BIOGRAPHICAL SKETCH

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NAME: GILBERT, Penney Marie

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POSITION TITLE: Associate Professor

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
Haverford College	BSc	05/1999	Cell & Developmental Biology
University of Pennsylvania	PhD	12/2006	Cell & Molecular Biology
University of California, San Francisco	Postdoctoral	05/2007	Breast Cancer Biology
Stanford University	Postdoctoral	07/2012	Skeletal Muscle Stem Cells

A. Personal Statement

The long-term goal of the Gilbert laboratory is to identify therapeutic interventions that boost skeletal muscle endogenous repair. We approach this challenge from the vantage that discovery-based science is key to unlocking the mysteries that guide the biology of stem cell mediated tissue repair. In this spirit, we seek to define interactions between muscle stem cells and the dynamic extracellular milieu that serve to orchestrate the elegant process by which a muscle stem cell switches from a state of quiescence, to activation, and then to specification, and how this process becomes derailed in disease states and in aging. We put a specific emphasis on evaluating how biomechanical stresses, like compressive forces, shear stress, or extracellular matrix stiffness, synergize with niche proteins to drive stem cell behavior. The native stem cell niche is a three-dimensional (3D) entity. While conceptually it is accepted that dimensionality is a critical feature of tissues that defines the location and timing of cellular events, understanding *how* dimensionality exerts such a powerful influence on muscle stem cell biology, and skeletal muscle biology more broadly speaking, is not well understood. By quantifying in vivo biomechanical stresses presiding over the quiescent and regenerating adult skeletal muscle niche, and engineering three-dimensional culture models to recreate the process of stem cell mediated repair ‘in a dish’, we elucidate how the native three-dimensional tissue exerts spatiotemporal control over muscle stem cell fate. In turn, our suite of tools and technologies to model and study human skeletal muscle biology in 3D culture act as pre-clinical testing platforms to support translational studies.

B. Positions, Scientific Appointments, and Honors

Positions

2007 – 2007 Postdoctoral Fellow, Department of Surgery, University of California, San Francisco, San Francisco, California (Laboratory of Dr. Valerie M. Weaver)

2007 – 2012 Postdoctoral Fellow, Baxter Laboratories for Stem Cell Biology, Stanford University, Menlo Park, California (Laboratory of Dr. Helen M. Blau)

2012 – 2018 Assistant Professor, Institute of Biomaterials and Biomedical Engineering (IBBME), University of Toronto, Toronto, Ontario

2018 – present Associate Professor, Institute of Biomedical Engineering (BME), University of Toronto, Toronto, Ontario

Scientific Positions (Selected)

2011 – 2013 Consultant, Didimi Inc., Menlo Park, California

2016 – 2017	Member, Collaborative Program in Cell & Dev Biology Steering Committee
2015 – 2018	Member, U of Toronto FOM & Pharmacy Animal Care Committee
2015 – 2018	Chair, IBBME Distinguished Seminar Series Committee
2016 – 2018	Associate Member, ASCB Women in Cell Biology
2016 – 2018	Advisor, CFREF 'Medicine by Design' Global Speaker Series
2015 – 2019	Council Member, Ontario Institute for Regenerative Medicine
2016 – 2019	Advisor, Ontario Institute for Regenerative Medicine Education & Outreach
2018 – present	Consultant, Pliant Therapeutics Inc., South San Francisco, California
2018 – 2019	Consultant, Boehringer Ingelheim, Ridgewood, Connecticut
2018 – 2022	Co-Organizer, 2022 TERMIS North America Conference (w/ A.McGuigan & C.Aguilar)
2019 – 2022	Co-Organizer, 2022 BMES CMBE-sig Conference (w/ B.Hoffman & W.Liu)
2022 – present	Co-Organizer, 2024 FASEB "SkM SCs & Regen" Conference (w/ D.Millay & A.Pyle)

Honors

1998	Howard Hughes Medical Institute Undergraduate Fellow
2010	Stanford University Postdoctoral Association Best Postdoc Award
2011	NIH K99/R00 Pathway to Independence Award
2013	Connaught New Investigator Award
2013	University of Toronto Faculty of Medicine Dean's New Investigator Award
2015	Dr. George Karpati Award (with Cohn, Minassian, Pearson, and Dowling Labs)
2016	Ontario Early Researcher Award
2016	Canada Research Chair in Endogenous Repair (Tier 2)
2017	Biomedical Engineering Society CMBE-Sig, Rising Star Award
2017	Cellular and Molecular Bioengineering, Young Innovator Award
2020	International Day for the Elimination of Racial Discrimination (IDERD) – Strategic Initiative Group Award
2021	Canada Research Chair in Endogenous Repair (Tier 2), Renewal
2022	Iwao Yasuda Award, BMES Cellular and Molecular Bioengineering – SIG

