BIOGRAPHICAL SKETCH

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NAME: Shen, Keyue

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

POSITION TITLE: Assistant 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
Tsinghua University, Beijing, China	B.Eng.	07/2001	Mechanical Engineering
Tsinghua University, Beijing, China	M.S.	07/2004	Biophysics
Columbia University	Ph.D.	02/2010	Biomedical Engineering
Harvard Medical School and Massachusetts General Hospital	Postdoctoral	12/2014	Engineering in Medicine

A. Personal Statement

The goal of my research is to develop microengineered cell culture models and platforms for identifying pathways /targets in tumor microenvironment, and editing immune cell functions for immunotherapeutics. Specifically, I will utilize micropatterning techniques to control the composition and spatial organization of cell components to capture the compositional and architectural details of *in vivo* tumor microenvironment. I will also develop synthetic surfaces that senses as well as modulates T cell activation, and controls downstream differentiation for cancer immunotherapy. I have expertise and resources to accomplish these goals. During my doctoral study, I focused on understanding how micro-/nano-scale details of cell microenvironment influence T cell activation and functions with micropatterning and microfluidic techniques. During my postdoctoral training, I developed a micropatterned cell-based assay to recapitulate tumor microenvironment, to study the role of tumor-stroma interaction in driving invasiveness in breast cancer. During my research trainings, I have interacted with colleagues and collaborators across disciplines, with engineers, biologists and clinical researchers. The current research directions build logically on my prior work. I have my primary appointment at Biomedical Engineering department, and I am eager to become a member of Norris Comprehensive Cancer Center to work with people across biological and medical disciplines to widen and deepen my research in this area. In summary, I have a demonstrated record of successful and productive research projects in using micro- and nano-technology for biomedical research. By joining Norris Comprehensive Cancer Center I will be able to build collaborations with and receive mentorships from other experts, which will allow me to produce novel, pertinent engineering tools to advance cancer research and therapeutics.

1. Shen K, Thomas VK, Dustin ML, Kam LC, Micropatterning of costimulatory ligands enhances CD4+ T cell function, *Proc. Natl. Acad. Sci. U S A*, 105(22):7791-6 (2008)
2. Shen K, Tsai J, Shi P, Kam LC, Self-aligned supported lipid bilayers for patterning cell-substrate interface, *J. Am. Chem. Soc.*, 131(37):13204-5 (2009)
3. O'Connor R, Hao X, Shen K, Bashour K, Kam L, Milone MC, Substrate Rigidity Regulates ex vivo T Cell Activation and Proliferation, *J. Immunol.* 2012, 189(3):1330-9
4. Lee J, Li M, Milwid J, Dunham J, Vinegoni C, Gorbatov R, Iwamoto Y, Wang F, Shen K, Ebert BL, Weissleder R, Yarmush ML, Parekkadan B, "Implantable Microenvironments to Attract Hematopoietic Stem/Cancer Cells", *Proc. Natl. Acad. Sci. U S A*, 2012, 109(48):19638-43

5. Kam L, Shen K, Dustin ML, “Micro- and Nanoscale Engineering of Cell Signaling”, *Annu. Rev. Biomed. Eng.*, 2013,15:305-26
6. Bashour K, Tsai J, Shen K, Lee JH, Sun E, Milone MC, Dustin ML, Kam LC, "Crosstalk between CD3 and CD28 is Spatially Modulated by Protein Lateral Mobility”, *Mol. Cell. Biol.*, 2013, 34(6):955-64
7. Bashour K, Gondarenko A, Chen H, Shen K, Liu X, Huse M, Hone JC, Kam LC, “CD28 and CD3 Have Complementary Roles in T Cell Traction Forces”, *Proc. Natl. Acad. Sci. U S A*, 111(6):2241-6
8. Shen K, Lee J, Yarmush ML, Parekkadan B, “Microcavity Substrates Casted from Self-Assembled Microsphere Monolayers for Spheroid Cell Culture”, *Biomed. Microdevices*, 2014, 16(4):609-15
9. Shen K*, Luk S, Hicks DF, Elman JS, Bohr S, Iwamoto Y, Murray R, Pena K, Wang F, Seker E, Weissleder R, Yarmush ML, Toner M, Sgroi D, Parekkadan B, “Resolving Cancer-Stroma Interfacial Signaling and Interventions with Micropatterned Tumor-Stromal Assays”, *Nat. Commun.*, 2014, Dec 9;5:5662 *(*: co-corresponding author)*

B. Positions and Honors

Positions and Employment

2001-2004	Graduate Research Assistant, Department of Biological Sciences and Biotechnology, Tsinghua University, Beijing China
2004-2010	Graduate Research Assistant, Department of Biomedical Engineering, Columbia University, New York, NY
2010-2014	Postdoctoral Research Fellow, Center for Engineering in Medicine, Harvard Medical School and Massachusetts General Hospital, Boston, MA
2015-	Assistant Professor, Department of Biomedical Engineering, University of Southern California, Los Angeles, CA

