# BIOGRAPHICAL SKETCH

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NAME: Heilshorn, Sarah C.

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

POSITION TITLE: Associate Professor of Materials Science and Engineering and Bioengineering (by courtesy)

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 |
|---|---|---|---|
| Georgia Institute of Technology, Atlanta, GA | B.S. | 06/1998 | Chemical Engineering |
| California Institute of Technology, Pasadena, CA | M.S. | 06/2000 | Chemical Engineering |
| Kyoto Institute of Technology, Kyoto, Japan | Visiting Sci. | 09/2002 | Polymer Science |
| California Institute of Technology, Pasadena, CA | Ph.D. | 06/2004 | Chem. Eng. and Biology |
| University of California, Berkeley, CA | Postdoc | 09/2006 | Cell Biology |

## A. Personal Statement

My scientific training spans the fields of cell biology, engineering, and materials science; this multidisciplinarity uniquely positions my research team to develop new technologies to address medical challenges and biological questions. In particular, my research group has a long-standing interest in the development of *protein-based scaffolds* for *in vitro* studies of cell-matrix interactions and *in vivo* regeneration studies. In particular, we have developed a strategy to create *protease-responsive biomaterials* with precisely controlled temporal and spatial degradation profiles independent from the initial matrix mechanical properties and cell adhesion properties. The protein-based biomaterials were specifically designed to include target sequences that degrade in response to two enzymes secreted by Schwann cells and by the tips of extending neurites: urokinase plasminogen activator (uPA) and tissue plasminogen activator (tPA). More recently, we have reported biomaterials that respond to the cell-surface protease, ADAM9, expressed by neural progenitors. For each of these cases, ours was the first use of these unique enzymes and their target sequences in engineered biomaterials. To assess the functionality of these injectable biomaterials, my group often establishes collaborative work with laboratories in the Stanford School of Medicine. For example, we actively collaborate with Profs. Giles Plant, Gary Steinberg, and Paul George in Stanford Neurosurgery and Profs. Joseph Woo and Ngan Huang in Stanford Cardiothoracic Surgery. Therefore, my laboratory is an ideal environment for providing training in the design and development of novel biomaterials for regenerative medicine.

a. Straley K, Heilshorn SC. Dynamic, three-dimensional pattern formation within enzyme-responsive hydrogels. ***Advanced Materials***, 21:4148-4152, 2009.
b. Madl CM, Katz L, Heilshorn SC. Bio-orthogonally crosslinked, engineered protein hydrogels with tunable mechanics and biochemistry for cell encapsulation. ***Advanced Functional Materials***, 26:3612-3620, 2016.
c. Quarta M, Brett J, DiMarco R, De Morree A, Boutet S, Chacon R, Gibbons M, Garcia V, Su J, Shrager J, Heilshorn SC, Rando T. An artificial niche preserves the quiescence of muscle stem cells and enhances their therapeutic efficacy. ***Nature Biotechnology***, 34:752–759, 2016.
d. Madl C, LeSavage B, Dewi R, Dinh C, Stowers R, Khariton M, Lampe K, Nguyen D, Chaudhuri O, Enejder A, Heilshorn SC. Maintenance of neural progenitor cell stemness in 3D hydrogels requires matrix remodeling. ***Nature Materials***, 16:1233-1242, 2017.

## B. Positions and Honors

**Positions and Employment**

2000-2004 Graduate Research Assistant, Division of Chemistry and Chemical Engineering, Caltech
2002 Visiting Scholar, Department of Polymer Science, Kyoto Institute of Technology
2004 - 2006 Post-doctoral Scholar, Molecular and Cell Biology Department, University of California, Berkeley
2006 - 2014 Assistant Professor, Department of Materials Science and Engineering, Stanford University
2011 - 2014 Assistant Professor, by courtesy, Department of Bioengineering, Stanford University
2011 - 2014 Assistant Professor, by courtesy, Department of Chemical Engineering, Stanford University
2014 - Associate Professor and Lee Otterson Faculty Scholar, Stanford University

