BIOGRAPHICAL SKETCH

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NAME: Helen M. Blau

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POSITION TITLE: Donald E. and Delia B. Baxter Foundation Professor
Director, Baxter Laboratory for Stem Cell Biology

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of York, York, England	B.A.	07/1969	Biology
Harvard University, Cambridge, MA	M.A.	06/1970	Biology
Harvard University, Cambridge, MA	Ph.D.	06/1975	Biology
University of California, San Francisco, CA	Postdoctoral	06/1978	Biochem. & Biophysics

A. Personal Statement

I am a full professor, PI, and Director of the Baxter Laboratory for Stem Cell Biology, with extensive experience running my own laboratory and a research program including three PIs and approximately 75 trainees and staff. I am a member of the National Academy of Sciences and the National Academy of Medicine. I am a co-inventor on 20 patents, 10 currently licensed, and my work is consistently high profile, with one quarter of my publications in *Science, Cell,* and *Nature* journals. Our laboratory's innovation has garnered an NIH MERIT Award, an NIH Director's Transformative Research Award, a NIH EUREKA Grant for Exceptionally Innovative Research, and a Milky Way Award. We have made seminal contributions in the area of nuclear reprogramming of the differentiated state. Our research encompasses cell and molecular approaches to regenerative medicine for acquired and inherited diseases. A central interest is the elucidation of the mechanisms that underlie changes in muscle stem cell function in aging, dystrophy, and diabetes. This knowledge is key to our understanding of stem cell self-renewal and expansion during tissue regeneration with a view toward medical applications for increasing muscle function and extending healthspan. A hallmark of our work is the development of interdisciplinary technologies that enable novel fundamental insights and drug discovery.

I have extensive experience mentoring over 90 postdoctoral fellows, graduate students, and undergraduates for academic independence. It is not uncommon and a source of pride that as many as 10-20% of speakers at FASEB or EMBO meetings on myogenesis are my ex-trainees. Trainees from my laboratory are now on the faculty at elite US universities, including Stanford University, the University of Pennsylvania, Harvard University, UCSD and UCSF. The overwhelming majority of my graduate students and postdoctoral fellows obtain independent funding from a variety of sources including the NIH, LSRF, MDA, AHA, and CIRM. Two of my current postdoctoral fellows have earned K99/R00 awards. This is an excellent T32 training program that produces top notch scientists, and I look forward to continuing to be a part of it.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2019 American Institute for Medical and Biological Engineering
2018 National Academy of Inventors
2018 Pontifical Academy of Sciences
2016 National Academy of Sciences
2011-2017 Pew Scholars Program National Advisory Committee

2009-2010 NIH Peer Review Advisory Committee (PRAC)
2007-2014 Ellison Medical Foundation Scientific Advisory Board
2005 Member, NIH Committee to Review Biology of Aging Program, the National Institute of Aging
2004-2010 Harvard Board of Overseers
2002-2004 President, International Society of Differentiation
2002-2004 Council Member, American Society for Cell Biology
2002-present Director, Baxter Laboratory for Stem Cell Biology, Stanford University, CA
2002-present Professor, Microbiology and Immunology, and member, Institute for Stem Cell Biology and Regenerative Medicine, Stanford University School of Medicine, Stanford, CA
1999-present Donald E. and Delia B. Baxter Endowed Professorship
1997-present Director, Gene Therapy Technology, Stanford University School of Medicine, CA
1997-2002 Chair, Molecular Pharmacology, Stanford University School of Medicine, CA
1996-2000 National Advisory Council, NIH Institute on Aging
1996 American Academy of Arts and Sciences
1995 National Academy of Medicine (aka Institute of Medicine)
1994-1995 President, Society for Developmental Biology
1991-2002 Professor, Molecular Pharmacology, Stanford University School of Medicine, CA
1991 Fellow of the American Association for the Advancement of Science
1986-1991 Associate Professor, Molecular Pharmacology, Stanford University School of Medicine, CA
1981-1984 William M. Hume Faculty Scholar
1979-1980 Mellon Foundation Faculty Fellow
1978-1986 Assistant Professor, Molecular Pharmacology, Stanford University School of Medicine, CA
1975-1978 Postdoctoral Fellow, Dept. of Biochem. & Biophysics, Div. of Medical Genetics, UCSF, CA
1969-1975 Predoctoral Fellow, Department of Biology, Harvard University, Cambridge, MA

