BIOGRAPHICAL SKETCH

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NAME: Amy J. Wagers

POSITION TITLE: Forst Family Professor of Stem Cell and Regenerative Biology

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

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
Johns Hopkins University, Baltimore, MD		05/1992	Biological Sciences
Northwestern University, Evanston, IL	B.A.	06/1994	Biological Sciences
Northwestern University Medical School, Chicago, IL	Ph.D.	06/1999	Immunology and Microbial Pathogenesis
Stanford University, Stanford, CA	Postdoc	08/2004	Stem Cell Biology

A. Personal Statement

I am an established investigator who has led a research laboratory studying aging and regenerative biology for >16 years, with continuous funding support from the NIH (including DP2 New Innovator and DP1 Pioneer Awards) and 11 years of involvement with the NIA-funded Boston OAIC. Research in my group focuses primarily on defining cellular and molecular mechanisms that regulate the migration, expansion, and repair potential of blood-forming and muscle-forming stem cells, with a particular emphasis on how these stem cell activities change with age. Studies from my lab have helped to develop a model in which age-variant circulating factors, metabolic regulators and intrinsic transcriptional programs play a crucial role in determining stem cell function and modulate the outcome of regenerative responses to tissue injury as well as tissue homeostasis. Our work also has revealed new functions for the small circulating protein GDF11 in age-related pathologies of the heart, brain and skeletal muscle, and provided exciting proof-of-concept evidence supporting the utility of gene editing in mature cells and stem cells *in vivo* as a novel approach to model and interrogate age- and disease-associated genomic lesions.

In addition to pursuing fundamental research in stem cell and aging biology, a major goal of my laboratory is to nurture the next generation of talented young researchers in aging biology by providing a rich scientific environment in which trainees are exposed to cutting-edge discoveries and innovations, as well as practical advice for career development. Over my 16+ years as an independent investigator, I have trained in my lab >25 pre- and post-doctoral fellows, who have successfully progressed in their careers to obtain competitive positions in industry, academia, and clinical medicine. In addition, as **Associate Director of the Research Education Component (REC) Core**, I have supported the career advancement and mentorship of 6 very promising early career scientists focused on translationally-oriented studies of function-promoting therapies. My established track record of significant independent and collaborative research and mentorship, with multiple impactful publications in aging biology, productive collaborations with other members of the Boston OAIC and Boston-area aging research community, and successful advancement of mentees in their chosen career paths, demonstrate that I have the appropriate expertise, experience and skills to successfully fulfill my role in this project. I look forward to continuing to work with Drs. Lipsitz and Marcantonio to provide support, education and training to advance the careers of our most promising early career investigators, so that they may obtain the knowledge and skills they will need to translate fundamental mechanisms of disease and disability into novel interventions that can improve the health, physical function, and well-being of people as they age.

Selected publications of particular relevance to the current submission:

1. Sinha M, Jang, YC, Oh J, Khong D, Wu EY, Manohar R, Miller C, Regalado SG, Loffredo FS, Pancoast JR, Hirshman M, Lebowitz J, Shadrach JL, Cerletti M, Kim MJ, Serwold T, Goodyear L, Rosner B, Lee RT,

Wagers AJ. Restoring systemic GDF11 levels reverses age-related dysfunction in mouse skeletal muscle. *Science* 2014;344:649-52. PMCID: PMC4104429

2. Oh J, **Sinha I**, Tan KY, Rosner B, Dreyfuss JM, Gjata O, Tran P, Shoelson SE, **Wagers AJ**. Age-associated NF-kB signaling in myofibers alters the satellite cell niche and restrains muscle stem cell function. *Aging* 2016;8:2871-96. PMCID: PMC5191876
3. Gabern J, Kristl A, Bassaneze V, Vujic A, Schoemaker H, Sereda R, Peng L, Ricci-Blair E, Goldstein J, Walker R, **Bhasin S, Wagers AJ,** Lee RT. Analysis of Cre-mediated genetic deletion of Gdf11 in cardiomyocytes of young mice. *AJP-Heart and Circ. Physiol.* 2019;317:H201-H212. PMCID: PMC6692736
4. Endo Y, Baldino K, Li B, Zhang Y, Sakthivel D, MacArthur M, Panayi A, Kip P, Spencer DJ, **Jasuja R**, Bagchi D, **Bhasin S**, Nuutila K, **Neppl RL, Wagers AJ, Sinha I**. Loss of ARNT in skeletal muscle limits muscle regeneration in aging. *FASEB J.* In Press.

