BIOGRAPHICAL SKETCH

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NAME: Timothy Mark O'Shea

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

POSITION TITLE: Assistant Professor, 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
Queensland University of Technology, Brisbane, Australia	B.E. (Hons I)	02/05 - 03/09	Medical Engineering
Queensland University of Technology, Brisbane, Australia	M.Eng	02/08 - 08/09	Engineering Management
Massachusetts Institute of Technology, Cambridge, MA	Ph.D.	09/09 - 06/15	Medical Engineering and Medical Physics
University of California, Los Angeles (UCLA), Los Angeles, CA	Postdoctoral	08/15-06/20	Neurobiology and Bioengineering

A. Personal Statement

I am an Early Stage Investigator in a tenure track Assistant Professor position in Biomedical Engineering at Boston University (BU) with expertise in biomaterials and neurobiology. I am drawing upon my technical research expertise in biomaterials synthesis, characterization, and their use in central nervous system disorder models as well as my experiences in mentoring and supervising predoctoral students to serve as the principal investigator (PI) of the Glia Engineering Lab.

I am currently establishing my multi-disciplinary group uniquely positioned at the interface of bioengineering and glia neurobiology. We are focused on developing new treatments for brain and spinal cord disorders by engineering the functions of glia. Glia are a collection of cells in the brain and spinal cord that interact directly with neurons to ensure healthy nervous system function. In the context of injury, glia are destroyed and are not naturally replenished. In certain disorders, glia dysfunction is the root cause of disease. We are interested in understanding how glia respond to injury using *in vivo* animal models of spinal cord injury and stroke and developing new bioengineering tools to regulate their functions. Biomaterials are the foundation of our bioengineering toolkit and within my group we are currently working on synthesizing and characterizing a variety of new glycan-based biomaterials that are composed of polymers with biologically inspired supramolecular functionalities that afford tunable physiochemical and biological properties. My group's focus on multi-disciplinary convergence research with a biomaterials emphasis is shaped by my interdisciplinary training. Through my PhD studies in medical engineering and medical physics in the Harvard and MIT Health Sciences and Technology program under the supervision of Robert Langer I honed skills in biomaterials synthesis and characterization. As part of this training I developed and tested strategies to improve delivery of therapies for neurological disorders by synthesizing new innovative biomaterials. My postdoctoral training in neurobiology was conducted under the guidance of Michael Sofroniew at UCLA. This neurobiology training was broadly focused on studying cell and molecular mechanisms of spinal cord injury and repair with an emphasis on contributions made by glial cells. To facilitate this work, I developed and used new bioengineering tools including biomaterials, neural progenitor cells and viral vectors. I also conducted complementary training in advanced polymer synthesis techniques under Timothy Deming during my UCLA postdoc.

Given my comprehensive technical training in biomaterials, my research interests, and my current supervision of biomedical engineering predoctoral students who are conducting biomaterials related research, I am well positioned to make significant and impactful contributions as a faculty mentor.

B. Positions and Honors

Positions and Employment:

2020-Present Assistant Professor, Biomedical Engineering Department, Boston University, Boston, MA, USA.
2015-2020 Postdoctoral Fellow, UCLA Neurobiology and Bioengineering, Michael Sofroniew and Timothy Deming Laboratories, Los Angeles, CA, USA.
2010-2015 Scientific Consultant and Research Scientist, In Vivo Therapeutics, Cambridge, MA, USA.
2009-2015 PhD Graduate Researcher, Harvard-MIT HST Program, Robert Langer Laboratory, MIT, Cambridge, MA, USA.
2006-2009 Recitation instructor and lecturer (Approximately 200 hours of teaching experience) across several undergraduate courses including: Engineering Professional Practice, Biomechanical Engineering Design, Engineering Materials, Biomaterials and Engineering Mechanics at QUT, Brisbane, Australia.

Professional Experience:

2019-Present Application Reviewer American Australian Association.
2018-Present Reviewer for Acta Biomaterialia and Nature Communications.
2015-Present General Sir John Monash Scholarship application reviewer.
2015-2020 UCLA undergraduate research mentor and advisor. (Research advisor and mentor to 3 undergraduate and PhD students).
2014 HST IDEA2 project evaluation committee.
2011 Organization committee, 2nd annual skin trailblazer workshop.
2010 Ohio State University Spinal Cord Injury Training Program (3 week NIH funded Spinal Cord Injury research methods training program).
2010 Rutgers University W. M. Keck Center for Collaborative Neuroscience Spinal Cord Injury Training Program.
2009-2015 MIT undergraduate research opportunity (UROP) mentor. (Research advisor and mentor to 7 undergraduate students).
2009-2011 HST Joint Council social chairperson.
2007-2009 Project Engineer and Manager, Appropriate medical technology initiative Christian Medical College (CMC) Hospital, Vellore, India.
2006-2009 Executive member engineers without borders (EWB) Australia, QUT Chapter.

