BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Prosser, Benjamin L

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

POSITION TITLE: Assistant Professor of Physiology

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
Wake Forest University, Winston-Salem, NC	B.S.	05/2002	Biomechanics
University of Maryland School of Medicine, Baltimore, MD	Ph.D.	05/2009	Molecular Medicine
Post-doc; Lab of W.J. Lederer. University of Maryland School of Medicine		10/09-12/13	Cellular and Molecular Cardiology

A. Personal Statement

The expertise of the Prosser lab lies in the field of muscle mechanobiology, with a focus on the role of the cytoskeleton. During my post-doc I developed novel techniques to attach and stretch muscle cells and measure force using MyoTak™ biological adhesive. With these tools, I characterized "X-ROS" signaling, a mechanical stress-dependent regulation of reactive oxygen species and subcellular calcium signals that is implicated in muscle disease. Recent advances in these stretch techniques now allow precise control of force/length relationships and the simultaneous evaluation of mechanical, electrical, and chemical signals in the single myocyte.

As part of the Pennsylvania Muscle Institute (PMI), Cardiovascular Institute (CVI), and Center for Engineering Mechanobiology (CEMB) at Penn, the Prosser lab has capitalized on the strength of these institutes to probe the role of the cytoskeleton, particularly microtubules, in muscle mechanics and mechano-signaling. Specifically, the lab has helped Carl Zeiss develop high-speed and super-resolution Airyscan imaging to elucidate the organization and dynamics of the inner workings of heart cells. We also simultaneously probe the mechanics of cells and tissue using atomic force microscopy and other mechanical measurements. In 2016, the Prosser lab characterized novel load bearing behavior of the microtubule network in beating cardiomyocytes, and identified post-translational detyrosination of microtubules as a key regulator of the mechanical properties of heart cells (Robison et al., *Science* 2016). In 2018, we found that suppressing detyrosination can lower stiffness and robustly improve contractile function in cardiomyocytes isolated from patients with heart failure (Chen et al., *Nature Medicine* 2018). In recognition of the lab's early work, I was named an Outstanding Early Career Investigator by the American Heart Association and given the Linda Montague Young Investigator Award for Penn School of Medicine in 2017, among other honors.

Current efforts in the lab are exploring both the translational potential of targeting the cardiac microtubule network in heart failure (Caporizzo et al., *Circulation* 2020; Chen and Salomon, *Circ Res* 2020), as well as elucidating the fundamental contributions of the cytoskeleton to cardiomyocyte homeostasis and growth (Heffler et al., *Circ Res* 2020; Cho et al., *Dev Cell* 2019). Our work has stimulated considerable international interest in the role of cardiac microtubules in health and disease, as reflected by the formation of a new Leducq Transatlantic Network of Excellence in January 2021 that is focused on this topic, of which I will serve as North American Cooridinator.

In the past year, the lab has added a new, neuro-centric arm. In 2018, I become a parent of a daughter with STXBP1 encephalopathy. Given the labs expertise in excitable cells, we quickly repurposed some of our electrophysiological and gene therapy approaches to the neuronal system. Working with fantastic clinical and basic science collaborators in Drs. Ingo Helbig and Beverly Davidson at Penn and the Children's Hospital of Pennsylvania (CHOP), we have rapidly developed and begun testing a new therapeutic strategy to treat genetically-defined neurodevelopmental disorders. In short time, we have conceptualized a new therapeutic strategy using site-blocking antisense olignonucleotides (ASOs) targeting microRNAs and collected robust data to support our approach. As our approach could benefit a large number of disorders that arise from monogenic loss-of-function mutations, it has generated considerable interest, resulting in a seed grant from the American Epilepsy Society and a Sponsored Research Agreement with Ionis Pharmaceuticals to develop ASOs targeting *STXBP1* and other genetic causes of neurodevelopmental disorders.

B. Research and Honors

Employment

2006-2009 Ph.D student – Laboratory of Martin Schneider, Ph.D. Univ. of Maryland School of Medicine, Graduate Program in Life Sciences
2009-2013 Postdoctoral Fellow (Laboratory of WJ Lederer, M.D., Ph.D.), Center for Biomedical Engineering and Technology (BioMET), University of Maryland Baltimore, Baltimore, MD.
2014- Assistant Professor, Department of Physiology, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA.
2020- Associate Director, Pennsylvania Muscle Institute, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA.