C. Contributions to Science (lifetime citations >5700; Google Scholar: https://tinyurl.com/2bnbcuet)

1. Strategies to compress the skeletal muscle endogenous repair drug discovery pipeline. To compress the drug discovery pipeline, my team has engineered a suite of tools, technologies, and methodologies that enable studies of healthy and diseased human skeletal muscle, neuromuscular junction development, and skeletal muscle stem cell mediated repair "in a dish" (*eLife*, 2019; *Sci Reports*, 2020; *eLife*, 2021; *Nat Comm*, 2021; *JoVE*, 2021; *Acta Biomaterialia*, 2021; *AJP:Cell Phys*, 2021; *Adv Funct Mat*, 2021; *Biofabrication*, 2022; *BioRxiv*, 2022). We create methods that are accessible, and we showcase biology that requires a 3D microenvironment. With our human neuromuscular co-culture system, we found that the acetylcholine receptor underwent the embryonic to adult developmental switch in 3D co-culture, but not in simpler culture settings (*eLife*, 2019; >130 citations). In companion studies (*Acta Biomaterialia*, 2021; *AJP:Cell Phys*, 2021), we offered the first evidence that 3D models of Duchenne muscular dystrophy mimic functional defects of the human disease and can be used as preclinical assays to evaluate therapeutics. We also invented a Muscle ENDogenous Repair (MEndR) assay that recreates the early phases of in vivo skeletal muscle regeneration "in a dish" and can be used to test for drugs that boost muscle stem cell mediated repair (*Adv Functional Mat*, 2021; IF=18). Hallmarks of stemness, such as expansion, differentiation, self-renewal, and niche repopulation are captured by the MEndR assay. Gilbert has delivered >50 invited seminars on these technologies over the past 4-yrs, and these technologies have formed the basis of numerous collaborative activities. For example, we offered evidence in human cells that inhibiting TGFβ signaling drives myotube lateral fusion, as our collaborators first discovered in mouse cells (*Nat Comm*, 2021). From a tech transfer stand-point, the work has culminated in 3 technology disclosures that form the basis of three active scientific research agreements with industry partners to generate pre-clinical data on lead molecules for the treatment of neuromuscular diseases. We also conducted a market-assessment on the MEndR assay, a technology we are now reducing to practice.

a. Bakooshli MA, Lippman ES, Mulcahy B, Iyer NI, Nguyen CT, Tung K, Stewart BA, Bigot A, Pegoraro E, Ahn H, Ginsberg H, Zhen M, Ashton RS, and Gilbert PM (2019). A 3D culture model of innervated human skeletal muscle enables studies of the adult neuromuscular junction and disease modeling. *eLife*, 8e44530. PMID: 31084710

b. Afshar M, Abraha H, Bakooshli MA, Davoudi S, Thavandiran N, Tung K, Ahn H, Ginsberg H, Zandstra PW, and Gilbert PM (2020). A 96-well culture plate enables longitudinal analyses of engineered human skeletal muscle microtissue strength. *Scientific Reports*, 10(1): 6918. PMID: 32332853
c. Girardi F, Taleb A, Ebrahimi M, Datye A, Gamage DG, Peccate C, Giordani L, Millay DP, Gilbert PM, Cadot B, and Le Grand F. (2021) TGFβ signaling curbs fusion and muscle regeneration. *Nature Communications*, 12,750: doi.org/10.1038/s41467-020-20289-8. PMID: 33531466
d. Ebrahimi M, Lad H, Fusto A, Tiper Y, Datye A, Nguyen CT, Jacques E, Moyle LA, Nguyen T, Musgrave B, Chávez-Madero C, Bigot A, Chen C, Turner S, Stewart BA, Pegoraro E, Vitiello L, and Gilbert PM. (2021) De novo revertant fiber formation and therapy testing in a 3D culture model of Duchenne muscular dystrophy skeletal muscle. *Acta Biomaterialia*, 132: 227-244. PMID: 34048976
e. Nguyen CT, Ebrahimi M, Gilbert PM, and Stewart BA. (2021) Electrophysiological analysis of healthy and dystrophic 3D bioengineered skeletal muscle tissues. *Am J of Physiology – Cell Phys,* 321(4): C749-C759. PMID: 34406904
f. Davoudi S, Xu B, Jacques E, Cadavid JL, McFee M, Chin C-Y, Meysami A, Ebrahimi M, Bakooshli MA, Tung K, Ahn H, Ginsberg HJ, McGuigan AP*, and Gilbert PM*. (2021) MEndR: An in vitro functional assay to predict in vivo muscle stem cell mediated repair. *Advanced Functional Materials*, https://doi.org/10.1002/adfm.202106548
g. Pieters VM, Rjaibi ST, Singh K, Li NT, Khan ST, Nunes SS, Dal Cin A, Gilbert PM*, and McGuigan AP* (2022) A three-dimensional human adipocyte model of fatty acid-induced obesity. *Biofabrication*, 14(4), doi: 10.1088/1758-5090/ac84b1. PMID: 35896099
h. Jacques E, Kuang Y, Kann AP, F Le Grand, Krauss RS, and Gilbert PM (2022) The mini-IDLE 3D biomimetic culture assay enables interrogation of mechanisms governing muscle stem cell quiescence and niche repopulation. *eLife*, https://elifesciences.org/articles/81738