Honors:

2019 Wings for Life Spinal Cord Foundation Research Fellowship
2018 Paralyzed Veterans of America (PVA) Research Foundation Fellowship
2018 American Australian Association Keith Murdoch Scholarship.
2016 Craig H Neilsen Postdoctoral Fellowship in Translational Spinal Cord Injury Research.
2015 HST Martha Gray Prize for Excellence in Research.
2015 MISTI Global Seed Fund Student Award for research collaboration with Ben Gurion University, Israel.
2013 Langer Summit on Neurotrauma Prize.
2012 Society of Chemical Industry Perkins Student Scholarship.
2012 HST Idea2 Fellowship for novel and inspiring ideas in medical research.
2009 Harvard-MIT Division of Health Sciences and Technology Fellowship.
2009 Suncorp Young Queenslander of the Year Finalist.
2008 General Sir John Monash Award: Awarded to up to eight outstanding Australian citizen per year to enable them to undertake postgraduate study abroad.
2008 John Kindler Memorial Medal: Awarded to one graduate of an engineering degree course at QUT per year for outstanding performance throughout the course, based on academic achievement and involvement in campus, community and leadership activities.
2008 QUT-DePuy Prize for best medical engineering final year thesis and poster.
2007 QUT Student Leadership Award.
2006-2008 QUT Dean's Scholarship for the Developing World.

C. Contributions to Science

My research contributions to date can be broadly categorized into four main areas:(i) biomaterial tool development, (ii) dissecting glial cell contributions to CNS disorders, (iii) stimulating repair and regeneration in central and peripheral nervous system injury, and (iv) characterizing and regulating the foreign body response to biomaterials in the CNS.

1. Biomaterial tool development

Biomaterials are used widely in devices, drug delivery systems and tissue scaffolds. There is a need to develop new biomaterials with unique chemical functionalities and enhanced control of physiochemical and biological properties to improve clinical performance. My PhD graduate research involved the development of novel biomaterial tools, composed of synthetic biocompatible polymers, functional excipients and peptides that were formulated to improve the controlled release and functional stability of a variety of identified candidate therapies for central and peripheral nervous system disorders. Specifically, these biomaterial tools included: (i) a library of amphiphilic multifunctional thiol and acrylate oligomers that could be formulated into injectable, non-swelling materials for tailorable drug delivery to volume-constrained anatomical sites such as the spine using thiol-ene Michael addition chemistry; and (ii) trehalose (glycan) based covalent crosslinked hydrogels that showed a unique capacity to stabilize the complex secondary and tertiary structure of complex and fragile biomolecules to improve duration of bioactivity during controlled release. Across these studies I developed an enzymatic catalyzed chemical synthesis approach to derive acrylate and thiol functionalized monomers and multifunctional oligomers. Within my postdoctoral studies I further advanced my capabilities in biomaterial tool development. Biomaterial synthesis and fabrication projects conducted in my postdoc included: (i) synthesis of new non-ionic diblock copolypeptides that self-assemble by non-covalent interactions into shear thinning hydrogels appropriate for use as cell transplantation carriers, and (ii) formulation of tunable microgels using inverse emulsion and phase separation techniques that can be used to tailor molecular delivery when impregnated in shear thinning hydrogel matrices. My contribution to these studies encompassed all aspects of design, experimentation, analysis and dissemination.

Key papers (* designates co-first author):

a) **O'Shea, T.M.,** Aimetti A.A., Kim E., Yesilyurt V. and Langer R., Synthesis and Characterization of in situ curing ethoxylated polyol thiol-ene hydrogels for tailorable macromolecule delivery. 2015. *Advanced Materials*. 27(1). 65-72.

b) **O'Shea, T.M**, Webber, M.J., Aimetti A.A., and Langer R. Covalent Incorporation of Trehalose within Hydrogels for Enhanced Long-Term Functional Stability and Controlled Release of Biomacromolecules. 2015. *Advanced Healthcare Materials*. 4(12):1802-12

c) *Wollenberg, A.L. ****O'Shea, T.M.***, Kim, J., Sofroniew M.V., and Deming, T.J. Injectable polypeptide hydrogels via methionine modification for neural stem cell delivery. 2018. *Biomaterials. 178:527-545.*

d) Pritchard, C.D., **O'Shea, T.M.**, Calo, E., Siegwart, D.J., Anderson, D.G., et al. A novel injectable thiol-acrylate poly(ethylene glycol) hydrogel for sustained release of methylprednisolone sodium succinate. 2011. Biomaterials. 32(2): 587-597.

