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

Please refer to the Biographical Sketch sample in order to complete sections A, B, C, and D of the Biographical Sketch.

A. Personal Statement

Our research is focused on the role of skeletal muscle stem cells in maintenance of skeletal muscle homeostasis. We focus on mechanisms that regulate skeletal muscle stem cell function in the niche and intracellular signals involved in cell fate determination. We investigate the changes in stem cells and their niche that occur in skeletal muscle disease and during aging. Our long term goals are to further understand the regulatory mechanisms that control skeletal muscle stem cell numbers and their function in order to evolve strategies for therapy development to treat skeletal muscle diseases and sarcopenia.

1. 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.
2. Hall, J. K. H., Banks, G., Chamberlain, J.S. and Olwin B. B. Prevention of Muscle Aging by Myofiber-Associated Satellite Cell Transplantation. Science Trans Med 2:57ra83 (DOI: 10.1126/scitranslmed.3001081; Featured Article and Cover).
3. 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.
4. Bernet, J.D., Doles J.D., Hall, J.K.,Kelly-Tanaka, K., Carter, T.A. and **Olwin, B.B.** P38 MAPK Signaling Underlies a Cell-Autonomous Loss of Stem Cell Self-Renewal in Aged Skeletal Muscle (2014) Nature Medicine **20**, 265-71. doi:10.1038/nm.3465.
5. Pawlikowski, Bradley, Crystal Pulliam, Nicole Dalla Betta, Gabrielle Kardon, and Bradley B Olwin. "Pervasive Satellite Cell Contribution to Uninjured Adult Muscle Fibers." *Skeletal muscle* 5, no. 1 (2015): doi:10.1186/s13395-015-0067-1.

B. Positions 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.

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

Service

1994-1996 NIH Molecular Cytology Study Section (member)
1999-2001 NIH CDF-5 Study Section (member)
2008-2010 NIH DEV1 Study Section (member)
2014-2018 NIH SMEP Study Section Standing Member.
2004- Muscular Dystrophy Association Scientific Advisory Board.

C. Contribution to Science

1. My early work directed at identifying the receptor for fibroblast growth factors (FGFs) led to 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 haran 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. Burrus, L.B., Zuber, M.E., Lueddecke, B.A. & **Olwin, B.B.** (1992) Identification of a cysteine-rich receptor for fibroblast growth factors. Mol. Cell. Biol. 12:5600-5609.

2. Concurrent with the discovery of the heparan sulfate requirement for FGF signaling, I 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 a number of 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. Riley, B., Savage, M., **Olwin, B.B.** & Fallon, J.F. (1993) Retroviral expression of FGF-2 (bFGF) affects patterning in chick limb bud. Development **118**:95-104.
   b. 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.
   c. Hall, J. K. H., Banks, G., Chamberlain, J.S. and Olwin B. B. Prevention of Muscle Aging by Myofiber-Associated Satellite Cell Transplantation. Science Trans Med 2:57ra83 (DOI: 10.1126/scitranslmed.3001081; Featured Article and Cover).
   d. Bernet, J.D., Doles J.D., Hall, J.K.,Kelly-Tanaka, K., Carter, T.A. and **Olwin, B.B.** P38 MAPK Signaling Underlies a Cell-Autonomous Loss of Stem Cell Self-Renewal in Aged Skeletal Muscle (2014) Nature Medicine 20, 265-71. doi:10.1038/nm.3465.

3. Accompanying my 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. Jones, N.C., Murphy, K., Nibarger, L., Stanley, H., Cornelison, D.D.W, Fedorov, Y.V. & **Olwin, B.B.** (2005) The Quiescent State of Skeletal Muscle Satellite Cells is Defined by the Activity of p38α/β MAPKs. Journal of Cell Biology **169:** 105-116.
   b. 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.
   c. Bernet, J.D., Doles J.D., Hall, J.K.,Kelly-Tanaka, K., Carter, T.A. and **Olwin, B.B.** P38 MAPK Signaling Underlies a Cell-Autonomous Loss of Stem Cell Self-Renewal in Aged Skeletal Muscle (2014) Nature Medicine 20, 265-71. doi:10.1038/nm.3465.
   d. 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.** Post-transcriptional regulation of satellite cell quiescence by TTP-mediated mRNA decay (eLife 2015;10.7554/eLife.03390).