Other Experience and Professional Memberships

2005-	Member, Biomedical Engineering Society
2007-	Member, Biophysical Society
2009-	Ad hoc reviewer, Cellular and Molecular Bioengineering
2011-	Ad hoc reviewer, Biomedical Microdevices
2011-	Ad hoc reviewer, Angewandte Chemie International Edition
2011-	Ad hoc reviewer, Analytical Chemistry
2013-	Member of Associate Editorial Board, Technology

Honors

1998	Hosogoe Award, Tsinghua University
1999	Schneider Electric Award, Tsinghua University
2000	Hosogoe Award, Tsinghua University
2001	Graduated *summa cum laude*, Tsinghua University
2006, 2007	SEAS Graduate fellowships, Columbia University
2008	Featured “From the Cover” article, *PNAS*, Vol. 105, No. 22
2010	PhD dissertation designated “*with Distinction*”
2011	Fund for Medical Discovery Fellowship, Massachusetts General Hospital

C. Contribution to Science

1. My early work focused on developing lab-on-chip devices for clinical diagnostic applications. Rapid sample preparation, nucleic acid extraction, and polymerase chain reaction (PCR) in a closed miniaturized system provides unique advantages over traditional clinical assays, with shorter processing, lower reagent costs, higher sensitivity, and without the risk of cross-contamination. I developed microfluidic chips for DNA extraction, devised and implemented a novel temperature control mechanism that greatly simplifies the design and fabrication of on-chip PCR devices. Those were further integrated to discriminate bacterial strains for clinical applications.
    a. Chen X, Shen K, Liu P, Guo M, Cheng J, Zhou Y, “Silica-based Solid Phase Extraction of DNA on a Microchip”, *Tsinghua Sci. Technol.*, 2004, 4(9):379-83

b. Shen K, Chen X, Guo M, Cheng J, “A Micro Chip-based PCR Device using Flexible Printed Circuit Technology”, *Sensor. Actuat. B-Chem.*, 2005, 105(2):251-8
c. Konry T, Bhushan A, Bale SS, Shen K, Polyak B, Seker E, “Microparticles and Microfluidics Merged: Perspectives of Highly Sensitive Diagnostic Detection”, *Microchim. Acta*, 2012, 176:251

2. One of my current research area centers on how the micro- and nano-scale details of the extracellular environment influence T cell activation. In my doctoral work I demonstrated for the first time that T cell activation is modulated by the spatial organization of T cell receptor (TCR) and CD28 signaling complexes, and discovered that the spatial regulation is mediated through Akt signaling. I also developed a microfluidic patterning platform of supported lipid bilayers to study the impact of membrane protein nanoscale mobility on T cell signaling, and showed parallel integrin clustering at the cell-bilayer interface upon spatially-segregated, collaterally-engaged TCR signaling, revealing IS spatial organization as a result of cytoskeletal reorganization and molecular sorting. In addition, I further investigated the role of cell-generated force on T cell activation, and demonstrated that cytokine secretion of T cells is influenced by the mechanical properties of the activating substrates, thus allowing for fine-tuning T cell function for adoptive T cell therapy.
    a. Shen K, Thomas VK, Dustin ML, Kam LC, Micropatterning of costimulatory ligands enhances CD4+ T cell function, *Proc. Natl. Acad. Sci. U S A*, 105(22):7791-6 (2008)
    b. Shen K, Tsai J, Shi P, Kam LC, Self-aligned supported lipid bilayers for patterning cell-substrate interface, *J. Am. Chem. Soc.*, 131(37):13204-5 (2009)
    c. Shen K, Qi J, Kam LC, Microcontact printing of proteins for cell biology, *J. Vis. Exp.*, (22). pii: 1065 (2008)
    d. Shen K, Milone MC, Dustin ML, Kam LC, Nanoengineering of Immune Cell Function, *Mater Res Soc Symp Proc*, 1209 (2009)
    e. O’Connor R, Hao X, Shen K, Bashour K, Kam L, Milone MC, Substrate Rigidity Regulates ex vivo T Cell Activation and Proliferation, *J. Immunol.* 2012, 189(3):1330-9
    f. Kam L, Shen K, Dustin ML, “Micro- and Nanoscale Engineering of Cell Signaling”, *Annu. Rev. Biomed. Eng.*, 2013, 2013,15:305-26
    g. Bashour K, Tsai J, Shen K, Lee JH, Sun E, Milone MC, Dustin ML, Kam LC, "Crosstalk between CD3 and CD28 is Spatially Modulated by Protein Lateral Mobility”, *Mol. Cell. Biol.*, 2013, 34(6):955-64
    h. Bashour K, Gondarenko A, Chen H, Shen K, Liu X, Huse M, Hone JC, Kam LC, “CD28 and CD3 Have Complementary Roles in T Cell Traction Forces”, *Proc. Natl. Acad. Sci. U S A*, 111(6):2241-6