B. Positions and Honors

Positions and Employment

5/2004-12/2007	**Assistant Professor**, Department of Pathology, Harvard Medical School, Boston, MA
1/2008-6/2009	**Assistant Professor**, Department of Stem Cell and Regenerative Biology, Harvard University and Harvard Medical School, Boston, MA
7/2009-6/2012	**Associate Professor**, Department of Stem Cell and Regenerative Biology, Harvard University and Harvard Medical School, Boston, MA
11/2009-10/2015	**Early Career Scientist**, Howard Hughes Medical Institute
7/2012-present	**Forst Family Professor of Stem Cell and Regenerative Biology**, Department of Stem Cell and Regenerative Biology, Harvard University, Cambridge, MA
9/2018-present	**Co-Chair**, Harvard University, Department of Stem Cell and Regenerative Biology, Harvard University and Harvard Medical School, Cambridge, MA

Other Experience and Professional Memberships

6/2004-present	**Member**, BBS Graduate Training Program, Harvard Medical School, Boston, MA
10/2004-present	**Director/co-Director**, DRC/HSCI Flow Cytometry Core, Joslin Diabetes Center, Boston, MA
12/2004-present	**Member**, Harvard Stem Cell Institute Executive Committee
2005-present	**Ad hoc member**, NIH Study Sections (NINDS, NIDDK, NHLBI, NIA)
11/2006-present	**Editorial Board**, *Cell Stem Cell*
1/2009-present	**Member**, American Federation for Aging Research Grant Review Committee
11/2009-6/2014	**Charter member**, CMAD Study Section
11/2010-11/2011	**Chair**, American Society of Hematology Committee on Stem Cells
9/2010-4/2014	**Editorial Board**, *Skeletal Muscle*
12/2010-12/2016	**Board of Directors**, International Society for Stem Cell Research
7/2012-6/2015	**Director**, PhD Program in Development and Regenerative Biology, Harvard Medical School, Boston, MA
11/2012-6/2016	**Editorial Board**, *Stem Cell Reports*
6/2014-6/2018	**Board of Reviewing Editors***, eLife*
6/2016-6/2020	**Associate Editor**, *Stem Cell Reports*
5/2018-present	**Member**, National Advisory Council on Aging, National Institute on Aging, NIH

Honors and Awards

Burroughs Wellcome Fund Career Award in the Biomedical Sciences (2003); Smith Family New Investigator Award (2004); Beckman Foundation Young Investigators Award (2007); Keck Foundation Distinguished Young Scholar (2007); **NIH Director's New Innovator Award (2008)**; Smith Family Medical Foundation Prize (2009); **HHMI Early Career Award (2009)**; Glenn Foundation Award for Research in Aging (2010); **Presidential Early Career Award for Scientists and Engineers (PECASE) (2010)**; Spark Award for Outstanding Women in Science (2011); Duke TIP Distinguished Alumni Award (2011) Paul F. Glenn Foundation Laboratory for Research in the Biological Mechanisms of Aging (2012); Anne McClaren Lecture, International Society for Differentiation (2012); **NYSCF-Robertson Stem Cell Prize for Significant Achievement in Translational Research (2013); National Institute on Aging Nathan Shock Award (2014); Vincent Cristofalo 'Rising Star' Award (2015);** NIH Florence Mahoney Lecture on Aging (2017), **Harvard College Professor (2018), NIH Pioneer Award (2018)**

