Bio-Design and Manufacturing (2020) 3:155–159
https://doi.org/10.1007/s42242-020-00080-w

EDITORIAL

Engineering in vitro human tissue models through bio-design and manufacturing

Yu Shrike Zhang[1] · **Ali Khademhosseini**[2]

Published online: 7 July 2020
© Zhejiang University Press 2020

In the era of burgeoning breakthroughs around medical and biomedical technologies, personalizing our medicine still sounds like a dream yet to be realized.

Take cancer as an example, while the pool of anti-cancer therapeutic agents is tremendously large, pinpointing a drug or a combination of drugs that would always work out well for a given patient, remains quite impossible—in fact, we are not even close to this ideal scenario. Such an incapability, of course, originates primarily from the overly complex, volumetrically structured and dynamic microenvironments in a patient's tumor, meaning that the same tumor as seen on Day 1 might be entirely different than when seen again a month later. Even worse, this is only the intratumor heterogeneity within a single patient. Intertumor heterogeneity further adds soils to the grave—Patient 1 can be dramatically different from Patient 2 despite that they bear the same tumor type, and by the next time they both show up in the clinic, such a difference between them may have well-changed again. Huh!

And it seems that we all know these problems, but what can be done, really, that will lead us closer toward our goal of personalizing medicine? Let us take a look. In the past decades with significant advancements in human genomics, the concept of precision medicine has emerged, which relies on molecular and genetic profiling of a patient's tumor for the selection of therapeutics for this specific patient [1]. Nevertheless, translation into a successful clinical outcome through finding a particular biomarker has not been as efficient as desired, at a typically below 30% rate, whether in chemotherapy [2, 3] or in immunotherapy [4].

As such, it has been increasingly understood that the spatiotemporal distribution of the cancer cells and associated cells, along with the matrix that pulls them together in the tumor microenvironment, plays a critical role in determining how a tumor would progress, disseminate, respond to therapeutics, and potentially acquire resistance. Realizing that the conventional planar, static cell culture models may not provide a biosimilar configuration with their respective native tissues, people have started pondering about alternative ways that could be more reliable. In tackling personalized cancer treatment, a neat idea lies in the use of the patient-derived xenograft (PDX) models, where cancer biopsy tissues obtained from a patient are implanted back into an animal host, typically mice, to reconstitute partially humanized tumor growth that carries the patient's tumor characteristics. Unfortunately, the excessively high costs associated with the animals, the labor, the timescale (as long as 6–8 months), and the low success rate (10–30%) have significantly limited the use of these PDX models [5]. While we have so far elaborated on cancer as an example of the personalized medicine problem, it is almost universally existent for many other disease types.

More recently, with also our growing capacity in a series of engineering technologies, a new field of tissue model engineering has emerged. Building on top of the long-existing tissue engineering concept [6], yet opposed to its aims at generating tissue substitutes to maintain, repair, or augment functions of the human body, tissue model engineering rather seeks to produce miniature copies of the human tissues or organs in vitro, potentially at a higher throughput, for applications in drug development and therapeutics screening [7]. Comparing to the conventional planar, static monolayer cell cultures in a dish, engineered tissue models are usually three-dimensional (3D), or oftentimes at least compartmentalized, which when combined with suitable physicochemically dynamic cues,

✉ Yu Shrike Zhang
yszhang@research.bwh.harvard.edu

✉ Ali Khademhosseini
khademh@terasaki.org

[1] Division of Engineering in Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Cambridge, MA 02139, USA

[2] Terasaki Institute for Biomedical Innovation (TIBI), Los Angeles, CA 90024, USA

would to a decent degree emulate desired human tissues in their architecture and functions. Sometimes, organ-level functionality is also possible, through meticulous bio-design and manufacturing, and reverse-engineering [8, 9].

Among the collection of tissue model engineering strategies, those based off bioprinting and organ-on-a-chip technologies have been most popular so far (Fig. 1).

Bioprinting refers to 3D positioning of a bioink or a combination of multiple bioinks into a structurally defined volumetric tissue construct through robotically programmed operations [10, 11]. Unlike how the tissues are fabricated before, 3D bioprinting due to its automation process enables complexity and reproducibility not quite previously possible. Such unique features of bioprinting have facilitated its adoption in tissue model engineering, with vast amount of exciting examples already pushed out into the literature, spanning across human-based models of the brain [12], the heart [13], the liver [14], the kidney [15], the vasculature [16], and the tumor [17, 18], among others.