**Other Experience and Professional Memberships**

2006 - Materials Research Society, symposium organizer for conferences in 2010, 2011, 2013, and 2015
2006 - National Science Foundation, grant review
2008 - Department of Energy, Basic Energy Sciences, Biomolecular Materials Program, grant review
2010 NIH, Bioengineering, Technology, and Surgical Sciences study section, ad hoc member
2011-13 NIH, Nanotechnology study section, ad hoc member
2012 Organizing Committee, 6th International Conference on Bioengineering and Nanotechnology
2012 - Editorial Advisory Board, *Biomacromolecules*, American Chemical Society
2013 Scientific Advisory Committee, Tissue Engineering & Regenerative Medicine International Society (TERMIS) Americas Meeting
2013 - Editorial Board, *Biomaterials Science*, Royal Society of Chemistry
2013 - Editorial Board, *Molecular Therapy: Methods and Clinical Development*, Nature Publishing Group
2014 Guest Editor, *Acta Biomaterialia*, Elsevier
2014 Editorial Advisory Board, *ACS Biomaterials Science & Engineering*, ACS
2014 - 16 Vice Chair, Gordon Research Conf., Signal Transduction by Engineered Extracellular Matrices
2015 Guest Editor, *Current Opinion in Solid State and Materials Science*, Elsevier
2015 Visiting Professor, University of Chicago, Institute for Molecular Engineering
2015 - Associate Editor, *Science Advances*, AAAS
2016 Visiting Professor, Department of Mechanical Engineering, University of Sydney, Australia
2016 - Editorial Advisory Board, *Advanced Biosystems*, Wiley
2016 - Editorial Advisory Board, *APL Bioengineering*, AIP Publishing
2016 Co-chair for international meeting of the Materials Research Society (MRS)
2017 - Standing member, MRS Programming Development Committee
2016 - 18 Chair, Gordon Research Conference, Signal Transduction by Engineered Extracellular Matrices

**Honors**

1998 National Science Foundation Graduate Student Fellowship
2002 International P.E.O. Fellowship for Women in Advanced Degree Programs
2002 National Science Foundation East Asia Summer Institute Fellow
2003 Everhart Lectureship, California Institute of Technology
2006 Terman Faculty Fellow, Stanford University
2006 Gabilan Faculty Fellow, Stanford University
2006 Powell Foundation Fellow, Stanford University
2008 Translational Nanoscience Young Scholar Award, University of Southern California
2008 Hellman Foundation Faculty Scholar
2009 National Science Foundation CAREER Award
2009 American Chemical Society, Petroleum Research Fund, Doctoral New Investigator Award
2009 National Institutes of Health, New Innovator Award
2012 Colburn Lectureship, Department of Chemical and Biomolecular Engineering, University of Delaware
2014 3M Non-tenured Faculty Award
2015 University of Sydney International Research Collaboration Award
2015 Stanford Lee Otterson Faculty Scholar
2016 Elected as a Fellow of the American Institute for Medical and Biological Engineering (AIMBE)
2016 William R. and Gretchen B. Kimball University Fellow in Undergraduate Education, Stanford
2017 Elected as a Fellow of the Royal Society of Chemistry

**C. Contributions to Science**

1. We designed a bio-resorbable, customizable hydrogel using protein-engineering technology to overcome several limitations of currently available, cell-delivery materials. Current protocols to encapsulate cells within hydrogels require substantial changes in environmental conditions (pH, temperature, or ionic strength) or the addition of chemical crosslinking reagents to initiate gelation. These conditions can be irreversibly detrimental to encapsulated cells and are often hard to reproduce, complicating their use in a clinical setting. To overcome this bottleneck, we utilized a *two-component, molecular-recognition gelation strategy* that enables cell encapsulation without environmental triggers or chemical crosslinkers. In this system, termed Mixing-Induced Two-Component Hydrogels (MITCH), the network assembly is driven by specific and stoichiometric peptide-peptide binding interactions, which enable a sol-gel phase transition to occur upon simple mixing. These materials embody the first demonstrated use of WW and proline-rich peptide domains in protein-engineered materials, thereby expanding the repertoire of peptides successfully designed into engineered proteins. By integrating protein science methodologies with polymer physics models, we demonstrated the direct ability to tune the sol-gel phase behavior and gel mechanics through variations in the molecular-level design.