C. Contribution to Science

My most significant contributions to science thus far are described below. This substantial body of published work includes 141 original, peer-reviewed articles and 33 reviews/editorials. My Web of Science h-index (All Databases) is 73, with an average 80.7 citations/paper. Since establishing my independent lab in 2004, my group has made key discoveries that have revealed novel intrinsic and extrinsic regulators of stem cell activity in injury repair, degenerative disease and malignancy and highlighted the critical role of blood-borne mediators, cellular niches, and inflammatory and metabolic cues in coordinating the functions of stem cells and their progeny throughout the body.

1. Physiological recirculation of hematopoietic stem cells. My lab has a long-standing interest in hematopoietic stem cell (HSC) migration, stemming in part from a surprising observation that I made as a postdoctoral fellow in Dr. Irv Weissman's lab, in which I used parabiotic mice to demonstrate that HSCs constantly recirculate through the bloodstream. This observation indicated that the migratory pathways and mechanisms required for stem cells to transit from the blood to the bone marrow (and from the bone marrow to the blood) pre-exist in transplant recipients prior to preconditioning, thereby providing an unexpected cellular mechanism to explain the success of bone marrow transplant. Building on this observation, as a faculty member at Harvard, I set out to identify the molecular mediators of the physiological recirculation of HSCs. Using comparative transcriptional profiling, we identified the transcriptional regulator **EGR1** (early growth response 1) as a compelling candidate. Functional and genomic analysis of EGR1 in the hematopoietic system revealed that its expression in HSCs is uniquely essential for restraining HSC proliferation and retaining HSCs within the bone marrow niche and that it represents one of only four candidate master regulators of HSC fate. Finally, in recent work we undertook a novel **phosphoproteomic approach** to define the activated signaling networks involved in HSC mobilization, and identified the GTPase activating protein ARHGAP25 as a novel stem cell retention factor in the bone marrow niche. These discoveries provided some of the first insights into the molecular coordination of stem cell migration and proliferation and reveal novel potential targets for the manipulation of HSC fate.

1. Wright DE*, **Wagers AJ***, Pathak Gulati A, Johnson FL, Weissman IL. Physiological migration of hematopoietic stem and progenitor cells. *Science* 2001;294:1933-6. *Equal contributors. PMID: 11729320
2. Min IM, Pietramaggiori G, Kim FS, Passegue E, Stevenson KE, **Wagers AJ**. The transcription factor EGR1 controls both the proliferation and localization of hematopoietic stem cells. *Cell Stem Cell* 2008;2:380-391. PMID: 18397757
3. Gazit R, Garrison BS, Nageswara Rao, T, Shay T, Costello J, Ericson J, Kim F, Collins JJ, Regev A, **Wagers AJ**, Rossi DJ and the Immunological Genome Project Consortium. Transcriptome analysis identifies novel regulators of hematopoietic stem and progenitor cells. *Stem Cell Reports* 2013;1:266-280. PMCID: PMC3849420
4. Wang LD, Ficarro SB, Hutchinson JN, Csepanyi-Komi R, Nguyen PT, Wisniewski E, Sullivan J, Hofmann O, Ligeti E, Marto J, **Wagers AJ**. Phosphoproteomic profiling of mouse primary hematopoietic stem and progenitor cells reveals new regulators of HSPC mobilization. *Blood* 2016;128:1465-74. PMCID: PMC5025898

