BIOGRAPHICAL SKETCH

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NAME: Sharon Gerecht

eRA COMMONS USER NAME (credential, e.g., agency login):

POSITION TITLE: Professor of Biomedical Engineering

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Technion-Israel Inst. Of Technology, Haifa, Israel	BA	1994	Biology
Tel-Aviv University, Tel-Aviv, Israel	MSc	1999	Medical Sciences
Technion-Israel Inst. Of Technology, Haifa, Israel	PhD	2004	Biotechnology Eng.
Technion-Israel Inst. Of Technology, Haifa, Israel	Postdoc	2004	Bioengineering
MIT- Massachusetts Inst. Of Technology, Cambridge	Postdoc	2007	Bioengineering

A. Personal Statement

Our lab studies the interactions between cells and their microenvironments with the long-term goal of understanding how the microenvironment guides differentiation, morphogenesis, homeostasis, as well as tumor growth and metastasis. Our research program is rooted in the fundamentals of interfacial science and engineering, and stem cell, vascular, and cancer biology. We employ engineering approaches to control the microenvironment in *in vitro* and *in vivo* experiments to uncover how the niche regulates vascular regeneration and tumor vascularization. The research in our laboratory has already yielded important results in the fields of vascular biology and stem cell engineering, as evidenced by more than 150 manuscripts published or in press in journals ranging from developmental and vascular biology to bioengineering, 25 book chapters, and three edited books.

B. Positions, Scientific Appointments and Honors

Positions, Scientific Appointments

2022- Present Professor of Biomedical Engineering, Duke University
2020- 2021 Edward J. Schaefer Professor in Engineering, Johns Hopkins University (JHU)
2017- 2021 Director, Institute for NanoBioTechnology (INBT), JHU
2017- 2021 Joint appointment, Oncology, School of Medicine|, JHU
2017- 2021 Secondary Appointment, Biomedical Engineering, JHU
2016- 2021 Professor, Chemical and Biomolecular Engineering, JHU
2012- 2021 Secondary Appointment, Materials Science and Engineering, JHU
2009- 2021 Lead Investigator, Johns Hopkins Engineering in Oncology Center
2007- 2021 Member of the Institute for NanoBioTechnology (INBT), JHU

Honors

2020 Elected Fellow of the American Association for the Advancement of Science (AAAS)
2020 Elected Member, National Academy of Inventors (NAI)
2019 Elected Member, National Academy of Medicine (NAM)
2017 Patrick C. Walsh Prostate Cancer Research Fund
2016 Elected Fellow of the American Institute for Medical and Biological Engineering (AIMBE)
2015 JHU Inaugural President's Frontier Award

2015-2019 American Heart Association (AHA) National Established Investigator Award
2015-2018 Inaugural Kent Gordon Croft Investment Management Faculty Scholar
2014-2017 W.W. Smith Charitable Trust Heart Award
2011-2016 NSF CAREER award
2009 North America Vascular Biology Organization Junior Investigator Award
2009-2011 March of Dimes Basil O'Connor Starter Scholar Research Award
2008 Maryland Academy of Sciences Outstanding Young Engineer Award, Allan C. Davis Medal
2008-2012 American Heart Association (AHA) National Scientist Development Award
2005-2007 Postdoctoral Fellowship Award, Juvenile Diabetes Research Foundation

C. Contributions to Science

1. Stem cell differentiation and vascular assembly

Human PSCs represent a unique opportunity to implement the study of human vascular development toward understand diseased mechanism and for regenerative medicine applications. We derived a bicellular vascular population from hPSCs, early vascular cells (EVCs), which can mature into functional ECs and pericytes. These EVCs can also self-organize to form microvascular networks in an engineered matrix that survive implantation, integrate with the host vasculature, and establish blood flow. We further have examined EVC differentiation under low O2 conditions, and found that low O2 environments during the early stages of differentiation enhance endothelial lineage commitment. In more recent work we further showed that surface stiffness regulate endothelial fate and that responses to flow. Differ among different hiPSC-derived ECs through cilia modulation. We further have examined vascular differentiation from type 1 diabetic (T1D) hiPSCs. We demonstrated that T1D-hiPSC can be directed to efficiently differentiate into EVCs. Early ECs derived from T1D-hiPSC are fully functional when mature and can assemble into 3D networks in hypoxic hydrogels, providing significant development for autologous vascular therapy in diabetic patients. These results highlight the potential of hPSCs as cell source for functional microvasculature to support tissue regeneration.