3. Another major area of my research is to create tumor microenvironment models and explore drug interventions that target tumor-stroma interactions. In my postdoctoral work, I developed an *in vitro* micropatterned tumor-stromal assay (μTSA) to capture *in vivo* organization of tumor and stromal cells and spatial constraints on contact- and paracrine-signaling in real tumors. By coupling μTSA with laser capture microdissection, I have revealed an unprecedented cancer field effect induced by interfacial tumor-stromal signaling and a novel spatial mechanism for drug actions. I have extended my study to discover a previously unknown mechanism of reversine, a chemotherapeutic drug, in targeting interfacial tumor-stromal interactions in a breast cancer model, and validated its efficacy (as predicted by μTSA) in an *in vivo* tumor model. It supports high *in vivo* relevancy of the μTSA platform for studying cancer progression with applications in drug discovery and development. In addition, I have developed a three-dimensional (3-D) spheroid culture platform for studying drug actions in a 3-D culture of cancer and stromal cells.
    a. Lee J, Li M, Milwid J, Dunham J, Vinegoni C, Gorbatov R, Iwamoto Y, Wang F, Shen K, Ebert BL, Weissleder R, Yarmush ML, Parekkadan B, “Implantable Microenvironments to Attract Hematopoietic Stem/Cancer Cells”, *Proc. Natl. Acad. Sci. U S A*, 2012, 109(48):19638-43
    b. Shen K, Lee J, Yarmush ML, Parekkadan B, “Microcavity Substrates Casted from Self-Assembled Microsphere Monolayers for Spheroid Cell Culture”, *Biomed. Microdevices*, 2014, 16(4):609-15
    c. Shen K*, Luk S, Hicks DF, Elman JS, Bohr S, Iwamoto Y, Murray R, Pena K, Wang F, Seker E, Weissleder R, Yarmush ML, Toner M, Sgroi D, Parekkadan B, “Resolving Cancer-Stroma Interfacial Signaling and Interventions with Micropatterned Tumor-Stromal Assays”, *Nat. Commun.*, 2014, Dec 9;5:5662 *(*: co-corresponding author)*

4. My research interests and activities also extend to stem cell biology and regenerative medicine. In addition to the contributions described above, I have worked with a team of collaborators on neuron function guidance and neural stem cell mechanobiology, immune modulation in skin burn-wound healing, genetic regulation of epidermal stem cell niche, and mesenchymal stem cell-based therapies. These studies revealed chemical, mechanical, and cellular cues in regulating stem cell phenotypes and tissue damage/regeneration.
    a. Shi P, Shen K, Kam LC, "Local Presentation of L1 and N-cadherin in Multicomponent, Microscale Patterns Differentially Direct Neuron Function in vitro", Dev. Neurobiol., 2007, 67(13):1765-76
    b. Shi P, Shen K, Ghassemi S, Hone J, Kam LC, "Dynamic Force Generation by Neural Stem Cells on Elastomer Pillar Arrays", Cell. Mol. Bioeng., 2009, 2(4):464-74
    c. Bohr S, Patel SJ, Shen K, Vitalo AG, Brines M, Cerami A, Berthiaume F, Yarmush ML, "Alternative Erythropoietin-mediated Signaling Prevents Secondary Microvascular Thrombosis and Inflammation within Cutaneous Burns", *Proc. Natl. Acad. Sci. U S A*, 2013, 110(9):3413-8
    d. Bohr S, Patel SJ, Vasko, R, Shen K, Huang G, Yarmush ML, Berthiaume F, "Constitutively Expressed Lhx2 Reflects a Dysregulated, Expanded Epidermal Stem Cell Niche in the Foxn1-/- Nude Mouse Phenotype", *PLoS ONE*, 2013, 8(5):e64223
    e. Milwid JM, Elman JS, Li M, Shen K, Manrai A, Gabow A, Jiao Y, Fletcher A, Lee, J, Cima MJ, Yarmush ML, Parekkadan B, "Profiling of Bone Marrow Stromal Cell Secretions Reveals Human MFAP5 and PENK as Potent Stimulators of Endogenous Interleukin-10 Secretion", *Mol. Ther.*, 2014, 22(5):999-1007
    f. Elman J, Murray R, Wang F, Shen K, Gao S, Conway KE, Yarmush ML, Tannous BA, Weissleder R, Parekkadan B, "Pharmacokinetics of Natural and Engineered Secreted Factors Delivered by Mesenchymal Stromal Cells", *PLoS ONE*, 2014, 9(2):e89882
    g. Bohr S, Patel SJ, Vasko R, Shen K, Iracheta-Vellve A, Lee J, Bale SS, Chakraborty N, Brines M, Cerami A, Berthiaume F, Yarmush ML, "Modulation of Cellular Stress Response via the Erythropoietin/CD131 Heteroreceptor Complex in Mouse Mesenchymal-derived Cells", *J Mol Med (Berl)*, 2015, Feb;93(2):199-210

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1HC260NMH_XQ3/bibliography/43215019/public/?sort=date&direction=ascending

D. Research Support

Completed Research Support

Fund for Medical Discovery Award Shen (PI) 01/01/12-12/31/12
Massachusetts General Hospital
"A Micropatterned Tumor-Stromal Assay for Studying Invasiveness and Drug Resistance in Breast Cancer"
The objective of this study is to develop a microengineered breast tumor model to 1) study breast cancer invasiveness progression, and 2) test drugs and design combinatorial therapies for breast cancer
Role: PI