Honors

2017 Stanford Office of Technology Licensing Hall of Fame
2015 Glenn Award for Research in Biological Mechanisms of Aging
2015 Stanford Office of Technology Licensing Outstanding Inventor Award
2014-2018 NIH Exceptionally Innovative Research (EUREKA) Award
2011-2018 NIH Director's Transformative Research Award
2011 AACR-Irving Weinstein Foundation Distinguished Award for Outstanding Innovation
2009-2011 NIH Challenge Grant
2007, 2011 Fulbright Senior Scholar Award
2003 Honorary Doctorate, University of Nijmegen, Holland
2001 McKnight Technological Innovations for Neuroscience Award
2000 NIH Director's Lectureship
1999 FASEB Excellence in Science Award
1995-2005 NIH MERIT Award
1995 Nobel Forum Lectureship, Karolinska Institute, Stockholm, Sweden
1992 Senior WICB Career Recognition Award of the American Society for Cell Biology
1989-1991 SmithKline and Beecham Junior Faculty Scholar Award
1984-1989 Research Career Development Award, National Institutes of Health
1978-1981 Basil O'Connor Starter Research Award from the March of Dimes

C. Contributions to Science

1. Muscle Repair and Regeneration by Muscle Stem Cells

Muscle stem cells in adult muscle form the basis for regeneration and repair of muscle tissue throughout adulthood. A major barrier in regenerative medicine and drug discovery aimed at muscle repair has been the difficulty in purifying sufficient quantities of muscle stem cells and maintaining them in an active state. My laboratory developed a combination of novel technologies, including bioengineered microenvironments, single cell tracking algorithms, and a non-invasive bioluminescence imaging (BLI) assay for monitoring muscle stem cell engraftment, self-renewal, and muscle repair in living mice (***Nature, 2008; Science, 2010***). Our work showed that in aging, two-thirds of muscle stem cells develop a cell autonomous defect that is largely responsible for the decreased regeneration observed with advanced age. Our platform enabled a screen that identified a small molecule capable of enhancing the numbers and function of the aged muscle stem cell population. Notably, we

found that transplantation of treated aged stem cell populations into injured muscles of aged mice restores muscle strength to a level comparable to that of young mice. A synergy between biophysical cues supplied by the microenvironment, and biochemical cues mediated by a small molecule kinase inhibitor, controls muscle stem cell self-renewal and leads to rejuvenation of aged muscle stem populations (***Nature Medicine, 2014***). An *in silico screen* identified the proinflammatory metabolite, PGE2, as a potent activator of endogenous muscle stem cell function that increases strength with therapeutic implications for muscle wasting that plagues the elderly (***PNAS, 2017***). Finally, single-cell mass cytometry (CyTOF) analysis of skeletal muscle uncovered the dynamics of skeletal muscle regeneration in vivo (***Nature Cell Biology, 201; Cell Reports, 2019***). These studies are of fundamental importance to regenerative medicine (***New England Journal of Medicine, 2019***) and pave the way for the proposed elucidation of the regulatory networks that underlie cell-state transitions in muscle diseases and aging.

a. Gilbert PM, Havenstrite KL, Magnusson KEG, Sacco A, Leonardi NA, Kraft PE, Nguyen NK, Thrun S, Lutolf MP, Blau HM (2010) Substrate elasticity regulates skeletal muscle stem cell self-renewal in culture. ***Science*** 329(5995):1078-1081 PMCID: PMC2929271.
b. Cosgrove BD, Gilbert PM, Porpiglia E, Mourkioti F, Lee SP, Corbel SY, Llewellyn ME, Delp SL, Blau HM (2014) Rejuvenation of the muscle stem cell population restores strength to injured aged muscles. ***Nature Medicine*** 20(3):255-264 PMCID: PMC3949152.
c. Porpiglia E, Samusik N, Ho ATV, Cosgrove BD, Mai T, Davis KL, Jager A, Nolan GP, Bendall SC, Fantl WJ, Blau HM (2017) High-resolution myogenic lineage mapping by single-cell mass cytometry. ***Nature Cell Biology*** 19(5):558-567 PMCID: PMC5728993.
d. Palla AR, Ravichandran M, Wang YX, Alexandrova L, Yang AV, Kraft P, Holbrook CA,Schurch CM, Ho ATV, and Blau HM (2021) Inhibition of prostaglandin-degrading enzyme 15-PGDH rejuvenates aged muscle mass and strength. ***Science*** Jan 29;371(6528). PMCID: PMC7938328