On the other hand, organ-on-a-chip easily brings in the advantages of compartmentalization and dynamic physico-chemical cues that are also characteristic of most human tissues, such as fluidic shear stresses, mechanical actuations, electrical signals, and circulating cells, growth factors, and cytokines [19]. Notable examples of human tissue models engineered with the on-a-chip platforms include the breathing lung-on-a-chip [20], the contracting heart-on-a-chip [13], the dilating/constricting blood vessel-on-a-chip [21], the renal reabsorption-on-a-chip [15], the peristaltic gut-on-a-chip [22], the foreign body response-on-a-chip [23], and of course the tumor-on-a-chip (e.g., tumor immunotherapy-on-a-chip [24])as well.

Interestingly, if our readers are careful enough reading through the past two paragraphs, they will perhaps notice that some literature cited have overlapped [13, 15]. Indeed,

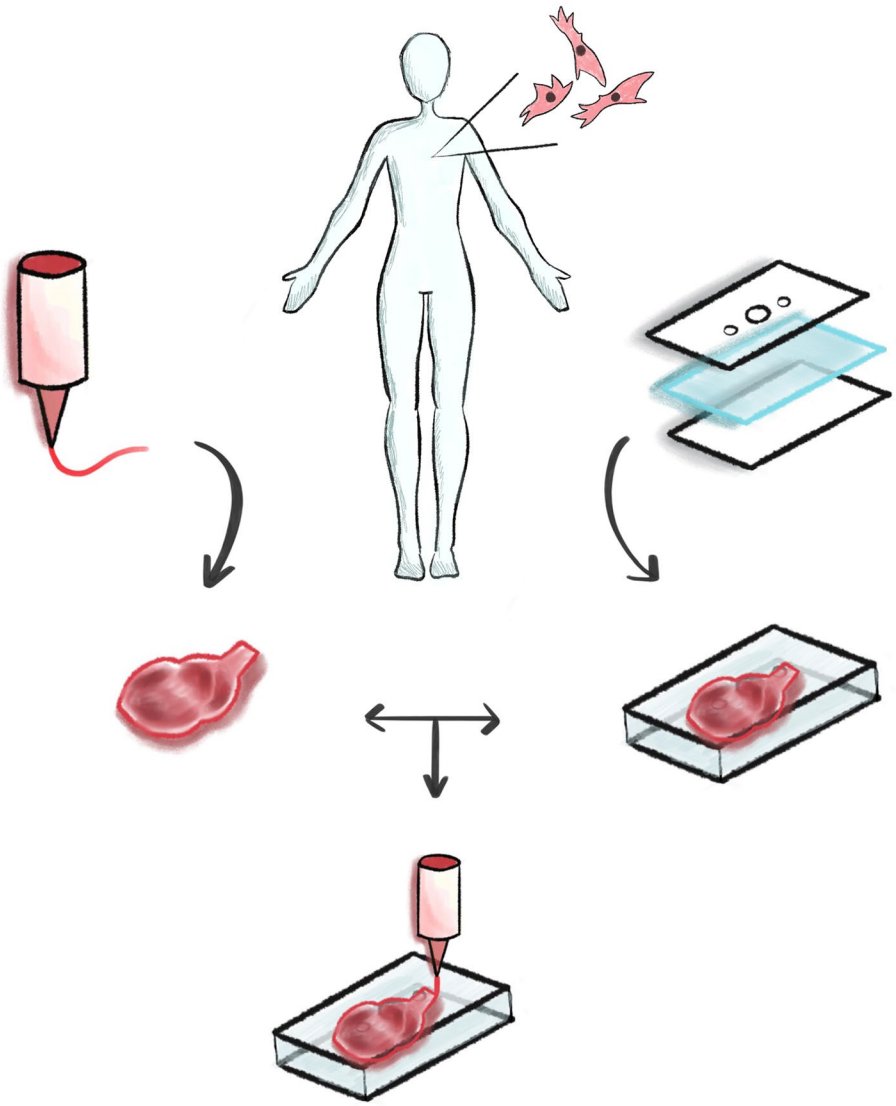


Fig. 1 Engineering in vitro personalizable, human-based tissue models through bioprinting, organ-on-a-chip, and/or their combination. Illustration by Zixuan Wang, used with permission

the two technologies are not entirely separate but are quite connected, and most frequently complementary to each other, provoking us to truly think about their potential combinations, i.e., bioprinting of a volumetric and structurally complex tissue model directly into a chip device [15] or post-loaded [13], where the chip further provides the additional compartmentalization and physicochemical cues needed for functional maturation and/or maintenance [25]. Other considerations include biosensor integration to make in-line, continual, and non-invasive monitoring of microtissue behaviors and responses possible [26], as well as multi-organ integration to allow for investigations into intertissue interactions and simultaneous examination of efficacy and side toxicity [27]. These all-human, precisely engineered, volumetric, dynamic, and personalizable systems will hopefully one day help us achieve true precision/personalized medicine [28].

