BIOGRAPHICAL SKETCH

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NAME: **BRETT A. COLSON**

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

POSITION TITLE: **Assistant Professor, Department of Cellular and Molecular Medicine**

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
University of Wisconsin, Madison, WI	**B.S.**	**05/2004**	**Molecular Biology**
University of Wisconsin, Madison, WI	**M.S.**	**08/2006**	**Physiology**
University of Wisconsin, Madison (R. Moss)	**Ph.D.**	**12/2009**	**Physiology**
University of Minnesota, Minneapolis, MN	**Postdoctoral**	**12/2012**	**Biochemistry**
University of Minnesota (D. Thomas)	**Research Assoc.**	**08/2015**	**Biophysics**

A. Personal Statement

My primary research focus, during my entire early-stage career, has been on the development and application of biophysical approaches for understanding the structure, dynamics, and function of muscle proteins in the myofilament, with particular emphasis on cardiac myosin-binding protein C (**cMyBP-C**). My research interests include muscle physiology, post-translational protein modifiers of contraction, and structure-based drug discovery. In my postdoctoral training and now in my independent career, my main research approach centers around **site-directed spectroscopic probe methods** in model systems and native environments to study fundamental mechanisms of the cardiac sarcomere and its myofibrillar proteins. This is a powerful approach, not only for understanding basic mechanisms that are crucial to molecular and cellular physiology, but also for understanding cardiac malfunction in disease. During the past decade, I have used biophysical approaches to uncover critical details of mechanisms underlying cardiac disease, such as heart failure and cardiomyopathy. This process has been greatly accelerated with my laboratory's incorporation of new technology in time-resolved fluorescence, increasing the throughput in fluorescence lifetime measurement by a factor of 10^5. This technology has now been adapted to a fluorescence microplate reader, and my laboratory's customized version of the instrument, coupled with my biosensor engineering technology for sensing nanometer distance/disorder changes, is the major focal point of my lab's research at the University of Arizona. Applying my structure-based **mechanistic discovery** platform to cMyBP-C in solution, in myofilament complexes, and within the intact sarcomere makes perfect sense. My recent results published in *PNAS*, focused on developing a biosensor for detecting differences in physiological structural states of MyBP-C *in vitro* and *in silico*, have inspired me to pursue an ambitious research program that develops this technology *in vivo* and *in situ*. My complementary methods of time-resolved phosphorescence anisotropy (TPA), electron paramagnetic resonance (EPR) spectroscopy, binding kinetics, muscle mechanics, and molecular dynamics (MD) simulations, add an attractive combination of precision, speed and resolution to quantitate cMyBP-C molecular interactions and dynamics. My next goal is to use these same assays used for mechanistic studies for drug discovery and rationale design of novel therapies to treat cardiac disease. I am confident that my past experience and novel instrumentation in my lab has **rigorously prepared** me to pursue these very exciting spectroscopic studies for advancing the understanding of cMyBP-C's interaction partners *in vivo*, for which there is currently very little information. The current project is the core of my research program **established in September of 2015**, and has thus far been highly productive and innovative. As an integral part of this project, I am strongly committed to mentoring the next generation of biophysical spectroscopists in muscle research.

B. Positions and Honors

2002 – 2004	Undergraduate Research Assistant, University of Wisconsin, Madison, WI (Pathology)
2004 – 2009	Graduate Research Assistant, University of Wisconsin, Madison, WI (Physiology)
09-12 / 2006	Teaching Assistant Fellow, University of Wisconsin, Madison, WI (Physiology)
2007 – 2009	AHA Predoctoral Fellow, University of Wisconsin, Madison, WI
2010 – 2012	Postdoctoral Researcher, University of Minnesota, Minneapolis, MN (Biophysics)
2010 – 2012	NIH NRSA Postdoctoral Fellow, University of Minnesota, Minneapolis, MN (NHLBI)
2013 – 2014	AHA Postdoctoral Fellow, University of Minnesota, Minneapolis, MN
2013 – 2015	Research Associate, University of Minnesota, Minneapolis, MN (Biophysics)
2013 – 2015	President, University of Minnesota Post-Doctoral Association (UMN-PDA)
2014 – 2015	NIH K99 Awardee, Postdoctoral Mentee, University of Minnesota, Minneapolis, MN (NHLBI)
2014 – 2015	University Senate Committee for Faculty Affairs, Postdoc Representative (UMN-SCFA)
2014 – 2015	Policy Liaison, Past-President, UMN Post-Doctoral Association (UMN-PDA)
2014 – 2015	Postdoc Representative to the Graduate School, Office of Post-Doctoral Affairs (OPDA)
2015 – present	NIH R00 Awardee, Assistant Professor, University of Arizona, Tucson, AZ (NHLBI)
2015 – present	Faculty member, University of Arizona Sarver Heart Center (SHC)
2015 – present	Arizona Biological and Biomedical Sciences (ABBS) Graduate Program faculty memberships: Biochemistry and Molecular & Cellular Biology (BMCB), Cellular and Molecular Medicine (CMM), Physiological Sciences (PS)
2015 – present	Graduate Interdisciplinary Program (GIDP) faculty memberships: Biomedical Engineering (BME), Physiological Sciences (PS), Biochemistry and Molecular & Cellular Biology (BMCB)

