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 the regenerative biology of aging for more than 10 years. Our prior work on aging has been funded by the Keck Foundation, Glenn Foundation, an NIH New Innovator Award, and awards from the NIA (including P30 AG031679 and RO1 AG033053). Studies from my lab have helped to develop a model in which circulating factors and metabolic regulators that change with age play a critical role in determining stem cell function and can modulate the outcome of regenerative responses to tissue injury as well as tissue homeostasis. In recent work, we collaborated with Dr. Richard Lee's lab to identify the circulating factor Growth Differentiation Factor 11 (GDF11) as a critical anti-geronic protein whose loss in older mice coincides with the onset of multiple age-associated pathologies (Loffredo et al., 2013). We further showed, together with Dr. Lee and Dr. Lee Rubin, that restoration of "youthful" levels of GDF11 in aged mice reverses multiple age-related pathologies in the heart (Loffredo et al, 2013), brain (Katsimpardi et al, 2014) and skeletal muscle (Sinha et al, 2014).

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 11+ years as an independent investigator, I have trained >25 pre- and post-doctoral fellows, who have successfully progressed in their careers to obtain competitive positions in industry, academia, and clinical medicine. As **Associate Director of the Research Education Component (REC) Core**, I look forward to working with Drs. Lipsitz and Marcantonio to provide support, education and training to advance the careers of our most promising postdoctoral trainees, 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.

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

Other Experience and Professional Memberships

8/2004-present	**Member**, Dana Farber/Harvard Cancer Center, Boston, MA
10/2004-present	**Director/co-Director**, DERC/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)
8/2006-11/2008	**Member**, State of Connecticut Stem Cell Research Advisory Committee
11/2006-present	**Editorial Board**, *Cell Stem Cell*
1/2007-present	**Member**, California Institute of Regenerative Medicine Grants Working Group
1/2009-present	**Member**, American Federation for Aging Research Grant Review Committee
11/2009-6/2014	**Charter member**, CMAD Study Section
11/2009-present	**Director**, HSCRB Flow Cytometry Core, Harvard University, Cambridge, MA
11/2010-11/2011	**Chair**, American Society of Hematology Committee on Stem Cells
9/2010-4/2014	**Editorial Board**, *Skeletal Muscle*
12/2010-12/2013	**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-present	**Editorial Board**, *Stem Cell Reports*
6/2014-present	**Board of Reviewing Editors***, eLife*

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)**

C. Contribution to Science

My most significant contributions to science in my career thus far are described below. This substantial body of work has revealed novel intrinsic and extrinsic regulators of stem cell activity, and highlights the key role of blood-borne mediators, including the small circulating protein GDF11, in coordinating the function of stem cells and their progeny throughout the body.

1. Lineage fidelity of hematopoietic stem cells. As a postdoctoral fellow in Irv Weissman's lab, and subsequently as an Assistant Professor at Harvard, I published 10 papers testing high profile, published claims that blood-forming hematopoietic stem cells (HSCs) from adult bone marrow could transdifferentiate to contribute to the replacement of cells in a variety of non-blood tissues, including the heart, brain and skeletal muscle. Using single-cell transplantation and parabiosis assays, I demonstrated that HSCs maintain hematopoietic commitment, and do not undergo lineage conversion to non-blood cell types in either the steady state or injury conditions. These studies further revealed that non-blood tissues are regenerated predominantly from local progenitor cells, and rarely, if ever, incorporate any cells that circulate in the bloodstream. While these discoveries may seem self-evident now, this work was extremely important at the time, as it occurred prior to the discovery of iPSC reprogramming techniques and against the backdrop of a national debate about the necessity of using human embryonic stem cells (ESCs) as a source of pluripotent cells. My publications played a key role in overturning the argument that adult HSCs could be used in place of ESCs, and re-affirmed the continued importance of pluripotent human ES cells for studies of lineage specification and cell replacement strategies. They further directed future studies aimed at identifying additional adult stem cell populations to focus on the local tissue environment, rather that the bloodstream, as a source of regenerative progenitors.

