BIOGRAPHICAL SKETCH

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NAME: Olwin, Bradley B

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

POSITION TITLE: 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
University of California, San Diego; La Jolla, CA	BA	1979	Chemistry/Russian Lit
University of Washington; Seattle, WA (Dan Storm, Advisor)	Ph.D.	1984	Pharmacology
University of California San Francisco (Zach Hall Advisor)	Postdoctoral	1984-85	Neuroscience
University of Washington, Seattle, WA (Steve Hauschka, Advisor)	Postdoctoral	1985-88	Cell Biology

A. Personal Statement

My research is focused on the role of skeletal muscle stem cells in maintenance of skeletal muscle homeostasis. I focus on mechanisms that regulate skeletal muscle stem cell function in the niche and intracellular signals involved in cell fate determination. My laboratory investigates the changes in stem cells and their niche that occur in skeletal muscle disease and during aging using mouse molecular genetics, stem cell lineage tracing, stem cell transplantation and generation of muscle stem cells from human iPSCs. My long-term goals are to further understand the regulatory mechanisms that control skeletal muscle stem cell numbers and their function to evolve strategies for therapy development to treat skeletal muscle diseases and sarcopenia. I established my laboratory in 1988 and have maintained a productive well-funded research group for the past 33 years, successfully training 24 PhDs, 2MD/PhDs and 18 postdoctoral fellows with two under-represented minorities among my trainees; the majority have careers as independent scientists in academia and industry. I am committed to enhancing undergraduate research, encouraging undergraduates to pursue careers in research. Typically, I will have five to eight undergraduates pursuing research projects concurrently; with over one hundred undergraduates gaining research experience where a number have authorships on publications.

Ongoing and recent projects I would like to highlight

NIH R01 AR049446.
4/1/23-3/31/28 Olwin PI

Mechanisms regulating muscle stem cell homeostasis

NIH R01 AR070360
8/1/22-7/31/27. Olwin PI
Replicative Potential of Muscle Stem Cells
A competitive renewal for this grant received a 6% and will be funded from 8/1/22 to ¶/30/27

Glenn Foundation for Biomedical Reasearch Breakthrough in Gerontology Award
07/01/21-06/30/24. Olwin PI
Improving Skeletal Muscle Stem Cell Health to Rescue Age-Induced Decline of Skeletal Muscle Function

Citations:

1. Tanaka, K.K., Hall, J.K., Troy, A.A., Cornelison, D.D., Majka, S.M., and **Olwin, B.B.** (2009). Syndecan-4-Expressing Muscle Progenitor Cells in the SP Engraft as Satellite Cells during Muscle Regeneration. Cell Stem Cell *4*, 217-225. (featured article).
2. Troy, A., Cadwallader, A.B., Federov, Y. F., Tyner, K., Tanaka, K. K. and **Olwin, B.B**. (2012) Coordination of Satellite Cell Activation and Asymmetric Division by Par Complex-Dependent Activation of p38α/β MAPK Cell Stem Cell. **11**:541-53. doi: 10.1016/j.stem.2012.05.025.(featured article).
3. Bernet, J.D., Doles J.D., Hall, J.K.,Kelly-Tanaka, K., Carter, T.A. and **Olwin, B.B.** (2014) P38 MAPK Signaling Underlies a Cell-Autonomous Loss of Stem Cell Self-Renewal in Aged Skeletal Muscle Nature Medicine **20**: 265-71. doi:10.1038/nm.3465.
4. Vogler, T.O., Wheeler, J.R., Nguyen, E.D., Hughes, M.P., Britson, K.A., Lester, E., Rao, B., Betta, N.D., Whitney, O.N., Ewachiw, T.E., Gomes, E., Shorter, J., Lloyd, T.E., Eisenberg, D.S., Taylor, J.P., Johnson, A.M., **Olwin, B.B.***, Parker, R.* (2018) TDP-43 and RNA form amyloid-like myo-granules in regenerating muscle. Nature. *563*, 508–513. (*co-corresponding authors).