2. Dissecting glial cell contributions to CNS disorders

Glia, together with neurons, comprise the parenchymal unit of the CNS. Glia are primary responders to perturbations in normal CNS function and their dysfunction is implicated in numerous diseases. However, there is much still unknown about how and why glia become reactive in specific disorders and what contribution these altered cell states have on amelioration or exacerbation of CNS disorder pathophysiology. Through my postdoc I conducted rigorous, mechanistic studies of glia functions in injury and disease contexts using modern cell and molecular biology techniques such as transcriptomics, transgenic loss of function mouse models, and cell specific lineage tracing. Using these techniques and incorporating some of the biomaterial tools described above we have made field-shaping discoveries including that: (i) astroglial scar formation is critical for spontaneous and stimulated axon regeneration in spinal cord injury (SCI), (ii) the contribution of ependymal cells to forming astroglial scar borders in SCI is minimal and depends on direct injury to the central canal, (iii) transcriptional regulation of astrocyte reactivity in CNS disorders is combinatorial, complex, diverse and context dependent; and (iv) SCI astroglial border formation is a dynamic process involving contribution from multiple glia cell types. My contributions to these studies included study design, surgical procedures, behavioral analysis, cell and

molecular characterizations, data analysis and manuscript preparations. Manuscripts for the last two projects are currently in revision and in preparation respectively.

Key papers

a) Anderson M. A., Burda J. E., Ren Y., Ao Y., **O'Shea, T.M.**, Kawaguchi R., Coppola G., Khakh B. S., Deming T. J. and Sofroniew M. V. Astrocyte scar formation aids central nervous system axon regeneration. 2016. *Nature.* 532(7598): 195-200.

b) Ren, Y., Ao Y., **O'Shea T. M.,** Burda J. E., Bernstein A. M., Brumm A. J., Muthusamy N., Ghashghaei H. T., Carmichael S. T., Cheng L. and Sofroniew M. V. Ependymal cell contribution to scar formation after spinal cord injury is minimal, local and dependent on direct ependymal injury. 2017. Scientific Reports. 7: 41122.

3. Stimulating repair and regeneration in central and peripheral nervous system injury

Traumatic injury to the central and peripheral nervous systems results in permanent loss of function as repair and regeneration of neural tissue is insufficient. Throughout my PhD and postdoc research I leveraged the biomaterials described above as tools to deliver treatments to a variety of different preclinical models of central and peripheral nervous system injury including: spinal cord injury (SCI), stroke, chronic compressive radicular pain, vitreous replacement for retinal injury, and peripheral nerve injury. These studies resulted in important contributions to the CNS and PNS injury fields. Combing Adeno-associated viruses (AAVs) and injectable shear thinning hydrogels to deliver polypeptide growth factor cues in a spatiotemporal manner we demonstrated that CNS axon regeneration can be stimulated in complete SCI by recapitulating developmental cues not present in the adult injury state. The use of injectable covalently cross-linked poly(ethylene glycol) based hydrogels demonstrated benefits for (i) long term management of chronic compressive radicular pain by facilitating prolonged methylprednisolone delivery, as well as (ii) delaying onset of demyelination following peripheral nerve injury by delivering oligonucleotide GapMers to disrupt specific transcriptional programs. Towards clinical translation of biomaterial-based therapies for CNS injury we showed that porous scaffolds composed of poly-lactic-co-glycolic acid and poly-l-lysine copolymer (PLGA/PLL) are safe, promote functional recovery and enhance fibrotic remodeling of lesion cores over cavitation in a primate model of acute spinal cord injury. Finally, we are currently finishing up a comprehensive study of neural progenitor cell (NPC) grafting in SCI and stroke where we demonstrate that the lesion microenvironment regulates survival and differentiation outcomes using graft cell specific transcriptomic analysis and immunohistochemistry evaluations. My contributions to these studies included study design, biomaterials synthesis and formulation, surgical procedures, behavioral analysis, cell and molecular characterizations, data analysis and manuscript preparations. A manuscript for the last described neural progenitor grafting project is currently in preparation.