2. Cell Plasticity and Differentiation

My early work on cell plasticity challenged the prevailing view that the state of differentiated cells is fixed and terminal. In the 1980s, we demonstrated that mammalian cell differentiation is plastic and reversible by reprogramming cells specialized for liver or skin to express previously silent muscle genes upon fusion in heterokaryons, proving that John Gurdon's nuclear reprogramming by somatic cell nuclear transfer was not limited to amphibians (***Cell 1983; Cell 1984; Cell 1985; Science 1985***). This work also demonstrated that the stoichiometry of trans-acting regulators is crucial to inducing nuclear reprogramming, a finding recently underscored by the induction of pluripotent stem cells (iPSCs) by transcription factor overexpression by Shinya Yamanaka. Our current work capitalizes on the unique ability of the heterokaryon system to generate "snapshots" of the sequential molecular, transcriptional, and epigenetic events in the remodeling of cell fate in the first minutes to hours of reprogramming. Using this approach, my laboratory has identified several novel early and transient regulators (AID, IL6, NKX-3) critical to the initiation of reprogramming to iPSCs (***Nature 2010; Cell 2011; Nature Cell Biology 2013***). In total, this body of work established the basis for diverse approaches, such as transcription factor overexpression now being used to control cell fate that constitute the bedrock for modern stem cell research and regenerative medicine.

a. Blau HM, Pavlath GK, Hardeman EC, Chiu C-P, Silberstein L, Webster SG, Miller SC, Webster C. (1985) Plasticity of the differentiated state. ***Science*** 230:758-766. PMID: 2414846
b. Bhutani N, Brady JJ, Damian M, Sacco A, Corbel SY, Blau HM (2009) Reprogramming towards pluripotency requires AID-dependent DNA demethylation. ***Nature*** 463(7284):1042-1047. PMCID: PMC2906123.
c. Brady JJ, Li M, Suthram S, Jiang H, Wong WH, Blau HM (2013) Early role for IL-6 signaling during generation of induced pluripotent stem cells revealed by heterokaryon RNA-Seq. ***Nature Cell Biology*** 15(10):1244-1252. PMCID: PMC4100556.
d. Mai T, Markov GJ, Brady JJ, Palla AR, Zeng H, Sebastiano V, Blau HM (2018) NKX3-1 is required for induced pluripotent stem cell reprogramming and can replace OCT4 in mouse and human iPSC induction. ***Nature Cell Biology.*** 20(8):900-908. PMCID: PMC6101038

3. Telomere Biology in Duchenne Muscular Dystrophy

Duchenne Muscular Dystrophy (DMD) is a major cause of death in childhood with an estimated worldwide incidence of 1 in 3,500 boys. There is no effective therapy, and the widely used mouse model that lacks dystrophin (mdx) exhibits only a very mild form of the disease. My laboratory revealed a defect in DMD myoblast progenitor cell proliferation (***PNAS 1983***), led a clinical trial of myoblast cell therapy and developed

novel analytic tools for detection of introduced genes in DMD patients (***Nature 1992; Nature Biotechnology 1996; Nature Medicine 1997***). Recently we discovered in a mouse model of DMD that reduced telomere length leads to exhaustion of stem cells in skeletal muscle and mitochondrial failure in cardiac muscle (***Cell 2010; Nature Cell Biology 2013; PNAS 2016***). Moreover, the findings in mice hold true for patients. In the cardiomyocytes of hearts of DMD patients, telomere lengths are ~50% shorter than cardiomyocytes of normal age-matched human hearts. Capitalizing on work we published with Joe Wu (***Nature Medicine* 2016**), we now propose to model DMD at the cellular level using patient-derived iPSC and isogenic controls differentiated into cardiomyocytes (hiPSC-CM) to elucidate the mechanism whereby contractile defects due to dystrophin deficiency drive telomere dysfunction causing lethal dilated cardiomyopathy.

a. Gussoni E, Blau HM, Kunkel L (1997) The fate of individual myoblasts following transplantation into muscles of DMD patients. ***Nature Medicine*** 3:970-977. PMID: 9288722
b. Mourkioti F, Kustan J, Kraft PE, Day JW, Zhao M-M, Kost-Alimova M, Protopopov A, DePinho RA, Bernstein D, Meeker AK, Blau HM (2013) Role of telomere dysfunction in cardiac failure in Duchenne muscular dystrophy. ***Nature Cell Biology*** 15(8):895-904. PMCID: PMC3774175
c. Chang ACY, Ong S-G, LaGory EL, Kraft PE, Giaccia AJ, Wu JC, Blau HM (2016) Telomere shortening and metabolic compromise underlie dystrophic cardiomyopathy. ***Proc. Natl. Acad. Sci. U.S.A.*** 113(46):13120-13125. PMCID: PMC5135315
d. Chang ACY, Chang ACH, Kirillova A, Sasagawa K, Su W, Weber G, Lin J, Termglinchan V, Karakikes I, Seeger T, Dainis AM, Hinson JT, Seidman J, Seidman CE, Day JW, Ashley E, Wu JC, Blau HM (2018) Telomere shortening is a hallmark of genetic cardiomyopathies. ***Proc. Natl. Acad. Sci. U.S.A.*** 115(37):9276-9281. PMCID: PMC6140486