2. *In vivo* and *ex vivo* gene editing of tissue stem and progenitor cells. Genome editing describes a scientific approach in which experimentally engineered programmable nucleases are used to insert, replace or remove segments of DNA within the genome of a living cell or organism. This approach holds tremendous promise, both for fundamental discovery and for the treatment of many human congenital diseases, but realizing this promise will require robust technologies to introduce gene editing complexes into specific target cells of interest. Towards this goal, my laboratory has developed **adenoassociated virus (AAV)** delivery strategies and reporter systems to track gene editing in vivo, with single cell resolution. We have further applied these strategies to targeted gene disruption and functional gene recovery of disease-relevant genomic sequences via TALEN and **CRISPR-Cas9 based editing** in hematopoietic and muscle stem cells. This work has demonstrated the feasibility and efficacy of *in vivo* gene editing to simultaneously target multiple organs and cell types of therapeutic interest and to restore Dystrophin protein reading frame, recover muscle function, and establish a pool of modified muscle stem cells that can participate in subsequent muscle regenerative events in a mouse model of Duchenne Muscular Dystrophy (DMD). This innovative work provides a critical technological advance towards **correcting disease-causing mutations** in patients with hematologic and skeletal muscle disease and towards the application of high throughput ***in vivo* gene screening technologies** to uncover novel biological and pathological mechanisms.

1. Cerletti M, Jurga S, Witczak CA, Hirshman MF, Shadrach JL, Goodyear LJ, **Wagers AJ***. Highly efficient, functional engraftment of skeletal muscle stem cells in dystrophic muscles. *Cell* 2008;134:37-47. *Corresponding author. PMCID: PMC3665268
2. Xu C, Tabebordbar M, Iovino S, Ciarlo C, Liu J, Castiglioni A, Price E, Liu M, Barton ER, Kahn CR, **Wagers AJ***, Zon LI*. A zebrafish embryo culture system defines factors that promote vertebrate myogenesis across species. *Cell* 2013;155:909-21. *Co-corresponding authors. PMCID: PMC3902670
3. Tabebordbar M, Zhu K, Cheng JKW, Chew WL, Widrick JJ, Yan WX, Maesner C, Wu EY, Xiao R, Ran FA, Cong L, Zhang F, Vandenberghe LH, Church GM, **Wagers AJ***. In vivo gene editing in dystrophic mouse muscle and muscle stem cells. *Science*, 2016;351:407-11. *Corresponding author. PMCID: PMC4924477
4. Goldstein JM, Tabebordbar M, Zhu K, Wang LD, Messemer KA, Peacker B, Ashrafi Kakhki S, Gonzalez-Celeiro M, Shwartz Y, Cheng JKW, Xiao R, Barungi T, Albright C, Hsu Y-C, Vandenberghe LH, **Wagers AJ**. In situ modification of tissue stem and progenitor cell genomes. *Cell Reports*, 2019;27:1254-64. PMCID: PMC6901511.

3. **Cellular origins, metabolic vulnerabilities and niche-dependent progression of blood and muscle tumors.** Rhabdomyosarcomas (RMS) are a subset of aggressive and highly variable soft-tissue tumors that are diagnosed most often in children and adolescents. Existing RMS therapies involve substantial treatment-related side effects, including major organ toxicities and secondary cancers. To advance sarcoma treatment and develop new approaches to cure these tumors, my lab established a novel mouse model that introduces sarcoma-relevant oncogenetic modifications into tissue stem cells found normally in the muscle. This work revealed that soft-tissue sarcomas can arise from transforming events in any of several muscle-resident precursor cell populations and defined a novel set of **sarcoma-enriched genes**, whose expression is induced in many human soft-tissue sarcomas, as well as some non-sarcomatous malignancies. We further employed pharmacological and functional genomic screening approaches to evaluate candidate therapeutic targets, ultimately revealing a critical dependence of stem cell derived soft-tissue sarcomas on adequate availability of the non-essential amino acid **asparagine**, which is needed for the generation of new protein biomass in rapidly proliferating tumor cells. In complementary studies of myeloid malignancies, we worked with Dr. Emmanuelle Passegue's lab to investigate a novel, self-reinforcing regulatory interaction that acts via inflammatory mediators to promote leukemic progression through functional modulation of osteolineage niche cells.