To this end, we have put up together an exciting Special Issue on the topic of "in vitro tissue models", emphasizing the bio-design and manufacturing aspects involved in engineering a range of tissue model types. We begin with an Editorial by He et al. [29] furthering the discussions about the rationale behind choosing 3D bioprinting for the fabrication of in vitro tissue models toward utilization in drug screening. The editorial outlines, through a comic-style presentation, the dilemmas of current drug screening, advantages of in vitro 3D models, as well as different bioprinting strategies and classification of these models, ending by projecting key challenges and key attributes.

A collection of Research Articles then ensues. Ma et al. [30] focuses on the bioprinting of the central nervous system using hyaluronic acid, the most abundant brain extracellular matrix component, as the main component of the bioink. The effect of the bioink formulation as well as bioprinting conditions was optimized for encapsulation of the glial cells, laying down a foundation for future modeling of brain lesions such as glioblastoma. Xie et al. [31] proposes a novel tumor array chip system featuring a 'layered cake' structure, where hydrogel droplet-encapsulated breast tumor cells were automatically deposited on a substrate with electrohydrodynamic 3D bioprinting, achieving higher-throughput drug screening. The third article by Sharifi et al. [32] presents a new dual chamber-on-a-chip platform to study hepatocellular carcinoma metastasis and treatment. One of the chambers was used as the primary hepatocellular carcinoma tissue, whereas the second was designated as the bone metastatic site; an interesting observation, i.e., the mineral-dependent seeding of the metastatic hepatocellular carcinoma cells in the bone-mimetic chamber, was made. The platform was subsequently applied toward examining the effects of a phytochemical anti-cancer drug thymoquinone, in both free form and nanoparticulate form, on inhibiting the metastasis process.

The Special Issue finally gathers five excellent reviews scattered across a few different important areas of in vitro tissue model engineering. Thakor et al. [33] cover the application of hydrogels as the biomaterials to engineer 3D tissue models utilizing brain tumor cells, via microscale biomanufacturing technologies such as electrospinning and bioprinting. Therapeutic potentials of hydrogels toward brain tumor were also briefly mentioned. In a related way, the next review by Ma et al. [34] expands on how 3D bioprinting in particular may be taken advantages of in the construction of in vitro tumor models, focusing on the bioprinting strategies and bioink designs with a subsequent illustration of currently reported bioprinted tumor models. The third review by Zubizarreta et al. [35] elaborates on a fairly new topic of the field, i.e., the bioengineering of the female reproductive system. Given the growing concerns over the female reproductive health and fertility, there is an ever-increasing demand to develop representative, effective, and efficient in vitro human-based models for studying this uniquely important yet largely overlooked system, for which the recent advances have been covered in the review. Li et al. [36] then follow by discussing methods of using the cost-effective paper-based biomaterials for the fabrication of in vitro tissue models, to enable convenient, disposable, and rapid means suitable for drug screening, potentially at the bedside using patient-derived materials. Lastly, we further tune the topic to biosensing integration into organ-on-a-chip systems, where Yang et al. [37] specifically summarize imaging-based bioanalysis of heart-on-a-chip models through built-in photonic crystal-enabled optical sensors.

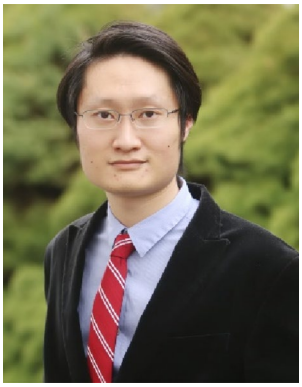
Ultimately, these examples only highlight the large body of work that is being done in the engineering of in vitro human tissue models. It is hoped that this Special Issue will serve as a collection of research and views from different angles, to spur further endeavors across disciplines that are aimed toward advancing this young field that nonetheless, will likely change how personalized medicine is practiced in the future.