4. Dedifferentiation of Post-mitotic Skeletal and Cardiac Myocytes

While robust regeneration of limbs and heart in several orders of lower vertebrates, including urodele amphibians and zebrafish occurs via a process of dedifferentiation, mammals only exhibit limited regeneration. My lab used an evolutionary comparison to identify differences between humans and newts that might underlie their disparate regenerative capacity (***Cell Stem Cell 2010; JAMA 2011; Development 2013***). We noted that newts lack the cell cycle regulatory protein p19/Arf which first arose in chickens and inactivate the cell cycle regulator Rb by phosphorylation. We reasoned and demonstrated that transient inactivation of both Rb and Arf, could induce post-mitotic mammalian cells to dedifferentiate, proliferate and contribute to muscle repair *in vivo*. To address the longterm enigma of how injury leads to dedifferentiation we showed that limb regeneration depends on a programmed cell death response by myofibers (***Nature Communications 2015***). Our focus now is human iPSC-cardiomyocyte models to study cardiac disease and screen for drugs (***Nature Medicine 2016***).

a. Pajcini KV, Corbel SC, Sage J, Pomerantz JH, Blau HM (2010) Transient inactivation of Rb and ARF yields regenerative cells from postmitotic mammalian muscle. ***Cell Stem Cell*** 7(2):198-213. PMCID: PMC2919350.
b. Blau HM and Pomerantz JH (2011) Re"evolutionary" regenerative medicine. ***JAMA*** 305(1):87-88. PMCID: PMC3105469.
c. Wang H, Lööf S, Borg P, Nader GA, Blau HM, Simon A (2015) Turning terminally differentiated skeletal muscle cells into regenerative progenitors. ***Nature Communications*** 6:7916. PMCID: PMC4765497.
d. Burridge PW, Li YF, Matsa E, Wu H, Ong S-G, Sharma A, Holmstrom A, Chang ACY, Coronado MJ, Ebert AD, Knowles JW, Telli ML, Witteles RM, Blau HM, Bernstein D, Altman RB, Wu JC (2016) Human induced pluripotent stem cell-derived cardiomyocytes recapitulate the predilection of breast cancer patients to doxorubicin-induced cardiotoxicity. ***Nature Medicine*** 22(5):547-56. PMCID: PMC5086256

5. Technological advances in protein interactions, bioengineering, and artificial intelligence

My lab pioneered the use of low affinity β-galactosidase (β-gal) complementation for monitoring protein-protein interactions in mammalian cells (***Nature Biotech 2000; Nature Genetics 2004; Nature Methods 2005, 2006***). This technology led to the identification of the ErbB family members targeted by Herceptin and insights into TrkA and p75 receptor interactions (***PNAS 2006; Neuron 2007; FASEB J. 2007a & b***), became a major drug discovery platform for DiscoveRx, and led to the discovery of numerous anti-cancer agents and G-coupled protein receptors ligands. We established that therapeutic angiogenesis requires a 'well-tempered vessel' -- the balanced delivery of VEGF and PDGF-BB (***Nature Medicine 2001; FASEB J. 2012***), pioneered

myoblast mediated gene therapy (***Science 1991; Science 1997***), developed inducible retroviral vectors to enable regulation of gene expression (***Nature Genetics 1998; PNAS 1999***) and transcriptional control to be converted from a rheostat to an on/off switch (***Molecular Cell 2000***). We developed AI approaches to disease diagnosis (***Nature 2017***) and bioengineered hydrogel materials to manipulate mechanosensing (***Science 2010; Nature 2018***).

a. Dhawan J, Pan LC, Pavlath GK, Travis MA, Lanctot AM, Blau HM (1991) Systemic delivery of human growth hormone by injection of genetically engineered myoblasts. ***Science*** 254:1509-1512. PMID: 1962213
b. Wehrman T, He X, Raab B, Dukipatti A, Blau HM, Garcia KC (2007) Structural and mechanistic insights into nerve growth factor interactions with the TrkA and p75 receptors. ***Neuron*** 53:25-38. PMID: 17196528
c. Esteva A, Kuprel B, Novoa RA, Ko J, Swetter SM, Blau HM, Thrun S (2017) Dermatologist-level classification of skin cancer with deep neural networks. ***Nature*** 542(7639):115-118. PMID: 28117445.
d. Madl CM, Heilshorn SC, Blau HM (2018) Bioengineering strategies to accelerate stem cell therapeutics. ***Nature*** 557(7705):335-342 PMCID: PMC6773426

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