4. When I identified the requirement of heparan sulfate for FGF signaling, I developed the idea that heparan sulfate GAGs could play a pivotal role in controlling growth factor accessibility and serve as storage and release sites for paracrine acting factors. Using adult muscle stem cells to test this idea, we found that heparan sulfate proteoglycans are components of the adult muscle stem cell niche and that they are required for maintenance of stem cells in the

niche, for homing to the niche and for maintaining quiescence. One of the publications describing a role for Syndecan-3 in homing of muscle stem cells to the niche is under review (Pisconti, A., Banks, G.B., Gebert, M.J., Babaijandaghi, F., Rossi, F.M.V., Chamberlain, J.S. and **Olwin, B.B.** Improving dystrophic muscle integrity and function by altering syndecan-3 in the satellite cell niche., under revision).

a. Cornelison, D.D.W., Filla, M., Stanley, H.M., Alan C. Rapraeger, A.C. & **Olwin, B.B.**. (2001) Syndecan-3 and syndecan-4 specifically mark skeletal muscle satellite cells and are implicated in satellite cell maintenance and muscle regeneration. Dev. Biol. **239:** 79-94.
b. 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.
c. 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).
d. Pisconti, A., Cornelison, D.D.W., Antwine, T.L. and Olwin, B.B. (2010) Syndecan-3 and Notch Cooperate in Regulating Adult Myogenesis J. Cell. Biol. 190: 427-441. (Featured article and Cover Photo) Faculty of 1000 Biology: evaluations for Pisconti A et al J Cell Biol 2010 Aug 9 190 (3) :427-41 http://f1000biology.com/article/id/4901956/evaluation.

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

D. Research Support

Current Support

NIH R01 AR049446 4/1/11-3/31/16.
Role of Syndecans in Satellite Cell Function.
The goals of this project are to investigate the role of Syndecans in satellite cell self-renewal and muscle regeneration.
Role: PI

AR049446S1 4/1/14-3/31/16
Role of Syndecans in Satellite Cell Function (Diversity Supplement).
Role: PI

NIH R01 AG040074 7/01/11-6/30/2016
Age-Dependent Regulation of Muscle Stem Cell Homeostasis.
The goals of this project are to lineage trace skeletal muscle stem cells and their myonuclear progeny by developing a novel, viral-based cellular barcoding delivery system and analysis by next generation sequencing.
Role: PI

Ellison Medical Foundation Senior Scholar in Aging Research Award 10/1/12-9/30/16
Reprogramming Muscle Stem Cells to Resist Aging.
In this proposal, we plan to examine the transplant environment perform lineage tracing on transplanted muscle stem cells in aged mice.
Role: PI

Linda Crnic Foundation Grand Challenge Award 4/1/2015-3/31/2016
Mechanisms of Muscle Dysfunction in Down Syndrome
The goals of this project are to determine if defects in skeletal muscle stem cells are responsible for deficiencies in skeletal muscle maintenance and regeneration in a mouse model of trisomy 21.
Role: PI

Muscular Dystrophy Association 02/01/16-01/31/19
Enhancing Regeneration to Improve Dystrophic Muscle
Our goals are to determine the efficacy of inhibiting Syndecan-3 expression to improve stem cell-mediated regeneration of dystrophic skeletal muscle

Role: PI

Glenn Foundation for Medical Research 12/01/15-11/30/17
Unsolicited Award for Aging-Related Research

Pending Support
NIH AR049446 12 **7/1/16-6/30/01**
Muscle Stem Cell Homeostasis
A competitive renewal application

NIH AR069955 **7/1/16-6/30/01**
Aging and Replicative Potential of Muscle Stem Cells

Past Support
Butcher Foundation Stem Cell Award **7/1/12-6/30/14**
Treatment of Lipoprotein Lipase Deficiency with Induced Pluripotent Stem Cell Technology
The goals are to rescue a striated muscle knockout of LPL by viral gene therapy in skeletal muscle
Role: Co-Investigator

Muscular Dystrophy Foundation **2/01/11-1/31/14**
Identification and Characterization of a Satellite Stem Cell
The goals were to identify the subpopulation of self-renewing muscle stem cells that are responsible for maintaining the muscle stem cell population.
Role: PI