2. Uncovering the link between tissue biomechanics and skeletal muscle endogenous repair. Muscle stem cells (MuSCs) exist within a mechanical environment that is incredibly active, and yet, we know very little about the mechanics of the native niche and how it influence MuSC fate. Towards this goal, my team focuses efforts on defining the niche from the biomechanical perspective (stiffness, shear, compressive, tensile stresses), determining if MuSCs 'feel' these mechanical stresses, and if so, how they respond. In the course of our studies in this area, we offered what we believe to be the first evidence that Notch activity and Notch ligand response could be tuned by substrate stiffness, and the first evidence that tissue stiffening during repair may serve to ensure an adequate supply of daughter cells is produced to meet regenerative demand. This work was published in a special issue of *Cellular and Molecular Bioengineering* (2017), was highlighted in a *Nature* "Technology Feature" piece, and garnered Gilbert a Biomedical Engineering Society (BMES) 'Young Innovator' award. By engineering a 3D biomimetic system, her team next discovered that niche stiffening during repair also influences MuSC fate: steric constraint orients MuSC division plane and primes the daughter cells to respond to a regenerative biomolecule (Wnt7a) by undergoing a symmetric division event (*Mol Biol Cell*, 2020). More recently, Gilbert and her Human Frontiers Science Program team grant collaborators in Germany also uncovered evidence that the homeostatic niche may shield MuSCs from mechanical perturbation so as to support a quiescent state (*eLife*, 2021). This body of work sheds new light on the process of MuSC endogenous repair and points to a need to consider the mechanical properties of the niche when designing endogenous repair therapeutic interventions so as to maximize their impact.

a. Safaee H, Bakooshli MA, Davoudi S, Cheng RY, Martowirogo AJ, Li EW, Simmons CA, and Gilbert PM (2017) Tethered Jagged-1 synergizes with culture substrate stiffness to modulate Notch-induced myogenic progenitor differentiation. *Cellular and Molecular Bioengineering*, 10(5): 501-513. PMID: 31719873
b. Moyle LA*, Cheng RY*, Liu H, Davoudi S, Ferreira SA, Nissar AA, Sun Y, Gentleman E, Simmons CA, and Gilbert PM. (2020). Three-dimensional niche stiffness synergizes with Wnt7a to modulate the extent of satellite cell symmetric self-renewal divisions. *Mol Biol Cell*, 31(16): 1703-1713. PMID: 32491970
c. Hofemeier AD, Limon T, Muenker TM, Wallmeyer B, Jurado A, Afshar ME, Ebrahimi M, Tsukanov R, Oleksiievets N, Enderlein J, Gilbert PM, and Betz T. (2021) Global and local tension measurements in biomimetic skeletal muscle tissues reveals early mechanical homeostasis. *eLife*, elifesciences.org/articles/60145. PMID: 33459593

d. Kann AP, Hung M, Wang W, Nguyen J, Gilbert PM, Wu W, and Krauss RS (2022) An injury-responsive Rac-to-Rho GTPase switch drives activation of muscle stem cells through rapid cytoskeletal remodeling. *Cell Stem Cell*, 29(6): 933-947. PMID: 35597234