1. Cho H^, Macklin BL^, Lin Y, Zhou L, Lai M, Lee G, **Gerecht S*,** Duh EJ*. iPSC-derived endothelial cell response to hypoxia via SDF1a-CXCR4 axis facilitates incorporation to re-vascularize the ischemic retina. *JCI Insight.* 2020;5:e131828.
2. Smith Q, Macklin B, Chan XY, Jones H, Trempel M, Yoder MC, **Gerecht S.** Differential HDAC6 activity modulates ciliogenesis and subsequent mechanosensing of endothelial cells derived from pluripotent stem cells. *Cell Reports.* 2018; 24:895–908
3. Chan XY, Black R, Dickerman K, Federico J, Levesque M, Mumm J, **Gerecht S.** Three-dimensional vascular network assembly from diabetic patient-derived induced pluripotent stem cells. *Arterioscler Thromb Vasc Biol*. 2015; 35:2677-2685.
4. Kusuma S, Shen Y-I, Hanjaya-Putra D, Mali P, Cheng L, **Gerecht S.** Self-Organized Vascular Networks from Human Pluripotent Stem Cells in a Synthetic Matrix. *Proc Natl Acad Sci U S A.* 2013; 110:12601-12606.

2. Understanding and controlling vascular assembly and angiogenesis

Network assembly and angiogenesis is spatially and temporally regulated by biochemical and biophysical cues of the ECM and surrounding microenvironment. We develop and utilize synthetic, tunable hydrogels to determine various ECM properties and signaling pathways that enable human endothelial progenitors to form efficient vascular networks *in vitro* and then test the mechanism *in vivo*. For example, we have shown that endothelial progenitors entrapped in polysaccharide-based, hyaluronic acid, hydrogels modified with cell adhesive RGD and MMP-cleavable crosslinker underwent tubulogenesis dependent on the cellular interactions with the hydrogel during each stage of vascular morphogenesis. Vacuole and lumen formed through integrins α5β1 and αVβ¬3, while branching and sprouting were enabled by hydrogel degradation via MT1-MMP –activated MMP1, and MMP2. With this tunable platform we can display the therapeutic targets, using a wide array of pathological in vivo model systems. In another set of studies, we synthesized another polysaccharide-based, dextran, hydrogel by incorporating various functional groups and found that incorporating amine groups while maintaining reducing degree of substitution into dextran gave rise to hydrogels that promote angiogenesis and allowing for complete wound healing. More recently, we engineered new biomaterial platform to study how matrix viscoelasticity regulates morphogenesis. Using this platform, we identify the viscoelasticity effect on vessel morphogenesis through cell contractility-integrin-FAK-MMP pathway activation. These results are confirmed *in vivo,* both during vasculogenesis and angiogenesis using subcutaneous mouse model. These results serve as

a framework for designing hydrogel biomaterials that can be applied to studying complex tissue assembly and regeneration and towards a range of therapeutics.

1. Wei Z, Schnellmann R, Pruitt HC, **Gerecht S**. Hydrogel network dynamics regulate vascular morphogenesis. *Cell Stem Cell.* 2020; 27:1-15.
2. Wei Z, **Gerecht S**. A self-healing hydrogel as an injectable instructive carrier for cellular morphogenesis. *Biomaterials.* 2018;185:86-96.
3. Shen Y-I, Song H-HG, Papa A, Burke J, Volk SW, **Gerecht S**. Acellular hydrogels for regenerative burn wound healing: translation from a porcine model. *J Invest Dermatol.* 2015: 135:2519-2529.
4. Hanjaya-Putra D, Bose V, Shen Y-I, Yee J, Khetan S, Fox-Talbot K, Steenbergen C, Burdick JA, **Gerecht S.** Controlled activation of morphogenesis to generate a functional human microvasculature in a synthetic matrix. *Blood.* 2011;118:804-815.

3. Impact of ECMs' physical and mechanical properties on cancerous processes

The influence of cell:matrix interactions has broad application for tissue engineering, wound healing, and cancer biology. Through the generation of highly controlled and tunable biomaterials our lab has established the role of matrix physical and mechanical properties on 3D cancer cell and T cell migration. Specifically, we have shown that ECM patterning as well as fiber density and stress relaxation impact the ability of cancer cells interact with vascular cells as well as their ability to migrate and metastasize. The tumor microenvironment contains highly modified ECM structures including regions of aligned collagen fibers. Current 3D culture systems do not have the capacity to control the physical orientation of collagen fiber alignment. We generated devices that allow us to aligned collagen fibers to model the physiological tumor microenvironment and asses its role in directional motility of T cells. Using these models we were able to demonstrate that activated CD8+ T cells migrate persistently along aligned collagen fibers; that hypoxia and matrix properties jointly modulate metastasis; and that matrix properties regulate vascular fate.

1. Pruitt HC, Lewis D, Ciccaglione M, Connor S, Smith Q, Hickey JW, Schneck JP, **Gerecht S**. Collagen fiber structure guides 3D motility of cytotoxic T lymphocytes. *Matrix Biol*. 2020; 85-86: 147-159.
2. Lewis DM, Pruitt HC, Jain N, Ciccaglione M, McCaffery JM, Xia Z, Weber K, Eisinger-Mathason TS, and **Gerecht S**. A feedback loop between hypoxia and matrix stress relaxation increase oxygen-axis migration and metastasis in sarcoma. *Cancer Res*. 2019; 79:1981-1995.
3. Lewis DM, Tang V, Jain N, Xia Z, **Gerecht S.** Collagen Fiber Architecture Regulate Hypoxic Sarcoma Cell Migration. *ACS Biomater Sci Eng.* 2018; 4, 2, 400–409.
4. Smith Q, Chan XY, Carmo AM, Trempell M, Saunders M, Gerecht S. Differentiation of Human Pluripotent Stem Cells on Compliant Substrates Leads to Robust and Reproducible Endothelial Fate. *Sci. Adv* 2017; 3: e1602883.