B. Positions Scientific Appointments and Honors

Positions

1980-1983 NIH Predoctoral Fellow: Daniel R. Storm, Advisor, Department of Pharmacology, University of Washington, Seattle, WA.

1984-1985 Muscular Dystrophy Association Postdoctoral Fellow: Advisor, Zach W. Hall, Division of Neurosciences, Univ. of California, San Francisco, CA.

1985-1986 Muscular Dystrophy Association Postdoctoral Fellow: Advisor, Stephen D. Hauschka, Department of Biochemistry, Univ. of Washington, Seattle, WA.

1986-1987 American Cancer Society Postdoctoral Fellow: Advisor, Stephen D. Hauschka, Univ. of Washington, Seattle, WA.

1988-1993 Assistant Professor, Department of Biochemistry, University of Wisconsin.

1993 Associate Professor, Department of Biochemistry, University of Wisconsin.

1993 Walther Associate Professor, Department of Biochemistry, Purdue University.

1996 Walther Associate Professor, Molecular, Cellular and Developmental Biology, University of Colorado.

2000 Professor, Molecular, Cellular and Developmental Biology, University of Colorado.

2016-2019 Associate Chair, Molecular, Cellular and Developmental Biology, University of Colorado.

Honors

1984 Achievement Reward for College Scientists, awarded for outstanding graduate research.

1988 Shaw Scholar Award.

1990 PEW Scholar in the Biomedical Sciences.

1991 Pound Research Award, College of Agriculture and Life Sciences, University of Wisconsin-Madison.

1991 ISI Most Highly Cited Paper of the Year.

1993 Showalter Research Trust Award, Purdue University.

1995 Lions Club Cancer Research Award, Lafayette, IN.

2003 Co-Chair for 3rd International Symposium on Skeletal Muscle Satellite and Stem Cells.

2006 Co-Chair and Founder for Gordon Conference on Fibroblast Growth Factors in Development and Disease Gordon Conference.

2006 Keynote Speaker at North Texas University Regional Stem Cell Symposium.

2008 Keynote Speaker for Satellite Cell Minisymposia on Aging, Experimental Biology, San Diego.

2010- Member Skeletal Muscle Editorial Board

2010 Member Scientific World Journal Editorial Board

2010 Interview finalist for NIH Pioneer Award

2012 Ellison Medical Foundation Senior Scholar Award in Aging Research.

2015 Glenn Foundation Award for Biomedical Research

2016 Aging Cell Editorial Board
2019 Keynote Speaker at World Muscle Society Annual Meeting
2020 AFAR/Glenn Foundation BIG Award (Breakthrough Ideas in Gerontology)

C. Contributions to Science

1. Our laboratory pioneered the discovery that heparan sulfate glycosaminoglycan chains were required for the binding of FGFs to the FGF receptor and that heparan sulfate GAG chains were required to transduce FGF signals. These experiments led to the development of an entire field identifying heparan sulfate GAGs as essential information carriers and regulators of signaling for hundreds of growth factors, particularly those that act as morphogens during development. This field rapidly expanded when heparan sulfate biosynthetic enzymes were identified in invertebrate genetic screens mutants in FGF signaling, sonic hedgehog signaling, wnt signaling and TGFß signaling. Heparan sulfate proteoglycans function to regulate the bioavailability and signaling of the majority of paracrine signaling growth factors.

a. **Olwin, B.B**. & Hauschka, S.D. (1986) Identification of the fibroblast growth factor receptor of Swiss 3T3 cells and mouse skeletal muscle myoblasts. Biochemistry 25:3487-3492.
b. Rapraeger, A.C., Krufka, A. & **Olwin, B.B.** (1991) Requirement of heparan sulfate for bFGF-mediated fibroblast growth and myoblast differentiation. Science 252:1705-1708.
c. **Olwin, B.B.** & Rapraeger, A.C. (1992) Repression of myogenic differentiation by aFGF, bFGF and K-FGF is dependent on cellular heparan sulfate. J. Cell Biol. 118:631-640.
d. Cornelison D.D.W., Wilcox-Adelman, S.A., Goetinck, P.F., Rauvala, H., Rapraeger, A.C. & Olwin, B.B. (2004) Syndecan- 3 and Syndecan-4 have unique and essential roles in skeletal muscle growth and regeneration. Genes and Development **18:** 2231-2236.

