissues while preserving their individual phenotypes is a challenge that needs to be addressed to allow modeling of whole-body physiology in health and disease. An approach to meet these conflicting requirements is to establish a modular, configurable multi-organ platform in which each human tissue is cultured in its own optimized environment and linked to other tissues by vascular perfusion. We showed that under these conditions, the connected tissues (heart, liver, skin, bone) can maintain their molecular, structural and functional phenotypes over four weeks of culture. The platform allows individualized studies, as all tissues, endothelium and circulating cells can be derived from the same iPS cells. To illustrate the utility of this approach, we use four examples: (i) a simple hearttumor platform that recapitulated clinical efficacy and toxicity for an anticancer drug, (ii) a platform that recapitulated the targeted metastasis of bone and lung tissues by breast cancer cells, (iii) studies of the acute and chronic radiation damage in human tissues and of the effects of tissue protective measures, and (iv) studies of the off-target toxicity of doxorubicin in liverheart-bone-skin platform. observed in pediatric and adult clinical studies. Finally, we discuss the opportunities and challenges for using these platforms in studies of development, physiology and disease.



Gordana Vunjak-Novakovic is University Professor, the highest academic rank at Columbia University and the first engineer at Columbia to receive this distinction. The focus of her lab is on engineering functional human tissues for use in regenerative medicine and patient specific "organs-on-achip" for studies of human physiology in health and disease. She is well published and highly cited (h=132), has mentored over 150 trainees, and launched four biotech companies form her lab. She is serving on the Council of the NIBIB, the HHMI Scientific Review Board, and on numerous editorial and scientific advisory boards. She was inducted into the Women in Technology International Hall of Fame, received the Clemson Award of the

Biomaterials Society, Pritzker Award of the Biomedical Engineering Society, Shu Chien Award of the AIChE, the AIMBE Pierre Galletti award, and the TERMIS Lifetime Achievement Award. She was decorated by the Order of Karadjordje Star - Serbia's highest honor, and elected to the Academia Europaea, Serbian Academy of Arts and Sciences, the National Academy of Engineering, National Academy of Medicine, National Academy of Inventors, the American Academy of Arts and Sciences and the International Academy for Medical and Biological Engineering.

Next-Generation Culture Models of Cardiovascular Physiology and Disease

Christopher S. Chen, M.D., Ph.D. Founding Director, The Biological Design Center; Distinguished Professor of Biomedical Engineering, Boston University; Wyss Institute for Biologically Inspired Engineering, Harvard University

Mammalian tissues operate as highly integrated systems that link physical structure and biological function, determining the effectiveness by which muscles generate force, glandular organs produce bile, milk, or saliva, and vasculature delivers oxygen and nutrients. I will describe our efforts in rebuilding from component cells tissue-like architectures such as cardiac muscle and tissues perfused with functional vasculature, and how these platforms ultimately will serve as experimental models of human physiology and disease.



Christopher S. Chen, M.D., Ph.D., is the William Fairfield Warren Distinguished Professor of Biomedical Engineering at Boston University, Founding Director of the Biological Design Center, and member of the Wyss Institute for Biologically Inspired Engineering at Harvard University. He also serves as Deputy Director of the National Science Foundation Engineering Research Center in Cellular Metamaterials and Co-PI of the National Science Foundation Science and Technology Center for Engineering Mechanobiology. Dr. Chen has been an instrumental figure in the development of engineered

cellular microenvironments to understand and control how cells build tissues. He has served, or is currently serving, as a member of the American Institute for Medical and Biological Engineering, Faculty of 1000, the Defense Sciences Study Group, and on numerous advisory boards and councils. He received his A.B. in Biochemistry from Harvard, M.S. in Mechanical Engineering from M.I.T., Ph.D. in Medical Engineering and Medical Physics from the Harvard-M.I.T. Health Sciences and Technology Program, and M.D. from the Harvard Medical School.

The Application and Prospect of Organoids in Biological Research

and Precision Medicine

Xinhua Lin

State Key Laboratory of Genetic Engineering, Institute of Genetics, Collaborative Innovation Center of Genetics and Development, School of Life Sciences, Fudan University, Shanghai, China.