4. Oxygen regulation in the three-dimensional extracellular environment

While hypoxia plays a pivotal role during various cellular processes, the design and utilization of a hypoxic 3D microenvironment to mimic the *in vivo* niche has not been realized. We first utilized HA hydrogels to study angiogenesis in hypoxic conditions. We then established novel O2-controlling hydrogel materials that can serve as 3D hypoxic microenvironment. We synthesized oxygen-controlling hypoxia-inducible (HI) gelatin or dextran hydrogels. Using our mathematical modeling detailed above we show that O_2 levels and gradients within the hydrogels can be accurately controlled and precisely predicted. We demonstrated the regulatory mechanism underlying hypoxic vascular network formation and angiogenesis. To the best of our knowledge, no other biomaterial is capable of controlling or manipulating O_2. Specifically, using the HI hydrogels, we presented a new concept in which O_2 acts as a 3D physio-tactic agent during sarcoma tumor invasion, findings that are important for the understanding of the metastatic process. Through this, we also establish the 3D *in vitro* model as a platform for testing therapeutic targets and interventions for the treatment of sarcoma and potentially other cancers.

1. Blatchley MB, Hall F, Wang S, Pruitt H, **Gerecht S**. Hypoxia and matrix viscoelasticity sequentially regulate endothelial progenitor cluster-based vasculogenesis. *Sci Adv.* 2019; 5:eaau7518
2. Lewis DM*, Blatchley M*, Park KM, **Gerecht S**. O_2-controllable hydrogels to study cellular responses to 3D hypoxic gradients. *Nat Protoc.* 2017; 12:1620-1638

3. Lewis D, Park KM, Tang V, Xu Y, Pak K, Eisinger-Mathason T.S.K, Simon CM, **Gerecht S.** Intratumoral oxygen gradients mediate sarcoma cell invasion. *Proc Natl Acad Sci U S A.* 2016; 113:9292-9297.
4. Park KM, **Gerecht S.** Hypoxia-inducible hydrogels. *Nat Commun.* 2014; 5:4075.

5. Fabricating 3D multicellular microvascular structures

Most studies on engineered vasculature focus on either capillary/microvasculature bed formation or large (>3 mm) vessel reconstruction. This is mainly due to the challenge of generating stable and robust tubular structures between 1-3mm in diameter. We established fibrin hydrogel microfibers made by a modified electrospinning technique as suitable candidates for guiding the sequential engineering of small vasculature, starting with the innermost layers. Endothelial seeded on these 3D fibrin microfibers were shown to follow the microfiber alignment, forming an organized endothelial monolayer. Remarkably, endothelial deposited ECM followed a circumferential organization around the microfibers. To build multicellular microvascular structures we introduced pericytes or SMCs on top of the endothelial monolayer. The resulting structures contain an endothelial monolayer with an ellipsoidal morphology and a fully invested perivascular multicellular layer expressing specific markers and ECM proteins. Building on these studies we recently delineated the therapeutic impact of these grafts. We fabricated luminal structures and following interposition implantation we found that the graft mediates neotissue formation and incorporation into the native tissue, and matches the native vessel size and mechanical properties. Our unique mimetic approach enables the creation of small vascular structures, providing the basis for mechanistic studies towards developing robust and regenerative arterial conduits as therapeutics.

1. Elliott MB, Ginn B, Fukunishi T, Bedja D, Suresh A, Chen T, Inoue T, Dietz HC, Santhanam L, Mao HQ, Hibino N, **Gerecht S**. Regenerative and Durable Small-Diameter Graft as an Arterial Conduit. *Proc Natl Acad Sci U S A*. 2019;116:12710-12719.
2. Barreto-Ortiz SF, Fradkin J, Eoh J, Trivero J, Davenport M, Ginn B, Mao H-Q, **Gerecht S**. Fabrication of 3D multicellular microvascular structures. *FASEB J.* 2015; 29:3302-3314.
3. Barreto-Ortiz SF, Zhang S, Davenport M, Fradkin J, Ginn B, Mao H-Q, **Gerecht S.** A Novel *In Vitro* Model for Microvasculature Reveals Regulation of Circumferential ECM Organization by Curvature. *PLos ONE* 2013; 8:e81061.
4. Zhang S, Liu X, Barreto-Ortiz FS, Yu Y, Ginn B, DeSantis N, Hutton LD, Grayson W, Cui F-Z, Korgel AB, **Gerecht S**, Mao H-Q. Creating Polymer Hydrogel Microfibers with Internal Alignment via Electrical and Mechanical Stretching. *Biomaterials.* 2014; 35: 3243-3251.

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