- **Wagers AJ**, Sherwood RI, Christensen JC, Weissman, IL. Little evidence for developmental plasticity of adult hematopoietic stem cells. *Science* 2002;297:2256-9. PMID: 12215650

- Balsam LB, **Wagers AJ**, Christensen JL, Kofidis T, Weissman IL, Robbins RC. Hematopoietic stem cells adopt mature hematopoietic fate in ischemic myocardium. *Nature* 2004;428:668-73. PMID: 15034594
- Sherwood RI, Christensen JL, Weissman IL, **Wagers AJ***. Determinants skeletal muscle contributions from circulating cells, bone marrow cells, and hematopoietic stem cells. *Stem Cells* 2004;22:1292-1304. *Corresponding author. PMID: 15579647
- Eggan K, Jurga S, Gosden R, Min IM, **Wagers AJ***. Ovulated oocytes in adult mice derive from non-circulating germ cells. *Nature* 2006;441:1109-14. *Corresponding author. PMID: 16799565

2. Physiological recirculation of hematopoietic stem cells. My continued interest in hematopoietic stem cell (HSC) migration stems 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, I set out to identify the molecular mediators of the physiological recirculation of HSCs. Using comparative transcriptional profiling, identified the transcriptional regulator **EGR1** (early growth response 1) as a compelling candidate. Functional 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. More recently, working in collaboration with Dr. Derrick Rossi (Children's Hospital Boston) we discovered that EGR1 represents one of only four candidate master regulators of HSC fate, with significant enrichment of predicted EGR1 binding sites in a large fraction of HSC-specific genes. These discoveries provide 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.

- 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
- 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
- Forsberg EC*, Passegue E*, Prohaska SS*, **Wagers AJ***, Koeva M, Stuart JM, Weissman IL. Molecular signatures of quiescent, mobilized and leukemia-initiating hematopoietic stem cells. *PLoS One* 2010 Jan 20;5(1):e8785. *Equal contributors. PMCID: PMC2808351
- 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

3. Isolation of mouse and human skeletal muscle stem cells (satellite cells). My laboratory was among the first to develop and apply marker-based cell sorting approaches to analyze precursor cells in mouse and human skeletal muscle. Our work established robust protocols for the purification of satellite cells – mononuclear cells found beneath the basal lamina surrounding mature muscle fibers that act as muscle regenerative cells. We further demonstrated that these unique stem cells exhibit robust self-renewal and myogenic differentiation activity, and can restore muscle function when transplanted into injured or diseased muscle. Recently, by combining this marker-based satellite cell purification system with a chemical screening approach in zebrafish embryos devised by Dr. Leonard Zon (Children's Hospital Boston), we identified a unique set of small molecules that can expand engraftable satellite cells in ex vivo culture and specify myogenic differentiation of human induced pluripotent stem cells (iPSCs).

- Sherwood, RI, Christensen JL, Conboy IM, Conboy MJ, Rando TA, Weissman IL, **Wagers AJ***. Isolation of adult mouse myogenic progenitors: functional heterogeneity of cells within and engrafting skeletal muscle. *Cell* 2004;119:543-54. *Corresponding author. PMID: 15537543
- 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
- Castiglioni A, Hettmer S, Lynes MD, Nageswara Rao, T, Tchessaolova D, Sinha I, Lee BT, Tseng YH, **Wagers AJ***. Isolation of progenitors that exhibit myogenic/osteogenic bipotency in vitro by

fluorescence activated cell sorting from human fetal muscle. *Stem Cell Reports* 2014;2:92-106. *Corresponding author. PMCID: PMC3966115

- 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

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 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 further implicate metabolic reprogramming as a possible mechanism by which healthy function may be restored to aging progenitor cells.