1. Concurrent with the discovery of the heparan sulfate requirement for FGF signaling, our laboratory began exploring the role for FGFs in skeletal muscle development, regulation of skeletal muscle stem cells and in the loss of skeletal muscle function during aging. This work continues in my laboratory today and has made several contributions, including the demonstration that FGF is required to repress myogenic differentiation, that FGF is involved in the self-renewal of skeletal muscle stem cells and that loss of FGF receptor 1 signaling is in part responsible for the reduction in muscle stem cell function that accompanies normal aging and the loss of skeletal muscle function during aging. We pioneered the use of retroviruses for manipulating protein function *in vivo* and continued with the development of novel transplant procedures to assess stem cell function *in vivo*.

a. Flanagan-Steet, H.F.; Hannon, K.H., McAvoy, M., Hullinger, R., & **Olwin B.B.** (2000) Loss of FGF Receptor-1 Signaling Reduces Skeletal Muscle Mass and Disrupts Myofiber Organization in the Developing Limb. Dev. Biol. **218:** 21-37.
b. Hall, J. K. H., Banks, G., Chamberlain, J.S. and **Olwin B. B.** Prevention of Muscle Aging by Myofiber-Associated Satellite Cell Transplantation. (2010) Science Trans Med 2:57ra83 (DOI: 10.1126/scitranslmed.3001081; Featured Article and Cover).
c. Bernet, J.D., Doles J.D., Hall, J.K., Kelly-Tanaka, K., Carter, T.A. and **Olwin, B.B.** (2014) P38 MAPK Signaling Underlies a Cell-Autonomous Loss of Stem Cell Self-Renewal in Aged Skeletal Muscle Nature Medicine 20, 265-71. doi:10.1038/nm.3465
d. Cutler, A. A.; Pawlikowski, B.; Wheeler, J. R.; Betta, N. D.; Elston, T.; O'Rourke, R.; Jones, K.; **Olwin, B. B**. The Regenerating Skeletal Muscle Niche Guides Muscle Stem Cell Self-Renewal. *bioRxiv* **2021**, 635805. https://doi.org/10.1101/635805.

3. Accompanying our efforts directed at understanding the role(s) for FGFs in skeletal muscle development, regeneration, and aging, I began examining the downstream signaling pathways responsible for mediating these effects. I eventually found that the p38 MAPK family plays essential roles in self-renewal and maintenance of adult skeletal muscle stem cells. The p38α/ß MAPK is required for adult muscle stem cell activation and asymmetric activation of p38α/ß MAPK during cell division promotes distinct daughter cell fates, resulting in one self-renewed stem cell and one committed transit amplifying cell that expresses MyoD called a myoblast. The asymmetric activation of p38α/ß MAPK is disrupted in aged mice and contributes to the loss of adult stem cells and loss of muscle function during aging, identifying the p38 MAPK family as a critical regulator of adult muscle stem cell function. In my most recent publication, we identified a novel post-transcriptional regulatory mechanism as a target of p38α/ß

MAPK in skeletal muscle stem cells. In the adult, quiescent stem cell the p38 MAPK pathway is inactive and an RNA binding protein, Tristetraprolin binds MyoD mRNA and promotes MyoD mRNA decay. Upon muscle injury, p38α/ß MAPK is activated, Tristetraprolin is phosphorylated and inactivated, promoting accumulation of MyoD mRNA, which transactivates its own transcription resulting in a feed forward loop committing the cell to a myoblast fate. I believe this will apply to many adult stem cells as it permits a rapid and precise response to tissue injury.