1. Hettmer S, Liu J, Miller CM, Lindsay MC, Sparks CA, Guertin DA, Bronson RT, Langenau DM, **Wagers AJ**. Sarcomas induced in discrete subsets of prospectively isolated skeletal muscle cells. *Proc. Natl. Acad. Sci. U.S.A.*, 2011;108:20002. PMCID: PMC3250188
2. Schepers K, Pietras EM, Reynaud D, Flach J, Binnewies M, Garg T, **Wagers AJ**, Hsiao EC, Passegue E. Myeloproliferative neoplasia remodels the endosteal bone marrow niche into a self-reinforcing leukemic niche. Cell Stem Cell, 2013;13:1-15. PMCID: PMC3769504
3. Wang LD, Rao TN, Rowe RG, Nguyen PT, Sullivan JL, Pearson DS, Doulatov S, Wu L, Lindsley RC, Zhu H, DeAngelo DJ, Daley GQ, Wagers AJ. The role of Lin28b in myeloid and mast cell differentiation and mast cell malignancy. Leukemia 2015;29:1320-30. PMCID: PMC4456252
4. Hettmer S, Schinzel AC, Tchessalova D, Schneider M, Parker CL, Bronson TR, Richards NGJ, Hahn WC, **Wagers AJ.** Functional genomic screening reveals asparagine dependence as a metabolic vulnerability in sarcoma. *eLife*, 2015;4:pii:e09436. PMCID: PMC4696385

4. Reversibility of aging characteristics of tissue stem cells and differentiated cells. Aging is typically accompanied by progressive deterioration of cells and tissues, which ultimately leads to loss or pathologic deregulation of normal function. However, studies from my lab, together with our colleagues and collaborators, demonstrate that such aging characteristics are reversible, and controlled in part by blood-borne mediators. Using **heterochronic parabiosis**, a model in which young and old mice are surgically joined such that they develop a common blood circulation, we demonstrated that exposure of tissues in aged animals to a young circulatory system both restores stem/progenitor cell function and remodels terminally differentiated post-mitotic cells to promote more healthy function in many (though not all) aged organs. These data reveal the existence of a conserved systemic regulatory axis that modulates tissue homeostasis and stem cell activity in an age-dependent manner across a wide variety of tissues that vary significantly in their intrinsic regenerative potential and normal tissue physiology. Related studies interrogating the myogenic function of satellite cells isolated from mice subjected to short term calorie restriction or exposed to interventions that suppress NF-kB activity further implicate **inflammatory lipids** and **metabolic reprogramming** as key mechanisms by which healthy function may be restored to aging progenitor cells.

1. Conboy IM, Conboy MJ, **Wagers AJ**, Girma ER, Weissman IL, Rando TA. Rejuvenation of aged progenitor cells by exposure to a young systemic environment. *Nature* 2005;433:760-4. PMID: 1576955
2. Cerletti M, Jang Y, Finley LWS, Haigis MC, **Wagers AJ**. Short-term calorie restriction enhances skeletal muscle stem cell function. *Cell Stem Cell* 2012;10:515-9. PMCID: PMC3561899
3. Katsimpardi L, Litterman NK, Schein PA, Miller C, Loffredo FS, Wojtkiewicz GR, Chen JW, Lee RT, **Wagers AJ**, Rubin LL. Vascular and neurogenic rejuvenation of the aging mouse brain by young systemic factors. *Science* 2014;344:630-34. PMCID: PMC4123747
4. Oh J, Sinha I, Tan KY, Rosner B, Dreyfuss JM, Gjata O, Tran P, Shoelson SE, **Wagers AJ**. Age-associated NF-kB signaling in myofibers alters the satellite cell niche and restrains muscle stem cell function. *Aging* 2016;8:2871-96. PMCID: PMC5191876