a. Wong Po Foo C, Lee JS, Mulyasasmita W, Parisi-Amon A, Heilshorn SC. Two-component protein-engineered physical hydrogels for cell encapsulation. ***Proceedings of the National Academy of Sciences USA***, 106 (52):22067-22072, 2009.
b. Cai L, Dewi RE, Heilshorn SC. Injectable Hydrogels with In Situ Double Network Formation Enhance Retention of Transplanted Stem Cells. ***Advanced Functional Materials***, 25(9):1344-51, 2015.
c. Wong Po Foo C, Heilshorn SC. "Hetero-assembled Hydrogels," **US Patent** # 9011914. Assigned to The Board of Trustees of the Leland Stanford Junior University. Issue Date: 4/21/2015.
d. Wang H, Zhu D, Paul A, Cai L, Enejder A, Yang F, Heilshorn SC. Covalently adaptable elastin-like protein–hyaluronic acid (ELP–HA) hybrid hydrogels with secondary thermoresponsive crosslinking for injectable stem cell delivery. ***Advanced Functional Materials***, 27:1605609, 2017.

2. My research group has a long-standing interest in the development of *injectable hydrogels for regenerative medicine therapies and 3D bio-printing*. Contradicting traditional lore within the medical community, we demonstrated that the shear stresses and pressure drops experienced by cells during typical injection procedures are not sufficient to induce cell death. In contrast, we identified extensional stretching forces experienced at the constriction point between the syringe and needle as a significant cause of mechanical cell membrane disruption, leading to a significant loss in acute cell viability. We further demonstrated that hydrogels of specific viscoelastic properties could provide protection from these damaging forces to a variety of clinically relevant cell types including endothelial cells, adipose-derived stem cells, marrow stromal cells, neural progenitor cells, and Schwann cells. More recently, we have demonstrated that these same injection-induced forces that cause cell membrane damage are also a major contributor to cell death during 3D bio-printing. As additive manufacturing of living tissues through use of 3D bio-printers becomes a more widely available and scalable technology, it will be critical to develop new bio-inks that are cell compatible and can protect cells from the mechanical forces experienced during the printing process. We have shown our newly developed, extrudable bio-inks can significantly improve cell membrane integrity after 3D bio-printing.

a. Aguado BA, Mulyasasmita W, Su J, Lampe KJ, Heilshorn SC. Improving viability of stem cells during syringe needle flow through the design of hydrogel cell carriers. ***Tissue Engineering Part A***, 18:806-815, 2012.
b. Mulyasasmita W, Cai L, Dewi R, Jha A, Ullmann SD, Luong RH, Huang NF, Heilshorn SC. Avidity-controlled hydrogels for injectable co-delivery of induced pluripotent stem cell-derived endothelial cells and growth factors. ***Journal of Controlled Release***, 191:71-81, 2014.
c. Dubbin K, Hori Y, Lewis K, Heilshorn SC. Dual-stage crosslinking of a gel-phase bioink improves cell viability and homogeneity for 3D bioprinting. ***Advanced Healthcare Materials***, 5(19): 2488-2492, 2016.
d. Steele A, Cai L, Truong V, Edwards B, Goldstone A, Eskandari A, Mitchell A, Marquardt L, Foster A, Cochran J, Heilshorn SC, Woo J. A novel protein-engineered hepatocyte growth factor analog released via a shear-thinning injectable hydrogel enhances post-infarction ventricular function. ***Biotechnology and Bioengineering***, 114: 2379–2389, 2017.