Honors

2011 Outstanding Post-Doctoral Fellow of the Year. University of Maryland School of Medicine
2012 European Society of Cardiology Young Investigator Travel Award
2017 Alexander M. Cruickshank (AMC) Lecturer Award nominee, Gordon Research Conferences
2017 Linda Montague Outstanding Early Career Investigator Award – Penn Perelman Sch of Med
2017 American Heart Association (AHA) Outstanding Early Career Investigator Award – BCVS.
2017 Rising Star Award – Cardiovascular Research Institute of Vermont
2018 Alumnus of the Year – University of Maryland School of Medicine
2022 Chair-Elect of the Gordon Research Conference "Cardiac Regulatory Mechanisms"

Professional Memberships

2006- Member, Biophysical Society
2012- Member, Cardiac Muscle Society
2016- Member, American Heart Association (AHA)
2019- Member, Scientific Advisory Board, STXBP1 Foundation

C. Contribution to Science

1. **Identification of detyrosinated microtubules as a regulator of muscle mechanics –** The Prosser lab recently identified a potent regulator of cytoskeletal mechanics. We found that post-translationally detyrosinated microtubules produce a viscoelastic mechanical resistance that impedes the motion of working cardiomyocytes. This finding was enabled by the first real time observations of microtubule mechanics in a working, beating myocyte. Further, we found that reducing detyrosination reduces stiffness and improves contractility in cardiomyocytes from patients with heart failure.
   Reference:
   a. Caporizzo MA, Chen CY, Bedi K, Margulies KB, **Prosser BL** (2020) Microtubules increase diastolic stiffness in failing human cardiomyocytes and myocardium. ***Circulation*** Jan 16. https://www.ncbi.nlm.nih.gov/pubmed/?term=Microtubules+increase+diastolic+stiffness
   b. Chen CY, Caporizzo MA, Bedi K, Vite A, Bogush AI, Robison P, Heffler JG, Salomon AK, Kelly NA, Babu A, Morley MP, Margulies KB, **Prosser BL** (2018) Suppression of detyrosinated microtubules improves cardiomyocyte function in human heart failure. ***Nature Medicine*** Jun 11. https://www.ncbi.nlm.nih.gov/pubmed/29892068

c. Robison PR, Caporizzo MA, Ahmadzadeh H, Bogush AI, Chen CY, Margulies KB, Shenoy VB, **Prosser BL** (2016) Detyrosinated microtubules buckle and bear load in contracting cardiomyocytes, ***Science*** Apr 22;352(6284):aaf0659. https://www.ncbi.nlm.nih.gov/pubmed/27102488

d. Caporizzo MA, Chen CY, Salomon AK, Margulies KB, **Prosser BL** (2018) Microtubules Provide a Viscoelastic Resistance to Myocyte Motion. ***Biophysical journal*** Nov 6;115(9):1796-1807. https://www.ncbi.nlm.nih.gov/pubmed/30322798

2. **Discovery of microtubule-dependent mechanotransduction pathways -** Dr. Prosser characterized X-ROS signaling, a novel mechanotransduction pathway in striated muscle where mechanical stress elicits signaling through reactive oxygen species and calcium ions. While this pathway normally enhances calcium release to tune cardiac excitation-contraction coupling, it can also drive oxidative stress and calcium dependent arrhythmia in cardiovascular disease. Dr. Prosser also helped identify a similar conserved mechanism in skeletal muscle, and demonstrated how the microtubule network was critical for this mechanosignaling. Importantly, alterations in the microtubule network were found to drive augmented mechanotransduction and subsequent muscle dysfunction in models of muscular dystrophy. While only discovered in late 2011, Dr. Prosser's publications on X-ROS signaling have been cited by more than 200 subsequent reports, and the complexity and importance of this mechanosignaling are rapidly being uncovered.