References

1. Van't Veer LJ, Bernards R (2008) Enabling personalized cancer medicine through analysis of gene-expression patterns. Nature 452(7187):564–570
2. Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, Bets D, Mueser M, Harstrick A, Verslype C (2004) Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. New Engl J Med 351(4):337–345
3. Van Cutsem E, Peeters M, Siena S, Humblet Y, Hendlisz A, Neyns B, Canon J-L, Van Laethem J-L, Maurel J, Richardson G (2007) Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in

patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol 25(13):1658–1664
4. Dirix L, Takacs I, Nikolinakos P, Jerusalem G, Arkenau H, Hamilton E, Von Heydebreck A, Grote H, Chin K, Lippman M (2016) Abstract S1-04: Avelumab (MSB0010718C), an anti-PD-L1 antibody, in patients with locally advanced or metastatic breast cancer: a phase Ib JAVELIN solid tumor trial. In: AACR
5. Byrne AT, Alferez DG, Amant F, Annibali D, Arribas J, Biankin AV, Bruna A, Budinska E, Caldas C, Chang DK, Clarke RB, Clevers H, Coukos G, Dangles-Marie V, Eckhardt SG, Gonzalez-Suarez E, Hermans E, Hidalgo M, Jarzabek MA, de Jong S, Jonkers J, Kemper K, Lanfrancone L, Maelandsmo GM, Marangoni E, Marine J-C, Medico E, Norum JH, Palmer HG, Peeper DS, Pelicci PG, Piris-Gimenez A, Roman-Roman S, Rueda OM, Seoane J, Serra V, Soucek L, Vanhecke D, Villanueva A, Vinolo E, Bertotti A, Trusolino L (2017) Interrogating open issues in cancer precision medicine with patient-derived xenografts. Nat Rev Cancer 17(4):254
6. Langer R, Vacanti JP (1993) Tissue engineering. Science 260(5110):920–926
7. Moroni L, Burdick JA, Highley C, Lee SJ, Morimoto Y, Takeuchi S, Yoo JJ (2018) Biofabrication strategies for 3D in vitro models and regenerative medicine. Nat Rev Mater 3(5):21–37
8. Bhatia SN, Ingber DE (2014) Microfluidic organs-on-chips. Nat Biotechnol 32(8):760–772
9. Ingber DE (2016) Reverse engineering human pathophysiology with organs-on-chips. Cell 164(6):1105–1109
10. Malda J, Visser J, Melchels FP, Jüngst T, Hennink WE, Dhert WJA, Groll J, Hutmacher DW (2013) 25th anniversary article: engineering hydrogels for biofabrication. Adv Mater 25(36):5011–5028
11. Zhang YS, Khademhosseini A (2017) Advances in engineering hydrogels. Science 356(6337):eaaf3627
12. Heinrich MA, Bansal R, Lammers T, Zhang YS, Schiffelers RM, Prakash J (2019) 3D-bioprinted mini-brain: a glioblastoma model to study cellular interactions and therapeutics. Adv Mater 15:1805510
13. Zhang YS, Arneri A, Bersini S, Shin S-R, Zhu K, Malekabadi ZG, Aleman J, Colosi C, Busignani F, Dell'Erba V, Bishop C, Shupe T, Demarchi D, Moretti M, Rasponi M, Dokmeci MR, Atala A, Khademhosseini A (2016) Bioprinting 3D microfibrous scaffolds for engineering endothelialized myocardium and heart-on-a-chip. Biomaterials 110:45–59
14. Ma X, Qu X, Zhu W, Li Y-S, Yuan S, Zhang H, Liu J, Wang P, Lai CSE, Zanella F, Feng G-S, Sheikh F, Chien S, Chen S (2016) Deterministically patterned biomimetic human iPSC-derived hepatic model via rapid 3D bioprinting. Proct Natl Acad Sci USA 113(8):2206–2211
15. Lin NYC, Homan KA, Robinson SS, Kolesky DB, Duarte N, Moisan A, Lewis JA (2019) Renal reabsorption in 3D vascularized proximal tubule models. Proct Natl Acad Sci USA 116(12):5399–5404
16. Zhang YS, Davoudi F, Walch P, Manbachi A, Luo X, Dell'Erba V, Miri AK, Albadawi H, Arneri A, Li X, Wang X, Dokmeci MR, Khademhosseini A, Oklu R (2016) Bioprinted thrombosis-on-a-chip. Lab Chip 16:4097–4105
17. Cao X, Ashfaq R, Cheng F, Maharjan S, Li J, Ying G, Hassan S, Xiao H, Yue K, Zhang YS (2019) A tumor-on-a-chip system with bioprinted blood and lymphatic vessel pair. Adv Funct Mater 29(31):1807173
18. Zhang YS, Duchamp M, Oklu R, Ellisen LW, Langer R, Khademhosseini A (2016) Bioprinting the cancer microenvironment. ACS Biomater Sci Eng 2(10):1710–1721