3. My laboratory has a long-standing focus on the design multi-functional materials composed of engineered proteins for use as _nervous tissue culture scaffolds_. These materials are synthesized with exact molecular-level precision through the use of genetic templates. This exquisite synthetic control results in the fabrication of materials that are ideal for fundamental studies of structure-property-function relationships and cell-matrix interactions. Our materials are engineered to mimic many of the essential functions of natural tissues including elasticity, cell-receptor binding (e.g. RGD ligands), and enzymatic remodeling. However, in contrast to naturally evolved matrix proteins, our engineered proteins are easily customized to allow independent tuning of multiple material properties. Recent results have explored the synergistic effects of RGD ligand presentation with soluble nerve growth factor stimulation to mediate Schwann cell migration and neurite outgrowth.

a. Straley K, Wong Po Foo C, Heilshorn SC. Biomaterial design strategies for the treatment of spinal cord injuries. ***Journal of Neurotrauma***, 27:1-19, 2010.
b. Lampe KJ, Heilshorn SC. Building stem cell niches from the molecule up through engineered peptide materials. ***Neuroscience Letters***, 519:138-146, 2012.
c. Lampe KJ, Antaris AL, Heilshorn SC. Design of 3D engineered protein hydrogels for tailored control of neurite growth. ***Acta Biomaterialia***, 9:5590-5599, 2013.
d. Romano N*, Madl CM*, Heilshorn SC. Matrix RGD ligand density and L1CAM-mediated Schwann cell interactions synergistically enhance neurite outgrowth. ***Acta Biomaterialia***, 11:48–7, 2015.

4. We have developed a number of different microdevice technologies to engineer 2D substrates and 3D scaffolds for study of _neurite development and path-finding_. In collaboration with the neurobiologist, Prof. Mu-ming Poo (UC Berkeley), we helped to identify novel mechanisms for axon initiation, specification, and long-range regulation. More recent results have uncovered a previously unknown trade-off in biomaterials design to promote neurite outgrowth: while higher RGD ligand concentrations promote longer neurite outgrowth, this comes at the expense of the neurite's path-finding ability within a gradient of nerve growth factor.

a. Shelly M, Cancedda L, Heilshorn SC, Sumbre G, Poo M. LKB1/STRAD promotes axon initiation during neuronal polarization. ***Cell***, 129:565-577, 2007.
b. Shelly M, Lim BK, Cancedda L, Heilshorn SC, Gao H, Poo MM. Local and long-range reciprocal regulation of cAMP and cGMP in axon/dendrite formation. ***Science***, 327:547-552, 2010.
c. Xu H, Ferreira MM, Heilshorn SC. Small-molecule axon-polarization studies enabled by a shear-free microfluidic gradient generator. ***Lab on a Chip***, 14:2047-2056, 2014.
d. Romano N, Lampe K, Xu H, Ferreira M, Heilshorn SC. Microfluidic gradients reveal enhanced neurite outgrowth but impaired guidance within 3D matrices with high integrin ligand densities. ***Small***, 11:722-730, 2015.

5. While designing our biomaterials, we wanted to introduce directional cues into the material that would guide the _migration and polarization of cells_. However, in looking through the literature to identify the figures of merit (e.g., minimal concentration to induce activity, maximal concentration that would be saturating, and gradient required for directionality), we quickly discovered that very little quantitative data have been collected in this field, and the data that were presented were often conflicting. In response, we developed a simple-to-use microfluidic device that exposes cells (either in 2D or 3D culture) to a stable, well-defined concentration gradient of soluble factors. This device has been adapted for use by several other groups; for example, in collaboration with the cell biologist Prof. Calvin Kuo (Stanford), we have identified a previously unknown receptor that is required for the chemotaxis of endothelial cells in the central nervous system. In our laboratory, we have used the device to quantify chemotaxis of human embryonic stem cell-derived neural progenitor cells.