   References:

   a) Kerr JK, Robison PR, Shi G, Bogush AI, Kempema AM, Hexum JK, Becerra N, Harki DA, Martin SS, Ratieri R, **Prosser BL***, Ward CW* (2015) Detyrosinated microtubules modulate mechanotransduction in heart and skeletal muscle. ***Nat Commun*** Oct 8;6:8526. https://www.ncbi.nlm.nih.gov/pubmed/26446751

   b) **Prosser BL**, Ward CW (2014) Mechano-chemo transduction tunes the heartstrings. ***Sci Signal*** Mar 18, 7:pe7. https://www.ncbi.nlm.nih.gov/pubmed/24643798

   c) Khairallah RJ, Shi G, Sbrana F, **Prosser BL**, Borroto C, Mazaitis MJ, Hoffman EP, Mahurkar A, Sachys F, Sun Y, Chen YW, Raiteri R, Lederer WJ, Dorsey SG, Ward CW (2012) Microtubules underlie dysfunction in Duchenne muscular dystrophy. ***Sci Signal*** Aug 7, 5:ra56. https://www.ncbi.nlm.nih.gov/pubmed/22871609

   d) **Prosser BL,** Ward CW, Lederer WJ (2011) X-ROS signaling: Rapid mechano-chemo transduction in heart. ***Science*** 333:1440-1445. https://www.ncbi.nlm.nih.gov/pubmed/23220288

3. **Development of new methodology to assay mechanical-signaling in single muscle cells –** Dr. Prosser was a co-inventor on a patent describing methods to attach single skeletal and cardiac muscle cells to mechanical equipment using a novel biological glue. This allows muscle physiologists to precisely control length and mechanical stresses on the muscle cell while measuring all relevant physiological parameters. This technology was licensed out to two leading companies who have developed systems to measure force/length relationships in muscle that are now operational in research labs worldwide, strengthening the fields ability to evaluate single muscle cell mechanics and mechano-signaling. Dr. Prosser also was an invited presenter on a webinar demonstrating how to utilize these techniques to facilitate skeletal and cardiac research, which has been viewed by over 400 scientists worldwide.

   More recently, Dr. Prosser has combined this cell stretch technology with Airyscan imaging to provide high-temporal and spatial resolution imaging of intracellular responses to changing mechanical stress. As one of the first scientists to test and provide feedback on the Airyscan system, Dr. Prosser was an invited presenter on a recent webinar hosted by Carl Zeiss on initial user experiences with Airyscan, and has provided feedback to Zeiss that has shaped software updates for this system.

   References:

   a. Inventor: **Prosser BL**, Ward CW, Lederer WJ. "Compositions and Methods for Adhesion of Intact Cells to an Apparatus". US Patent. USA Patent Number 8,921,066, 2014.

   b. **Benjamin L. Prosse**r, Michiel Helmes: Webinar - "Measuring Force in single heart cells", presented by Inside Scientific. Inside Scientific September 2014.

   c. **Benjamin L. Prosser**; invited speaker: Webinar: First impressions with Airyscan: New insights into cytoskeletal biology. Webinar hosted by Carl Zeiss 2015.

4. **Characterization of the role of small calcium binding proteins in the regulation of skeletal excitation-contraction coupling –** In his Ph.D work Dr. Prosser described how 2 small calcium binding

proteins, S100A1 and calmodulin, influence skeletal excitation-contraction coupling and muscle function. The work, which resulted in 7 publications, 6 first author for Dr. Prosser, utilized structural, biochemical, electrophysiological and imaging approaches to show how these 2 proteins regulate the ryanodine receptor calcium release channel to modulate EC coupling.