Other Selected Experience and Professional Memberships

2006 – present	Biophysical Society Member
2007 – present	International Society for Heart Research Member
2007	Session moderator and poster presenter at International Society for Heart Research Meeting, Bologna, Italy.
2008	Young Researcher Highlighted Poster, Motility Subgroup, Biophysical Society Annual Meeting, Long Beach, CA.
2009	Greg Marzolf Jr. Foundation Symposium, Paul and Sheila Wellstone Muscular Dystrophy Center, University of Minnesota, Invited talk as PhD candidate “Ultrastructural basis for accelerated force development in myocardium due to phosphorylation of cMyBP-C”
2010 – present	American Heart Association Member
2010 – present	Manuscript reviews/Editorial Board for journals: *Proc. Natl. Acad. Sci. U.S.A., Journal of Molecular Biology, Circulation Research, Biophysical Journal, PloS One, Journal of Molecular and Cellular Cardiology, Frontiers in Physiology, Science Advances, Journal of Applied Physiology, Journal of Structural Biology*
2012	Speaker and Co-Chair of Platform session at Biophysical Society Annual Meeting in San Diego, CA. Platform: “Myosin Binding Proteins” – “Effects of Myosin Binding Protein-C Isoform, Phosphorylation, and Domains on the Rotational Dynamics of Actin Filaments”.
2012 – 2014	Volunteer and Poster Presenter, Muscular Dystrophy Center Lab Day with Muscular Dystrophy Families, MD Awareness Month, University of Minnesota
2013	Speaker and Co-Chair of Platform session at Biophysical Society Annual Meeting in Philadelphia, PA. Platform: “Cardiac Muscle” – “Structural Dynamics of Actin-Myosin Bound and Unbound States of Cardiac Myosin Binding Protein-C Detected by Dipolar EPR”.
2013	Invited speaker, International Workshop on Electron Spin Resonance, Awaji, Japan.
2013	Attendee, Heart Failure Society of America Annual Meeting, Orlando, FL
2014	Speaker at Madison Myofilament Meeting, Madison, WI, “Structural Dynamics of Cardiac Myosin Binding Protein-C Phosphorylation”
2015	Speaker and Co-Chair of Platform session at Biophysical Society Annual Meeting in Baltimore, MD. Platform: Skeletal Muscle Mechanics, Structure, and Regulation – “The Myosin Super-Relaxed State is Regulated by Estradiol”
2015	University of Arizona, Department of Cellular and Molecular Medicine, Invited talk “Structural Dynamics of Cardiac Muscle Protein Phosphorylation”
2015	University of California, Irvine, Department of Physiology and Biophysics, Invited talk “Structural Dynamics of Muscle Protein Phosphorylation”
2015	Loyola University Chicago, Department of Physiology and Biophysics, Invited talk “Structural Dynamics of Cardiac Muscle Protein Phosphorylation”