a. Kuhnert F, Mancuso MR, Shamloo A, Wang HT, Choksi V, Florek M, Su H, Fruttiger M, Young WL, Heilshorn SC, Kuo CJ. Essential regulation of CNS angiogenesis by the orphan G protein-coupled receptor GPR124. ***Science***, 330:985-989, 2010.
b. Shamloo A, Heilshorn SC. Matrix density mediates polarization and lumen formation of endothelial sprouts in VEGF gradients. ***Lab on a Chip***, 10:3061-3068, 2010.
c. Huang NF, Dewi RE, Okogbaa J, Lee JC, Rufaihah A, Heilshorn SC, Cooke JP. Chemotaxis of human induced pluripotent stem cell-derived endothelial cells. ***Amer. J. Translational Res.***, 5:510-520, 2013.
d. Xu H, Heilshorn SC. Microfluidic investigation of BDNF enhanced neural stem cell chemotaxis in CXCL12 gradients. ***Small***, 9:585-595, 2013.

**Online List of Published Work**
http://www.ncbi.nlm.nih.gov/pubmed/?term=heilshorn+s

**D. Additional Information: Research Support**

**Ongoing Research Support**

RT3-07948 (Heilshorn: PI) 02/01/15 - 01/31/18
California Institute of Regenerative Medicine
*Injectable hydrogels for the delivery, maturation, and engraftment of clinically relevant numbers of human induced pluripotent stem cell-derived neural progenitors to the central nervous system*
The major goal of this project is to develop and tune an optimized extracellular matrix to improve the delivery, maturation, and engraftment of transplanted neural stem cells in a spinal cord injury model.

NSF DMR-1508006 (Heilshorn: PI)
National Science Foundation 06/01/15 - 05/31/18
*Design of self-assembling bio-inks for cell-based 3D printing*
The major goal is to develop a new, cell-compatible biomaterials for 3-dimensional printing with cells.

U19 AI-116484 (Kuo: Lead PI, Heilshorn: PI) 05/01/15 - 04/30/20
National Institutes of Health
*Stanford Cooperative Research Center for Novel, Alternative Model Systems for Enteric Diseases*
The major goal of this project is to design and develop and a novel, organoid-based model system to characterize enteric diseases.

R21 HL-138042 (Heilshorn: Lead PI, Woo: PI) 07/01/17 - 06/30/19
National Institutes of Health
*Engineered Protein Hydrogels to Modulate Adipose-derived Stromal Cell Secretome and Exosomes for Injectable Myocardial Infarction Therapy*
The major goal of this project is to develop and tune an optimized extracellular matrix to improve the treatment of myocardial infarction using exosomes.

**Selected Recent Completed Research Support**

DP2 OD-006477 New Innovator Award (Heilshorn: PI) 10/01/09 – 09/30/14
National Institutes of Health
*Engineering 3D* in vitro *niches to reveal fundamentals of cellular biomechanics*
The goal of this grant was to develop new *in vitro* cell culture techniques that recapitulate the *in vivo* niche for quantitative studies of neural progenitor cell migration.

DMR-0846363 CAREER (Heilshorn: PI) 09/01/09 – 08/30/14
National Science Foundation
*Adaptable biomaterials that enable cell-induced remodeling and drug delivery*
The goal of this grant was to develop a theoretical model and experimental platform to deliver multiple pharmaceutical peptides with distinct release profiles from a single hydrogel scaffold.

RT2-01938 (Heilshorn: PI) 06/01/11 - 05/31/14
California Institute for Regenerative Medicine
*Preparation and Delivery of Clinically Relevant Numbers of Stem Cells Using 3D Hydrogels*
The goal was to develop an injectable hydrogel for the efficient delivery of a stem cell-derived therapy.

R21 EB018407 (Heilshorn: PI) 09/30/14 - 08/31/16
National Institutes of Health
*Engineered intestinal microenvironments as preclinical drug screening platforms*
The goal was to modify drug transport through epithelial cell monolayers by controlling cell-matrix interactions.

R21 EB020235-01 (Heilshorn: PI, Huang: Co-PI) 04/01/15 - 03/31/17
National Institutes of Health
*Injectable hydrogels to improve the efficacy of iPSC-derived therapies*
The major goal of this project is to develop a hydrogel formulation that would improve the efficacy of iPSC-derived therapies in models of peripheral arterial disease.