a. Troy, A., Cadwallader, A.B., Fedorov, Y. F., Tyner, K., Tanaka, K. K. and **Olwin, B.B**. (2012) Coordination of Satellite Cell Activation and Asymmetric Division by Par Complex-Dependent Activation of p38α/β MAPK Cell Stem Cell. **11**:541-53. doi: 10.1016/j.stem.2012.05.025.
b. Bernet, J.D., Doles J.D., Hall, J.K., Kelly-Tanaka, K., Carter, T.A. and **Olwin, B.B.** (2014) P38 MAPK Signaling Underlies a Cell-Autonomous Loss of Stem Cell Self-Renewal in Aged Skeletal Muscle Nature Medicine 20, 265-71. doi:10.1038/nm.3465.
c. Hausburg, M. A., Doles, J.D. Clement, S.L., Cadwallader, A.B., Hall, M.N., Blackshear, P.J., Lykke-Andersen, J., and **Olwin, B.B.** (2015**)** Post-transcriptional regulation of satellite cell quiescence by TTP-mediated mRNA decay (eLife 2015;10.7554/eLife.03390).
d. Tanaka, K.K., Hall, J.K., Troy, A.A., Cornelison, D.D., Majka, S.M., and **Olwin, B.B.** (2009). Syndecan-4-Expressing Muscle Progenitor Cells in the SP Engraft as Satellite Cells during Muscle Regeneration. Cell Stem Cell *4*, 217-225. (featured article for the March Issue).

4. Our efforts at understanding muscle stem cell function led to broader questions exploring how stem cells function to maintain skeletal muscle and how skeletal muscle stem cell function is affected during aging and diseases. These inquires have led to distinct research thrusts. One is aimed at delineating the behavior of muscle stem cells directly *in vivo* using new single cell technologies and advances in mouse molecular genetics. A second began with a novel discovery via a collaboration between my laboratory and Roy Parker's laboratory where we identified a previously unknown RNP we termed a myo-granule. Myo-granules are proposed to protect, transport, and provide localized translation of mRNAs required to build sarcomeres. Roy and I are co-corresponding authors on this initial discovery where our groups provided an equal and synergistic effort. A third involves examining the environmental influence on muscle regeneration and function and to apply that knowledge to recapitulate that environment in culture with Krista Anseth's laboratory. Our continued collaborations are aimed at determining how skeletal muscle is rebuilt following an injury and how the changes in muscle and the surrounding environment that go awry during aging and in progressive neuromuscular diseases.

a. Pawlikowski, B., Pulliam, C., Betta, N.D., Kardon, G. & **Olwin, B.B**. (2015) Pervasive satellite cell contribution to uninjured adult muscle fibers. *Skeletal Muscle* **5**, 1–13 (2015).
b. Vogler, T.O., Wheeler, J.R., Nguyen, E.D., Hughes, M.P., Britson, K.A., Lester, E., Rao, B., Betta, N.D., Whitney, O.N., Ewachiw, T.E., Gomes, E., Shorter, J., Lloyd, T.E., Eisenberg, D.S., Taylor, J.P., Johnson, A.M., **Olwin, B.B.***, Parker, R.* (2018) TDP-43 and RNA form amyloid-like myo-granules in regenerating muscle. Nature *563*, 508–513. (*co-corresponding authors).
c. Silver, J.S., K. Arda Günay, A., Cutler, A.A. Thomas Vogler,T. O., Tobin E. Brown, T.E., Pawlikowski, B.T., Bednarski, O.J, Kendra L. Bannister, K.L., Rogowski, C.J., Mckay, A.G., DelRio, F.W., **Olwin, B.B***., and Kristi S. Anseth, K.S*. (2021) Injury mediated stiffening persistently activates muscle stem cells through YAP and TAZ mechanotransduction. *Sci. Adv.* **2021**, *7* (11), eabe4501. https://doi.org/10.1126/sciadv.abe4501.
d. Günay, KA, Jason S. Silver, JS, Bednarski, OJ, Bannister, KL, Cameron J. Rogowski, CJ, **Olwin, B.B.***, and Anseth, KS*, Myoblast mechanotransduction and myotube morphology is dependent on BAG3 regulation of YAP and TAZ, *Biomaterials*. 2021 Oct;277:121097. doi: 10.1016/j.biomaterials.2021.121097.

* Indicates co-corresponding authors

http://www.ncbi.nlm.nih.gov/sites/myncbi/bradley.olwin.1/bibliography/41825435/public/?sort=date&direction=ascendingh