2015	Muscular Dystrophy Center Seminar Series, University of Minnesota, Invited talk as Research Associate Professor “Structural Dynamics of Muscle Protein Phosphorylation”
2015	Alternative Muscle Club, speaker, University of Arizona “Site-directed spectroscopy of cardiac myosin binding protein-C reveals effects of phosphorylation on protein structural dynamics”
2015	Sanofi, Innovation Park high-tech campus, Invited Talk, “Muscle Protein Structural Dynamics Applied to Development of Drug and Small Molecule Therapies” Oro Valley, AZ
2016	Evaluator for University of Arizona College of Medicine Medical student applicant visit day in the Multiple Mini-Interview (MMI) process
2016	Invited Speaker, Early Career Investigator, Madison Myofilament Meeting, Madison, WI
2016	University of Arizona, Graduate Program Forum speaker: Physiology GIDP, BMCB GIDP, and BME GIDP, Fall Semester
2016	Amgen Inc., Oyster Point campus, Invited Talk, “Spectroscopic studies of cardiac myosin-binding protein C: Mechanistic insights for protein structural dynamics and therapeutic discovery” South San Francisco, CA
2017	Poster Presentation at Biophysical Society Annual Meeting in New Orleans, LA. Cardiac Muscle Mechanics & Structure – “Structural Dynamics of Human Cardiac Myosin-binding Protein C Revealed by Time-Resolved FRET”
2017	Invited Speaker, Sarver Heart Center Women’s Committee, University of Arizona, “Interaction of Estrogen, Age, and Activity on Muscle Strength in Females”

Honors

2006	Graduated from the National School on Neutron and X-ray Scattering, Argonne National Laboratories. 1 of 40 students accepted annually out of 275 applicants.
2007 – 2009	American Heart Association (AHA) Predoctoral Fellow, “Ultrastructural basis for functional effects in murine myocardium due to ablation of cMyBP-C.”
2007	Press release, “Deconstructing Heart Muscle.” Appeared in the Advanced Photon Source (APS) Annual Report. Article was written by J. R. Minkel, a contributing journalist to Scientific American, based on my J Mol Biol 2007 publication, recognized as one of the outstanding research results from the Biophysics Collaborative Access Team (BioCAT) X-ray facility located at the APS.
2008	Cover Figure for August 1, 2008 issue of Circulation Research (103, 244-251). This figure was also used as the cover image for large format posters to advertise journal at national scientific meetings, such as American Heart Association meetings.
2009	Graduated from the University of Wisconsin, Madison with PhD in Physiology. Dissertation: “Regulation of Myocardial Cross-bridge Cycling Kinetics by Myosin Binding Protein-C: Structural Insights from X-Ray Diffraction Studies.” Advisor: Richard L. Moss, PhD.
2010 – 2011	NIH T32 Muscle Postdoctoral Training Grant trainee, University of Minnesota
2011 – 2013	Awarded NIH F32 NRSA Postdoctoral Fellowship, “Structural Dynamics of Cardiac Muscle.”
2011 – 2012	Mentor to undergraduate scholar. UROP awarded to Michael Nagel (now at St. Jude Medical after B.S. degree) and Morgan Lillehei (now at Medtronic after B.S. degree).
2012	Mentor to undergraduate scholars. LSSURP awarded to Jillian Johnson (now in Medical School at the University of Minnesota after B.S. degree) and Brett Lane (now at St. Jude Medical after B.S. degree).
2013	Awarded AHA Postdoctoral Fellowship, “Structural Dynamics of Cardiac Muscle Contraction”
2013 – 2014	Mentor to undergraduate scholars awarded from Greg Marzolf Jr. Muscular Dystrophy Foundation and UROP to Jillian Johnson and Ben Zeman for studies of skeletal muscle disease distal arthrogryposis.
2014 – 2018	Awarded NIH K99/R00 Pathway to Independence Award, “Structural Dynamics of Cardiac Myosin Binding Protein-C”
2016	Graduated from Eureka Institute for Translational Medicine Certificate Program, Sicily, Italy
2016	Mentor to University of Arizona Master’s students in Colson lab: Matthew Bills (BME GIDP with summer internship at Sanofi) and Ali Hussani (CMM Program with summer work-study)
2016 – 2017	Awarded UA Sarver Heart Center’s Novel Research Project Award in the Area of Cardiovascular Disease and Medicine, “Identifying novel heart muscle therapeutics to target sudden cardiac arrest"

C. Contribution to Science

1. **X-ray Diffraction of Cardiac Muscle with Cardiomyopathy to Probe Myosin Cross-Bridge Structure:** As a graduate student in the laboratory of Dr. Richard Moss, I determined the changes in muscle ultrastructure in mouse models of human cardiomyopathy and heart failure. The specific structural and functional effects of contractile protein phosphorylation was also determined. Results from these four publications continue to be important for understanding cardiac dysfunction in sudden cardiac death and genetic heart disease, such as hypertrophic cardiomyopathy (HCM), most often due to mutations in cMyBP-C.