3. Biomimetic culture methods to rejuvenate and expand aged SCs outside of the body. A major hurdle in the adult stem cell field is the development of methodologies to propagate these rare, but potent stem cells outside the body. We speculated that if adult stem cell self-renewal is regulated by biophysical properties of the microenvironment, like tissue stiffness, then culturing muscle stem cells on biomimetic substrates might maintain their 'stemness' ex vivo – a timely concept that had yet to be shown scientifically. Using a combination of stem cell biology, biomaterials technology, time-lapse microscopy, single cell assays, computer algorithm development, and functional assays in mice we revealed the biomechanical regulation of muscle stem cell self-renewal for the first time. This has amassed more than 1550 citations and Faculty of 1000 classified it as 'Exceptional' (2010. F1000/4942962). In a follow-up study, we defined a synergistic pharmacological/biomaterial strategy to rejuvenate and expand aged MuSC populations outside of the body that restored youth-like strength when transplanted into aged, injured muscle (>550 citations). Highlighted in *Nature* News & Views and *Science* Editor's Choice articles, this story provided the first evidence that a stem cell transplant can restore strength to aged skeletal muscle.

a. Lutolf MP, Gilbert PM, Blau HM. Designing materials to direct stem-cell fate. *Nature*. 2009 Nov 26;462(7272):433-41. Review. PMID: 19940913
b. Gilbert PM, Havenstrite KL, Magnusson KE, Sacco A, Leonardi NA, Kraft P, Nguyen NK, Thrun S, Lutolf MP, Blau HM. Substrate elasticity regulates skeletal muscle stem cell self-renewal in culture. *Science*. 2010 Aug 27;329(5995):1078-81. PMID: 20647425
c. Gilbert PM, Corbel S, Doyonnas R, Havenstrite K, Magnusson KE, Blau HM. A single cell bioengineering approach to elucidate mechanisms of adult stem cell self-renewal. *Integr Biol* (Camb). 2012 Apr;4(4):360-7. Review. PMID: 22327505
d. Cosgrove BD, Gilbert PM*, Porpiglia E, Mourkioti F, Lee SP, Corbel SY, Llewellyn ME, Delp SL, Blau HM*. Rejuvenation of the muscle stem cell population restores strength to injured aged muscles. *Nat Medicine*. 2014 Mar;20(3):255-64. PMID: 24531378 *Co-Corresponding Authors

4. A link between tissue mechanics and breast cancer progression. Woman with a hereditary mutation in the BRCA1 tumor suppressor gene have a >50% chance of breast cancer affliction in their lifetime. Mutant BRCA1-carriers who do get breast cancers are highly likely to have the aggressive ER/PR/HER2 triple-negative subtype. Interestingly, physicians note that many patients have breast cancers that 'look' like a BRCA1 cancer, though gene mutations are absent. My PhD thesis studies identified a novel breast tumor suppressor role for the homeobox developmental regulator HOXA9. Re-expression of HOXA9 in breast tumor cells induced BRCA1 expression and restored normal 3D mammary morphogenesis. Indeed, we found that HOXA9 directly regulates BRCA1 expression and our studies showed that triple-negative cancers without detectable BRCA1 mutations display low levels of HOXA9. These findings were somewhat unexpected given the well-documented oncogenic effect of HOXA9 over-expression in the blood system. Most recently, we reported that the tissue stiffening that accompanies tumor progression upregulates expression of mir-18a, which then serves to downregulate HOXA9 and PTEN, thereby providing novel mechanistic insight into triple-negative breast cancer development.

a. Weaver VM, Gilbert P. Watch thy neighbor: cancer is a communal affair. *J Cell Sci*. 2004 Mar 15;117(Pt 8):1287-90. PMID: 15020668.
b. Gilbert PM, Mouw JK, Unger MA, Lakins JN, Gbegnon MK, Clemmer VB, Benezra M, Licht JD, Boudreau NJ, Tsai KK, Welm AL, Feldman MD, Weber BL, Weaver VM. HOXA9 regulates BRCA1 expression to modulate human breast tumor phenotype. *J Clin Invest*. 2010 May;120(5):1535-50. PMID: 20389018
c. Mouw JK, Yui Y, Damiano L, Bainer RO, Lakins JN, Acerbi I, Ou G, Wijekoon AC, Levental KR, Gilbert PM, Hwang ES, Chen YY, Weaver VM. Tissue mechanics modulates microRNA-dependent PTEN expression to regulate malignant progression. *Nat Med*. 2014 Apr;20(4):360-7. PMID: 24633304

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