19. Zhang B, Korolj A, Lai BFL, Radisic M (2018) Advances in organ-on-a-chip engineering. Nat Rev Mater 3(8):257–278
20. Huh D, Matthews BD, Mammoto A, Montoya-Zavala M, Hsin HY, Ingber DE (2010) Reconstituting organ-level lung functions on a chip. Science 328(5986):1662–1668
21. Ribas J, Zhang YS, Pitrez PR, Leijten J, Miscuglio M, Rouwkema J, Dokmeci MR, Nissan X, Ferreira L, Khademhosseini A (2017) Biomechanical strain exacerbates inflammation on a progeria-on-a-chip model. Small 13(15):1603737
22. Kim HJ, Huh D, Hamilton G, Ingber DE (2012) Human gut-on-a-chip inhabited by microbial flora that experiences intestinal peristalsis-like motions and flow. Lab Chip 12(12):2165–2174
23. Sharifi F, Htwe SS, Righi M, Liu H, Pietralunga A, Yesil-Celiktas O, Maharjan S, Cha B-H, Shin SR, Dokmeci MR, Vrana NE, Ghaemmaghami AM, Khademhosseini A, Zhang YS (2019) A foreign body response-on-a-chip platform. Adv Healthcare Mater 8(4):1801425
24. Aref AR, Campisi M, Ivanova E, Portell A, Larios D, Piel BP, Mathur N, Zhou C, Coakley RV, Bartels A, Bowden M, Herbert Z, Hill S, Gilhooley S, Carter J, Cañadas I, Thai TC, Kitajima S, Chiono V, Paweletz CP, Barbie DA, Kamm RD, Jenkins RW (2018) 3D microfluidic ex vivo culture of organotypic tumor spheroids to model immune checkpoint blockade. Lab Chip 18(20):3129–3143
25. Parrish J, Lim K, Zhang B, Radisic M, Woodfield TBF (2019) New frontiers for biofabrication and bioreactor design in microphysiological system development. Trends Biotechnol 37(12):1327–1343
26. Zhang YS, Aleman J, Shin SR, Kilic T, Kim D, Shaegh SAM, Massa S, Riahi R, Chae S-K, Hu N, Avci H, Zhang W, Silvestri A, Manbohi A, Polini A, Calzone G, Shaikh N, Sanati A, Alerasool P, Bhise NS, Budina E, Pourmand A, Skardal A, Shupe T, Bishop C, Dokmeci MR, Atala A, Khademhosseini A (2017) Multi-sensor-integrated organs-on-chips platform for automated and continual in situ monitoring of organoid behaviors. Proc Natl Acad Sci USA 114(12):E2293–E2302
27. McAleer CW, Long CJ, Elbrecht D, Sasserath T, Bridges LR, Rumsey JW, Martin C, Schnepper M, Wang Y, Schuler F, Roth AB, Funk C, Shuler ML, Hickman JJ (2019) Multi-organ system for the evaluation of efficacy and off-target toxicity of anticancer therapeutics. Sci Transl Med 11(497):eaav1386
28. Zhang YS (2019) The ultimate in personalized medicine: your body on a chip. In: IEEE spectrum, IEEE
29. He Y, Nie J, Xie M, Gao Q (2020) Why choose 3D bioprinting? Part III: printing in vitro 3D models for drug screening. Bio-Des Manuf 3(3). https://doi.org/10.1007/s42242-020-00067-7
30. Ma L, Li Y, Wu Y, Yu M, Azazmi A, Gao L, Xue Q, Luo Y, Zhou H, Zhang B, Yang H (2020) 3D-bioprinted hyaluronic acid based cell-laden scaffold for brain microenvironment simulation. Bio-Des Manuf 3(3). https://doi.org/10.1007/s42242-020-00076-6
31. Xie M, Gao Q, Fu J, Chen Z, He Y (2020) Bioprinting of novel 3D tumor array chip for drug screening. Bio-Des Manuf 3(3). https://doi.org/10.1007/s42242-020-00078-4
32. Sharifi F, Ozlem Y-C, Kazan A, Maharjan S, Saghazadeh S, Firoozbakhsh K, Firoozabadi B (2020) A hepatocellular carcinoma-bone metastasis-on-a-chip model for studying thymoquinone-loaded anti-cancer nanoparticles. Bio-Des Manuf 3(3). https://doi.org/10.1007/s42242-020-00074-8
33. Thakor J, Ahadian S, Niakan A, Banton E, Nasrollahi F, Hasani-Sadrabadi MM, Khademhosseini A (2020) Engineered hydrogels for brain tumor culture and therapy. Bio-Des Manuf 3(3). https://doi.org/10.1007/s42242-020-00084-6
34. Ma L, Li Y, Wu Y, Aazmi A, Zhang B, Zhou H, Yang H (2020) The construction of in vitro tumor models based on 3D bioprinting. Bio-Des Manuf 3(3). https://doi.org/10.1007/s42242-020-00068-6