a. Colson, BA, Bekyarova, T, Fitzsimons, DP, Irving, TC, Moss, RL. "Radial Displacement of Myosin Cross-bridges in Mouse Myocardium due to Ablation of Myosin Binding Protein-C." *Journal of Molecular Biology.* (2007) 367, 36-41. PMID 17254601. PMC1892277.
b. Colson, BA, Bekyarova, T, Locher, MR, Fitzsimons, DP, Irving, TC, Moss, RL. "Protein Kinase A-Mediated Phosphorylation of cMyBP-C Increases Proximity of Myosin Heads to Actin in Resting Myocardium." *Circulation Research.* (2008) 103, 244-251. PMID 18599866. PMC2810832.
c. Colson, BA, Locher MR, Bekyarova T, Patel JR, Fitzsimons DP, Irving TC, Moss RL. "Differential roles of regulatory light chain and myosin binding protein-C phosphorylations in the modulation of cardiac force development." *Journal of Physiology.* (2010) 588, 981-993. PMID 20123786. PMC2849963.
d. Colson, BA, Patel, JR, Chen, PP, Bekyarova, T, Abdalla, MI, Tong, CW, Fitzsimons, DP, Irving, TC, Moss, RL. "Myosin Binding Protein-C Phosphorylation is the Principal Mediator of Protein Kinase A Effects on Thick Filament Structure in Myocardium." *Journal of Molecular and Cellular Cardiology.* (2012) 53, 609-16. PMID 22850286. PMC3472100.

2. **Spectroscopic Probes of Muscle Protein Phosphorylation:** As a postdoctoral fellow in the laboratory of Dr. David Thomas, I established spectroscopic technologies and site-directed probes on muscle proteins in order to determine effects of structural dynamics due to protein binding and post-translational modifications, such as phosphorylation. These studies using time-resolved phosphorescence anisotropy (TPA), time-resolved fluorescence resonance energy transfer (TR-FRET), molecular dynamics (MD) simulation, electron paramagnetic resonance (EPR), and double electron-electron resonance (DEER) have laid the foundation for my ongoing studies using fluorescence and magnetic resonance in cardiac muscle proteins and fibers. *As an independent investigator, I will use my protein biosensor technologies for novel cardiovascular drug discovery.*

a. Thomas, DD, Muretta, JM, Colson, BA, Mello, RM, Kast, DK. "Spectroscopic Probes of Muscle Proteins." *Comprehensive Biophysics.* (2011) Vol. 4, Ch. 15, 226-250 (text book).
b. Colson, BA, Rybakova, IN, Prochniewicz, E, Moss, RL,Thomas DD. "Cardiac Myosin Binding Protein-C Restricts Intrafilament Torsional Dynamics of Actin in a Phosphorylation-dependent Manner." *Proc Natl Acad Sci USA* (2012) 109(5), 20437-42. PMID 23169656. PMC3472100.
c. Colson, BA, Gruber, SJ, Thomas, DD. "Structural Dynamics of Muscle Protein Phosphorylation." *Journal of Muscle Research and Cellular Motility.* (2012) 33, 419-29. PMID 22930331. PMC3528524.
d. Colson, BA, Thompson, AR, Espinoza-Fonseca, LM, Thomas, DD. "Site-directed Spectroscopy of Cardiac Myosin Binding Protein-C Reveals Effects of Phosphorylation on Protein Structural Dynamics." *Proc Natl Acad Sci USA* (2016) PMID 26908877. PMC4812748.

3. **Altered Muscle Thermogenesis due to Aging and Sex Hormones:** As I expanded my scientific circle to include new collaborations, I tested the hypothesis that estrogen signaling affects muscle force production thermogenesis. My findings, using fluorescent nucleotides and time-resolved confocal microscopy suggest that the myosin structure and function is altered by the ovarian hormone estradiol, which may be important for weakness in aging, especially in post-menopausal women. This will continue to be a useful assay to study structure, function, and metabolic properties of muscle in health, disease, and aging. Myosin isoform and phosphorylation appear to be key regulators of the thermogenic properties of muscle. MD simulations revealed that unique thermodynamic energy landscapes are important for the regulation of contraction. I will also continue to further broaden my aging and sex hormone related studies, applying my scientific toolkit to other areas of cardiovascular disease, including redox imbalance and fibrosis.