5. Role of GDF11 in regulating mammalian aging phenotypes. In collaboration with Dr. Richard Lee's lab, we discovered that supplementation of GDF11, a circulating hormone in mice and humans, can recapitulate at least some of the effects of heterochronic parabiosis when provided systemically in aged mice. Indeed, our studies suggest that systemic supplementation with recombinant **GDF11** (at physiological levels) produces a striking reversal of age-related pathologies in the heart, brain, and skeletal muscle. Our results have been supported by other groups, including genetic studies in flies and mice (Demontis et al. *Cell Reports* 2014; Zhou et al. *J. Gerontol. A. Biol. Sci. Med. Sci.* 2016), and longitudinal studies of levels of GDF11, and the highly related protein GDF8 (Myostatin/MSTN), in human patients with coronary artery disease (Olson et al. *Eur. Heart J.* 2015). Our discovery of GDF11 as a hormone that regulates aging and mediates restoration of aged tissue structure and function across multiple, biologically diverse cell types, organs and organisms has uncovered an entirely new mechanism through which the physiology of aging tissues may be regulated, and also raised some controversy, particularly among investigators who have studied the highly related MSTN protein. Our current work seeks to resolve this controversy, and develop a rigorous, mechanistic understanding of GDF11 functions during adulthood and aging.

1. Loffredo FS, Steinhauser ML, Jay SM, Gannon J, Pancoast JR, Yalamanchi P, Sinha M, Dall'Osso C, Khong D, Shadrach JL, Miller CM, Singer BS, Stewart A, Psychogios N, Gerszten RE, Hartigan AJ, Kim MJ, Serwold T, **Wagers AJ***, Lee RT*. Growth differentiation factor 11 is a circulating factor that reverses age-related cardiac hypertrophy. *Cell* 2013;153:828-39. *Co-corresponding authors. PMCID: PMC3677132
2. Sinha M, Jang, YC, Oh J, Khong D, Wu EY, Manohar R, Miller C, Regalado SG, Loffredo FS, Pancoast JR, Hirshman M, Lebowitz J, Shadrach JL, Cerletti M, Kim MJ, Serwold T, Goodyear L, Rosner B, Lee RT, **Wagers AJ**. Restoring systemic GDF11 levels reverses age-related dysfunction in mouse skeletal muscle. *Science* 2014;344:649-52. PMCID: PMC4104429
3. Poggioli T, Vujic A, Yang P, Macias-Trevino C, Uygur A, Loffredo FS, Pancoast JR, Cho M, Goldstein J, Tandias RM, Gonzalez E, Walker RG, Thompson TB, **Wagers AJ**, Fong YW, Lee RT. Circulating growth differentiation factor 11/8 levels decline with age. *Circ. Res*. 2015; pii:CIRCRESAHA.115.307521. [Epub ahead of print]. PMCID: PMC4748736
4. Goldstein J, Valido A, Lewandowski J, Walker RG, Mills MJ, Messemer KA, Besseling P, Lee KH, Wattrus SJ, Cho M, Lee RT, **Wagers AJ**. Variation in zygotic CRISPR/Cas9 gene editing outcomes generates novel reporter and deletion alleles at the *Gdf11* locus. *Sci. Rep.* 2019;9:18613. PMCID: PMC6901511

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/amy.wagers.1/bibliography/40828266/public/?sort=date&direction=ascending.

D. Research Support

Ongoing Research Support (Selected)

NIH RO1 AG048917 (Wagers) *Role: PI* 04/15/2016 – 03/31/2021
Regulation and function of Growth Differentiation Factor 11 during development and aging

NIH RO1 AG048917 (Wagers) *Role: PI* 09/15/2017 – 05/31/2021
Investigating GDF11 and MSTN as candidate circulating geronic factors

Elevian, Inc. (Wagers) *Role: PI* 12/01/2017 – 11/30/2020
Discovering physiological drivers of age-related changes in blood-borne geroproteins

The Glenn Foundation (Wagers) *Role: PI* 01/01/2018 – 12/31/2020
Systemic regulators of tissue homeostasis and repair during aging

NIH DP1 AG048917 (Wagers) *Role: PI* 09/30/2018 – 06/30/2023
Uncovering molecular effectors of mammalian aging