References:

a. **Prosser BL**, Wright NT, Hernández-Ochoa EH, Varney KM, Liu Y, Olojo RO, Zimmer DB, Weber DJ, Schneider MF. "S100A1 binds to the calmodulin binding site of ryanodine receptor and modulates skeletal muscle excitation-contraction coupling." *J Biol Chem*. 2008 Feb 22;283(8):5046-57. Full Text:http://www.jbc.org/cgi/pmidlookup?view=long&pmid=18089560

b. **Prosser BL,** Hernández-Ochoa EH, Zimmer DB, Schneider MF. "Simultaneous recording of intra-membrane charge movement components and calcium release in wild type and S100A1$^{-/-}$ muscle fibres*." J Physiol. 2009* Sep 15;587(Pt 18):4543-59. PMCID: PMC2766656

c. **Prosser BL,** Hernández-Ochoa EH, Zimmer DB, Schneider MF. "The Qγ component of intra-membrane charge movement is present in mammalian muscle fibres, but suppressed in the absence of S100A1." J *Physiol*. 2009 Sep 15;587(Pt 18):4523-41. PMCID: PMC2766655

d. Yamaguchi N, **Prosser BL***, Ghassemi F, Xu L, Pasek D, Eu J, Hernandez-Ochoa E, Cannon B, Wilder P, Lovering R, Weber D, Melzer W, Schneider M, Meissner G. "Modulation of sarcoplasmic reticulum Ca^{2+} release in skeletal muscle expressing ryanodine receptor impaired in regulation by calmodulin and S100A1." *Am J Physiol Cell Physiol*. 2011 May; 200(5):C998-C1012. PMCID: PMC3093939 ***denotes co-first authorship**

Complete List of Published Work in MyBibliography:

http://www.ncbi.nlm.nih.gov/sites/myncbi/benjamin.prosser.1/bibliography/41430386/public/?sort=date&direction=ascending

D. Research Support

Active

NIH-NHLBI R01 (Prosser and Margulies, MPI) 03/20-02/25

Mechanical Stress Dependent Regulation of the Cardiac Cytoskeleton

The proposed work will utilizing novel bioengineering approaches to determine how different mechanical stresses experienced by the cardiomyocyte drive remodeling of the cytoskeleton.

NIH-NIDCD R01 (Prosser Co-I) 01/20-12/24

Role of Gas2 in Cytoskeletal Architecture Support, Cell Stiffness and Cochlear Function

The work explores a novel role of Gas2 in stabilizing actin and microtubules in the pillar cells of the inner ear to facilitate hearing.

NIH-NHLBI R01 HL133080-01 (Prosser PI) 07/16-06/21

Detyrosinated microtubules in cardiomyocyte mechanics

The proposed work will examine mechanisms of detyrosination and determine the effect of modification of the microtubule cytoskeleton on myocyte mechanics using single myocyte biophysical approaches.

Department of Defense (Prosser, Co-I) 09/18 – 8/21

Functional Genetics of Peripartum Cardiomyopathy

This proposal aims to determine the underlying mechanistic basis of peripartum cardiomyopathy, with a focus on describing the role of titin-truncating varients in the pathogenesis of this disease.

Children's Hospital of Philadelphia- Ionis Pharmaceuticals (Prosser, Davidson MPI) 7/28/20 – 7/28/20

MicroRNA site-blocking oligonucleotides as a novel therapy for STXBP1 encephalopathy

Collaboration between Ionis and Penn/CHOP to establish a robust pipeline for the development of antisense oligonucleotides (ASOs) capable of disrupting miR-based repression of haploinsufficient genes that cause neurodevelopmental disease.

US Israel Binational Science Foundation (MPI: Prosser and Kehat) 10/1/20 – 9/30/24

RNA trafficking and localized translation in cardiac homeostasis and hypertrophy

A highly collaborative study that builds on the long-standing interests and strengths of both labs to explore the interplay between the cytoskeleton, RNA trafficking and local translation in the heart.

Leducq Foundation For Cardiovascular Research (PI: Prosser) 01/1/21 – 12/31/25
Transatlantic Networks of Excellence
Cytoskeletal regulation of cardiomyocyte homeostasis in health and disease
This Leducq Cytoskeletal Network (LCN) of 7 investigators will evaluate how alterations to the cytoskeleton effect sarcomere health and function, with a specific focus on mRNA delivery, protein synthesis, and waste disposal in health and heart failure. The LCN will also utilize machine learning to systematically characterize cytoskeletal remodeling in diverse heart failure, and examine drivers of proliferation and modification of the cytoskeleton. Prosser serves as Network Coordinator.