Key papers (* designates co-first author):

a) *Anderson, M.A., ****O'Shea, T.M.,*** Burda, J.E., Ao, Y., Barlatey, S.L., Bernstein A.M., Kim, J.H., James, N.D., Rogers, A., Kato, B., Wollenberg, A.L., Kawaguchi, R., Coppola, G., Wang, C., Deming, T.J., He, Z., Courtine, G., and Sofroniew M.V. 2018. Required growth facilitators propel axon regeneration across complete spinal cord injury. *Nature*. 561: 396–400.

b) Slotkin J.R., Ness J.K., Snyder K.M., Skiles A.A., Woodard E.J., **O'Shea, T.M.**, Reynolds F.M., Layer R.T., Aimetti A.A., Toms S.A., Langer R., and Tapinos N. Sustained local release of methylprednisolone from a thiol-acrylate poly(ethylene glycol) hydrogel for treating chronic compressive radicular pain. 2016. *Journal of Neurosurgery.* 12(6). A1576.

c) Slotkin, J. R., Pritchard C. D., Luque B., Ye J., Layer R. T., Lawrence M. S., **O'Shea T. M.**, Roy R.R., Zhong H., Vollenweider I., Edgerton V. R., Courtine G., Woodard E. J., and Langer, R. Biodegradable scaffolds promote tissue remodeling and functional improvement in non-human primates with acute spinal cord injury. 2017. *Biomaterials.* 123: 63-76.

d) Martinez-Moreno, M., **O'Shea, T.M**., Zepecki, J.P., Olaru, A., Ness, J.K., Langer, R. and Tapinos, N. Regulation of peripheral myelination through transcriptional buffering of Egr2 by an antisense long noncoding RNA. 2017. *Cell Reports*. 20(8):1950-1963.

4. Characterizing and regulating the foreign body response to biomaterials in the CNS

The implantation of neuroprostheses and other biomaterial-based devices (e.g. local drug delivery carriers or tissue engineering scaffolds) into the CNS initiates a foreign body response (FBR) that likely mimics

many characteristic features of the CNS wound response. However, the study of CNS FBRs to biomaterials *in vivo* has not kept pace with recent advances made in the cell biology of CNS injury and little is known about molecular factors that determine CNS FBRs in vivo, or about how such responses influence biomaterial function. A severe FBR can disrupt the long-term function of devices used in the CNS and represents a significant clinical problem across all neural interfacing fields. Therefore, in my postdoc, I conducted fundamental neurobiology studies that dissected the molecular mechanisms that drive foreign body responses (FBRs) to biomaterials in the CNS in order to improve the design of future biomaterials used in the CNS. We showed that the FBR to biomaterials in the CNS exists on a severity spectrum that is determined by definable biomaterial physiochemical properties that can be modified to minimize or evoke specific responses. Further, we have demonstrated that FBR severity directly alters numerous biomaterial functions including molecular delivery to uninjured and stroke injured neural tissue as well as biomaterial persistence and degradation. My contributions to these studies included study design, biomaterials synthesis and formulation, surgical procedures, cell and molecular characterizations, data analysis and manuscript preparations.

Key paper

a) O'Shea, T.M., Wollenberg, A.L., Kim, J.H., Ao, Y. Deming, T.J. and Sofroniew M.V. Foreign body responses in mouse central nervous system mimic natural wound responses and alter biomaterial functions. 2020. *Nature Communications*. 11: 6203.

D. Additional Information: Research Support and/or Scholastic Performance

Throughout my time as a postdoc at UCLA I was supported by a number of prestigious fellowships in which I served as the PI under the direct mentorship of Michael Sofroniew:

381357 O'Shea 08/01/2016 – 08/01/2018
Craig H. Neilsen Postdoctoral Fellowship Research Grant
Improving neural stem cell graft performance in SCI using hydrogels
Role: PI.

O'Shea 10/01/2018 – 09/31/2019
American Australian Association Sir Keith Murdoch Scholarship
Bioengineering neural repair in spinal cord injury
Role: PI.

3170 O'Shea 01/01/2019 – 12/31/2020
PVA Research Foundation Grant
Bioengineering neural tissue in fibrotic compartments of chronic spinal cord injury
Role: PI.

O'Shea 07/01/2019 – 06/30/2020
Wings for Life Spinal Cord Research Foundation
Bioengineering a CNS glial framework in fibrotic compartments of chronic spinal cord injury to support neural regeneration
Role: PI.