Organoid technology has sprung up in recent years and is considered a breakthrough of the cutting-edge sciences and technologies and has overcome the limit of traditional in vivo and in vitro models. The deriving organoids represent their source tissues in construct architecture, cell types, self-renewal capacities, physiological functions, etc. Thus, the organoid technology has demonstrated its advantages in the research areas of developmental biology, disease modelling, precise medicine, drug discovery, gene and cell therapy, immunology, regenerative medicine, etc. With an organoid center established at Fudan University, our team has: 1) uncovered the role of Znhit l in maintaining the stemness of intestinal adult stem cells, a pioneer finding that reveals how chromatin-remodeling integrates signals for the fate determination of stem cells, 2) established the world's first SARS-COV-2-infected human organoid model (interviewed by Nature News and highlighted on Nature's website), 3) illustrated the role of Yap signaling in hepatoblastoma progression and small molecule inhibitors of tumorigenesis, 4) established human organoid models of rectal polyps that retains tissue characteristics and taken advantage of high-throughput screening for drug discovery, 5) been developing culture medium for human liver organoids with defined chemical components to decipher the essential signals that allow bipotent liver progenitor cells to proliferate.



Since July 2016, Xinhua Lin has been a professor at Fudan University, where he is currently the Executive Dean of School of Life Sciences, the Director of State Key Laboratory of Genetic Engineering, and the Director of Institute of Genetics. He also holds the position of Executive Director at the Greater Bay Area Institute of Precision Medicine (Guangzhou). He was among the first talents recruited by China's "Thousand Talents Plan," directed by the Organization Department of the CPC Central Committee. He was also the Chief Scientist of China's National Key Basic Research Program (Program 973). He received many awards and honors, including the American Cancer Society Research Scholar Grants, an honorary

professorship at Zhejiang University School of Medicine, and the March of Dimes Foundation's Basil O'Connor Scholar Award. Before joining Fudan University, he obtained his bachelor's degree from Hangzhou University (now Zhejiang University) in 1984. In 1987, he earned his master's degree from the Chinese Academy of Sciences'Shanghai Institute of Biochemistry and Cell Biology. In 1995, he received his Ph.D. degree in the U.S. from Washington University in St. Louis. From 1995 to 2000, he trained as a post-doctoral researcher at Harvard Medical School. From 2000 to 2009, he taught at Cincinnati Children's Hospital Medical Center (CCHMC), where he held the positions of Assistant Professor (2000), Associate Professor (2005), and Professor (2008). From 2009 to 2015, he was a Principal Investigator and the Director of the State Key Laboratory of Membrane Biology at the Chinese Academy of Sciences' Institute of Zoology. He currently serves as the Managing Director of the China Zoological Society, the Associate Editor-in-Chief of Reproductive and Developmental Medicine, Heraditas (Beijing), and the Chinese Journal of Cell Biology, as well as the Editorial Board Member of Fly. Prof. Xinhua Lin is interested in developmental biology, genetics and stem cell biology. His research directions include: 1) the roles of Wnt, BMP, Hh, JAK/STAT signaling pathways in

development in fruit flies, mice and human organoids, 2) the homeostasis and regeneration of endodermal organs regulated by signal transduction, transcription regulation and epigenetic modulation, 3) the roles of signal transduction, genetic mutation and epigenetic alteration in development and human diseases (e.g. tumors and birth defects). Prof. Xinhua Lin has published over 70 papers in Cell, Nature, Nature Cell Biology, Developmental Cell, Cell Research, Nature Communication, Journal of Clinical Investigation, etc. as the first/last author, altogether cited over 7,000 times.