35. Zubizarreta ME, Xiao S (2020) Bioengineering models of female reproduction. Bio-Des Manuf 3(3). https://doi.org/10.1007/s42242-020-00082-8
36. Li H, Cheng F, Robledo-Lara JA, Liao J, Wang Z, Zhang YS (2020) Fabrication of paper-based devices for in vitro tissue modeling. Bio-Des Manuf 3(3). https://doi.org/10.1007/s42242-020-00077-5
37. Shang Y, Chen Z, Zhang Z, Yang Y, Zhao Y (2020) Heart-on-chips screening based on photonic crystals. Bio-Des Manuf 3(3). https://doi.org/10.1007/s42242-020-00073-9



Guest Editor-in-Chief:
Dr. Yu Shrike Zhang received a B.Eng. in Biomedical Engineering from Southeast University, China (2008), a M.S. in Biomedical Engineering from Washington University in St. Louis (2011), and a Ph.D. in Biomedical Engineering at Georgia Institute of Technology/Emory University (2013). Dr. Zhang is currently an Assistant Professor at Harvard Medical School and Associate Bioengineer at Brigham and Women's Hospital. Dr. Zhang's research is focused on innovating medical engineering technologies, including bioprinting, organs-onchips, microfluidics, and bioanalysis, to recreate functional tissues and their biomimetic models towards applications in precision medicine. He has authored >190 journal papers (H-index = 53, >10,500 citations). He is a recipient of >40 regional, national, and international awards, and has delivered >120 invited/keynote lectures. Dr. Zhang serves on the editorial board of numerous journals and has been the Associate Editor of Bio-Design and Manufacturing since 2018.

Guest Editor-in-Chief:
Ali Khademhosseini As of April 2020, Dr. Khademhosseini is the CEO and Founding Director of the Terasaki Institute for Biomedical Innovation. In addition, he is also a principal researcher at Amazon Web Services (AWS) Inc. He was previously a Professor of Bioengineering, Chemical Engineering and Radiology at the University of California-Los Angeles (UCLA). He joined UCLA as the Levi Knight Chair in November of 2017 from Harvard University where he was a Professor at the Harvard Medical School (HMS) and faculty at the Harvard-MIT's Division of Health Sciences and Technology (HST), Brigham and Women's Hospital (BWH) as well as associate faculty at the Wyss Institute for Biologically Inspired Engineering. At Harvard University, he directed the Biomaterials Innovation Research Center (BIRC), a leading initiative in making engineered biomedical materials. He is recognized as a leader in combining micro- and nanoengineering approaches with advanced biomaterials for regenerative medicine applications. In particular, his laboratory has pioneered numerous technologies and materials for controlling the architecture and function of engineered vascularized tissues. He has authored >650 journal papers (H-index=128, >61,300 citations) and 70 books/chapters. In addition, he has delivered 300+ invited/keynote lectures. Dr. Khademhosseini's interdisciplinary research has been recognized by over 60 major national and international awards. He serves on the editorial board of numerous leading journals as well as an Associate Editor for ACS Nano, and has been an Editorial Board Member of Bio-Design and Manufacturing since 2018. He received his Ph.D. in bioengineering from MIT (2005), and MASc (2001) and BASc (1999) degrees from University of Toronto both in chemical engineering.