a. Espinoza-Fonseca, LM, Colson, BA, Thomas, DD. "Effects of Pseudophosphorylation Mutants on the Structural Dynamics of Smooth Muscle Myosin Regulatory Light Chain." *Mol Biosyst.* (2014) 10:2693-8. PMID: 25091814. PMC4219086.
b. Colson, BA, Petersen, KJ, Collins, BC, Lowe, DA, Thomas, DD. "The Myosin Super-Relaxed State is Disrupted by Estradiol Deficiency." *Biochem Biophys Res Commun.* (2015) 456:151-5. PMID: 25446114. PMC4276479.

c. Lai, S, Collins, BC, Colson, BA, Kararigas, G, Lowe, DA." Estradiol Modulates Myosin Regulatory Light Chain Phosphorylation and Contractility in Skeletal Muscle of Female Mice." *American Journal of Physiology – Endocrinology and Metabolism* (2016) PMID 26956186.
d. Palumbo, S, Shin, YJ, Ahmad, K, Desai, AA, Quijada, H, Mohamed, M, Knox, A, Sammani, S, Colson, BA, Wang, T, Garcia, JG, Hecker, L. "Dysregulated Nox4 Ubiquitination Contributes to Redox Imbalance and Age-related Severity of Acute Lung Injury." *Am J Physiol Lung Cell Mol Physiol.* (2017) Epub ahead of print. PMID: 28062482.

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/48055464/?sort=date&direction=ascending

D. Research Support

Current

NIH K99/R00 "Pathway to Independence" HL122397 09/01/2014 – 08/31/2018
"Structural Dynamics of Cardiac Myosin Binding Protein-C." The purpose of this career development and research project is to evaluate the actin and myosin dynamics perturbed by myosin binding protein-C using spectroscopy with site-directed probes on muscle proteins. Role: PI

University of Arizona Sarver Heart Center Investigator Award 12/01/2016 – 11/30/2017
"Identifying novel heart muscle therapeutics to target sudden cardiac arrest." The purpose of this Novel Research Project Award in the Area of Cardiovascular Disease and Medicine is to develop a spectroscopic assay for high-throughput screens of chemical compound libraries to find drugs that bind to cMyBP-C, perturb its structure to mimic the phosphorylated state, and determine structure-activity relationships in hit compounds for novel therapies to treat heart failure and prevent sudden cardiac arrest. Role: PI

Department of Defense PR160292 (L. Hecker, PI) 06/01/2017 05/31/2020
"Pre-clinical development of Nox4 inhibitors for the treatment of pulmonary fibrosis." The goal of this project is to develop a therapeutic product that demonstrates efficacy in the most rigorous animal models and a favorable toxicology profile in rats and beagles, which is ready to advance into good laboratory practice (GLP)-IND enabling toxicity studies (required for Phase I human clinical trials). We have partnered with Lovelace Respiratory Research Institute, the nation's leading contract research organization specializing in respiratory therapeutic development, to carry out these studies. Role: Co-Investigator

Completed Research (*Postdoctoral/Research Associate*)

NIH R01 AR32961 (D. Thomas, PI) 03/01/2014 – 02/28/2019 (started 1983)
"Molecular Dynamics of Muscle Contraction" The focus of this work is to study site-directed spectroscopic probes of structural dynamics of force generation and regulation, focusing on myosin and actin.
Role: Investigator *(Research Associate)*

NIH R01 AG31743 (D. Lowe, PI) 02/01/2015 – 01/31/2019 (started 2009)
"Interaction of Estrogen, Age and Activity on Musculoskeletal Strength in Females" The major goal of this project is to elucidate estrogenic-mediated mechanisms that contribute to strength loss in aged females.
Role: Co-Investigator *(Research Associate)*

American Heart Association (AHA) Postdoctoral Fellow 07/01/2013 – 06/30/2015
"Structural Dynamics of Cardiac Muscle Contraction." The purpose of this project is to evaluate the structural dynamics of actin filaments and myosin in muscle fibers and in protein assemblies in solution as affected by muscle proteins and phosphorylation using EPR spectroscopies with site-directed probes on myosin, actin and accessory proteins. Role: PI

NIH F32 Postdoctoral Fellowship 01/01/2011 – 12/31/2013
"Structural Dynamics of Cardiac Muscle Contraction." The purpose of this project was to evaluate the structural dynamics of actin filaments and myosin in muscle fibers as affected by myosin binding protein-C and its phosphorylation using optical and EPR spectroscopies with established site-directed probes of tissue purified and expressed muscle proteins. Role: PI