Human Islet Organoid Development and Angiopoietin Signaling Pathways

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The ability to generate islet organoids from iPSCs enables the development of physiologically functional human islets that can serve as a personalized disease model for diabetes pathophysiological study and precision medicine. They can be integrated into an organ-on-a-chip for drug screening and diabetes pathophysiology study. We have developed an innovative tissue assembly technology for generating pancreatic islet organoids directly from iPSCs. These organoids exhibited a tissue architecture similar to human pancreatic islets, consisting of pancreatic α , β , δ , and PP cells. The majority of β cells were found to be mono-hormone expressing cells, suggesting a high degree of beta cell specificity. These organoids are capable of secreting not only insulin but also glucagon in response to glucose levels, suggesting their physiological insulin- and glucagon-secretion capability. More importantly, most insulin-secreting cells did not express glucagon, somatostatin, or PP. The expressions of mature β cell marker genes such as Pdx1, Ngn3, Insulin, MafA, and Glut2 were detected in these islet organoids. In another study, we discovered an angiopoietin signaling pathway responsible for inducing human islet organoid assembly and maturation from iPSCs. We revealed, for the first time, that angiopoietins, including angiopoietin-1 (Ang1) and angiopoietin-2 (Ang2) permit the generation of islets from iPSCs with elevated glucose responsiveness. Angiopoietin-stimulated islets exhibited glucose synchronized calcium ion influx in repetitive glucose challenges. Moreover, Ang2 augmented the expression of all islet hormones, including insulin, glucagon, somatostatin, and pancreatic polypeptide; and β cell transcription factors, including NKX6.1, MAFA, UCN3, and PDX1. Furthermore, we showed that the Ang2 stimulated islets were able to regulate insulin exocytosis through actin-filament polymerization and depolymerization upon glucose challenge, presumably through the CDC42-RAC1-gelsolin mediated insulin secretion signaling pathway. We also discovered the formation of endothelium within the islets under the Ang2 stimulation. These results strongly suggest that angiopoietin acts as a signaling molecule to endorse in vitro islet development from iPSCs.



Dr. Kaiming Ye is Professor and Chair of Biomedical Engineering and Director of the Center of Biomanufacturing for Regenerative Medicine at Binghamton University (BU), SUNY. He is one of the world-leading scientists in advanced biomanufacturing. He is fellow of AIMBE, Fellow of the Biomedical Engineering Society, and senior member of IEEE. He is Chair of the Council of Chairs of Biomedical Engineering and a member of NIH/NIDDK Rebuilding Kidney Consortium's Advisory Committee. Dr. Ye pioneered islet organoid development from human pluripotent stem cells (HPSCs). His group is the first one that demonstrated the feasibility of generating functional human islets from

HPSCs. His other creative works include 3D tissue bioprinting, cancer immunotherapy, and cancer organoid development. Dr. Ye is one of the pioneers who designed fluorescence resonance energy transfer nanosensors for continuous glucose monitoring. He has contributed significantly to national policy-making in science and engineering. During his tenure at the NSF, he directed a biomedical engineering program. He was a member of the Interagency Workgroup for Neuroscience, Interagency Modeling and Analysis Workgroup, and Multiagency Tissue Engineering and Regenerative Medicine Workgroup.

Integrative Biofabrication Technologies for High-Content Modeling of Human Tissues and Diseases *in vitro*

Y. Shrike Zhang Department of Medicine, Harvard Medical School Division of Engineering in Medicine, Brigham and Women's Hospital Harvard Stem Cell Institute, Harvard University

Microphysiological systems are microfluidic three-dimensional miniature human tissue and organ models that recapitulate the important biological and physiological parameters of their *in vivo* counterparts. These biomimetic microtissues are anticipated to supplement the conventional planar, static cell cultures, and to bridge the gaps between the current pre-clinical animal models and the human body. In addition, multiple microtissues may be channeled together through the microfluidics in a similar manner they arrange *in vivo*, providing the capacity to analyze interactions among these models. In this talk, I will discuss our recent efforts on developing organ-on-chip platforms formed by integration of biofabrication technologies harnessing sophisticated microfluidics and volumetric tissue configurations. A reverse-engineered human alveolar lung-on-a-chip model will be used to exemplify such concept. These platforms will likely provide new opportunities in constructing functional tissue and disease models for drug discovery, therapeutics screening, and precision medicine.



Dr. Zhang is currently an Assistant Professor of Medicine at Harvard Medical School and Associate Bioengineer in the Division of Engineering in Medicine at the Brigham and Women's Hospital. Dr. Zhang's research is focused on innovating medical engineering technologies, including 3D bioprinting, organs-on-chips, microfluidics, and bioanalysis, to recreate functional tissues and their biomimetic models. In collaboration with a multidisciplinary team encompassing biomedical, mechanical, electrical, and computer engineers as well as biologists and clinicians, his laboratory seeks to ultimately translate these cutting-edge technologies into the clinics. He is an author of >250 peer-reviewed publications (h-index: 67) and his

scientific contributions have been recognized by >40 international, national, and regional awards.