- 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
- Ruckh J, Zhao J-W, Shadrach J, van Wijngaarden P, Nageswara Rao T, **Wagers AJ***, Franklin RJM*. Rejuvenation of regeneration in the aging central nervous system. *Cell Stem Cell* 2012;10:96-103. *Co-corresponding authors. PMCID: PMC3714794
- Painter MW, Brosius-Lutz A, Cheng YC, Latremoliere A, Duong K, Miller CM, Posada S, Cobos EJ, **Wagers AJ**, Barres B, Omura T, Woolf CJ. Diminished Schwann cell repair responses underlie age-associated impairment in axonal regeneration. *Neuron* 2014;83:331-43. PMCID: PMC4106408
- 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. *Corresponding author. PMCID: PMC3561899

5. GDF11 is acts as a "rejuvenator" of aging phenotypes in mammals. The most important discovery of my career thus far arose through our collaboration with Dr. Richard Lee's lab, through which we discovered that GDF11, a circulating hormone in mice and humans that declines with advancing age, can recapitulate the effects of heterochronic parabiosis when restored to "youthful" levels in aged mice. As discussed further in this application, systemic supplementation with GDF11 for as little as 30 days produces a striking reversal of age-related pathologies in the heart, brain, and skeletal muscle. Our discovery of this new hormone that regulates aging and mediates restoration of aged tissue structure and function across multiple, biologically diverse cell types and organs has uncovered an entirely new mechanism through which the physiology of aging tissues is regulated. Moreover, this work has the potential to provide transformative new therapies based on manipulation of GDF11 levels and signaling, which may be useful to restore organ function in the context of multiple age-associated diseases that previously have been studied (and treated) as unrelated pathologies.

- 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
- 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
- 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. *Corresponding author. PMCID: PMC4104429

- 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., in press.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40828266/?sort=date&direction=ascending

D. Ongoing Research Support (Selected)

R01 AG033053 (Wagers) 08/15/2009 – 7/31/2016
NIH/NIA
Reversing age-related dysfunction of skeletal muscle stem cells
The primary goals of this grant are to determine if enhanced local inflammation promotes age-associated dysfunction of muscle stem cells and whether inhibition of inflammation can rejuvenate muscle repair function.
Role: PI

R56 AG048917 (Wagers) 04/15/2015 - 03/31/2016
NIH/NIA
Regulation and function of Growth Differentiation Factor 11 during development and aging
In this project, we will answer questions crucial to understanding the regulation and activity of GDF-11 and its potential for regulating developmental and aging phenotypes in mice and humans.
Role: PI

The Glenn Foundation (Wagers) 01/01/2015 - 12/31/2017
Systemic regulators of tissue homeostasis and repair during aging
The Wagers Lab will pursue studies of tissue homeostasis and repair during aging, as well as related studies of effective tissue repair vehicles in specific disease areas and of tissue generation from IPS cells and the potential of stem cell technology to repair aging organs.
Role: PI

UO1 HL100402 (Scadden) 09/30/2009 – 04/30/2016
NIH/NHLBI
Progenitor Cell Biology Consortium: Microenvironmental control of progenitors in organ dysfunction and repair
This is a UO1 grant to establish a hub for Progenitor Cell Biology Research. Dr. Wagers will participate as a sub-contract PI in the evaluation of microenvironmental inputs into determination of stem and progenitor cell function in the blood, lung, and cardiac muscle.
Role: Co-I

Completed Research Support (Selected)

DP2 OD004345 (Wagers) 09/30/2008 – 06/30/2013
NIH/OD
Aging and Rejuvenation of the hematopoietic stem cell niche
This project aimed to: (1) identify mechanisms of hematopoietic stem cell aging and rejuvenation, (2) determine the relationship between stem cell rejuvenating activity and longevity, and (3) reveal signaling pathways that may be useful for halting or reversing acquired HSC dysfunction during aging.
Role: PI

R01 AR060636 (Lee) 08/01/2010 – 07/31/2015
NIH/NIAMS
Characterization of myostatin and GDF-11
This is a subcontract from Johns Hopkins University. Under this project, Dr. Wagers will assist Dr. Se-Jin Lee in the design and performance of experiments involving the sorting and analysis of skeletal muscle precursor cells and their differentiated progeny.
Role: Co-I