The application of vascular immune organoids from human pluripotent stem cells in cancer immunotherapy and SARS-CoV-2 modeling

Rio Sugimura

School of Biomedical Sciences, Li Ka Shing Faculty of Medicine, University of Hong Kong

Organoid technology has advanced our understanding of development and disease models. Organoids derived from either human pluripotent stem cells or tissue stem cells offer us the amenable platform to genetically intervene in human organ development. The advance of genetic engineering and stem cell technology pushed the limit of what organoids can do. However, the current lack of both vasculatures and immune cells hinders the understanding of how vasculatures and immune cells regulate organ development as well as their role in pathologic conditions such as cancer and infection. We have previously established a unique organoid system from human pluripotent stem cells (Ohta et al., 2019; Sugimura et al., 2020, 2017). Followed by mesodermal patterning and hemato-endothelial specification with define factors, we achieved vascular immune organoids (VIOs). We identified the highly vascularized structure of VIOs. The repertoire of cells encompasses innate immune cells such as macrophages, neutrophils, erythroblasts, and NK cells, which demonstrated functional maturity. In this talk, we will share our recent efforts in i) engineering functional immune cells for cancer immunotherapy, ii) modeling vasculitis in SARS-CoV-2 infection. We propose that VIOs could further enhance the organoid technology in both cancer immunotherapy and SARS-CoV-2 modeling.

References

Ohta, R., Sugimura, R., Niwa, A., Saito, M.K., 2019. Hemogenic Endothelium Differentiation from Human Pluripotent Stem Cells in A Feeder- and Xeno-free Defined Condition. J. Vis. Exp. JoVE. https://doi.org/10.3791/59823

Sugimura, R., Jha, D.K., Han, A., Soria-Valles, C., da Rocha, E.L., Lu, Y.-F., Goettel, J.A., Serrao, E., Rowe, R.G., Malleshaiah, M., Wong, I., Sousa, P., Zhu, T.N., Ditadi, A., Keller, G., Engelman, A.N., Snapper, S.B., Doulatov, S., Daley, G.Q., 2017. Haematopoietic stem and progenitor cells from human pluripotent stem cells. Nature 545, 432–438. https://doi.org/10.1038/nature22370

Sugimura, R., Ohta, R., Mori, C., Li, A., Mano, T., Sano, E., Kosugi, K., Nakahata, T., Niwa, A., Saito, M.K., Torisawa, Y.-S., 2020. Biomimetic aorta-gonad-Mesonephros-on-a-Chip to study human developmental hematopoiesis. Biomed. Microdevices 22, 34. https://doi.org/10.1007/s10544-020-00488-2



Rio Sugimura is an Assistant Professor in the School of Biomedical Sciences, The University of Hong Kong. Dr. Sugimura is a full faculty member of the Stem Cells & Regeneration Section in F1000Prime, a member of American Association of Immunologists (AAI), American Society of Hematology (ASH), Biomedical Engineering Society (BMES), Association for Cancer Immunotherapy (CIMT), Federation of American Societies for Experimental Biology (FASEB), International Society of Experimental Hematology (ISEH), International Union of Immunological Societies (IUIS), the North American Vascular Biology Organization (NAVBO), Society for Immunotherapy of Cancer (SITC), and a co-founder of the medical branch

of Kagakusha-Net. Dr. Sugimura is a recipient of the ASH Scholar Award, March of Dimes, Early Career Grant from Japanese Ministry, Genius Award from Young Hematologist Meeting in Japan, Takeda Science Foundation, iPS Academia Japan Foundation, SMRF Fellowship, Kanehara Memorial

Foundation, and Uehara Memorial Foundation.

Dr. Sugimura is an accomplished scientist, recognized for his outstanding contributions to the field of hematology and stem cell biology. He is interested in using single-cell barcoding technology to delineate single-cell lineage maps of blood/immune cells in human organoids and exploring druggable targets of anti-cancer immunity.