BIOGRAPHICAL SKETCH

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NAME: Mary K. Baylies

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

POSITION TITLE: Member, Developmental Biology Program, Sloan Kettering Institute

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
Dartmouth College, Hanover, NH	A.B.	06/1982	Biology
Rockefeller University, New York, NY	PhD	06/1991	Genetics/Molecular Biology
University of Cambridge, Cambridge, UK	Post-Doc	06/1996	Developmental Biology

A. Personal Statement

The goal of the Baylies lab is to characterize the genes and mechanisms that are essential for the specification, morphogenesis, and homeostasis of skeletal muscle. Our past work has lead to the identification of signal transduction pathways (i.e. RTK, Notch, Wnt and BMP) and transcription factors (i.e. Twist, Daughterless, Emc) critical for the specification of individual muscles in *Drosophila*. Building on this work, we now are addressing several key issues confronting muscle biology: 1) How is identity information for cell size, shape and orientation encoded? How is this information translated into morphology? 2) What are the cellular processes necessary for the acquisition and maintenance of muscle size and shape? 3) Lastly, how does the muscle paradigm found in model systems apply to human myogenesis and disease? Using several models, including fly, mouse myoblasts/myofibers and human myoblasts/myofibers, the lab is developing and applying genetic and cell biological approaches, including time-lapse imaging, to understand the fundamental processes involved in cell fate commitment, cell movement, cell-cell fusion, and organelle movement, positioning and organization in muscle. We explore these issues both in developmental and disease contexts, including Nemaline and Centronuclear Myopathies, Rhabdomyosarcoma, and cancer cachexia. Our investigation of basic mechanisms driving muscle formation and homeostasis provide a platform to pinpoint the underlying mechanisms of disease pathogenesis and to identify novel therapeutics.

B. Positions and Honors.

Professional Experience

1996-2003	Assistant Member, Molecular Biology Program, Sloan Kettering Institute
	Assistant Professor, Weill Graduate School of Medical Sciences, Cornell University
2003-2008	Associate Member, Developmental Biology Program, Sloan Kettering Institute
	Associate Member, Gerstner Graduate School at Memorial Sloan Kettering Cancer Center
	Assistant Professor, Weill Graduate School of Medical Sciences, Cornell University
2008-Present	Member, Developmental Biology Program, Sloan Kettering Institute
	Member, Gerstner Graduate School at Memorial Sloan Kettering Cancer Center
	Professor, Weill Graduate School of Medical Sciences, Cornell University
2005-Present	Adhoc Grant Reviewer for NSF, MDA, European Union and Welcome Trust Grants
2008-2012	Member, Skeletal Muscle and Exercise Physiology Study Section NIH
2009-2012	President, Society of Muscle Biology
2012- present	Adhoc Grant Reviewer for NIH

Other Experiences and Professional Memberships

2005	Co-organizer of New England SDB meeting

2006-Present	Organizer of SKI, Cornell and City College Fly Group Meetings
2008-2010	Co-organizer of the New York Area Fly Meeting
2009-2012	Co-organizer of the Society for Muscle Biology 2012 Myogenesis Meeting
2011-Present	Member of the Editorial Board of Mechanisms of Development
2011-Present	Member of the Editorial Board of Skeletal Muscle
2014-Present	Member of the Editorial Board of BMC Developmental Biology

Honors and Awards

1985-1988	National Science Foundation Graduate Fellow
1991-1993	NATO-NSF Postdoctoral Fellow
1997-2003	Frederick Adler Chair for Junior Faculty - Memorial Sloan Kettering Cancer Center

Reviewer for Cell Journals, Nature Journals, Science Journals, Development, Developmental Biology, Journal of Cell Biology, PLoS Journals and others.

C. Contributions to Science

As a postdoctoral fellow with Michael Bate, I investigated the initial steps in somatic or body wall muscle formation. While it was appreciated that mesoderm and muscle formed in the *Drosophila* embryos, the steps guiding mesodermal progenitors to the formation of specific body muscles were unknown. I identified a key transcriptional regulator, the bHLH factor Twist, that directs uncommitted mesodermal cells to the somatic fate and a second regulator, DMef2, that controls muscle differentiation. Moreover, I identified that patterning of the mesoderm depends on signals (Wnt, BMP) generated and also used by the ectoderm.

1. Baylies, MK and Bate, M. (1996) Twist: a myogenic switch in Drosophila. *Science* 272(5267): 1481-84. PMID: 8633240.

2. Staehling-Hampton K, Hoffmann FM, Baylies MK, Rushton E, Bate, M. (1994) Dpp induces mesodermal gene expression in Drosophila. *Nature* 372(6508): 783-6. PMID: 7997266.

3. Baylies, MK, Martinez-Arias, A, and Bate, M. (1995) Wingless is required for the formation of a subset of muscle founder cells during Drosophila embryogenesis. *Development* 121 (11):3829-3837. PMID: 8582292.

4. Taylor MV, Beatty KE, Hunter HK, Baylies MK. (1995) Drosophila MEF2 is regulated by Twist and is expressed in the primordia and differentiated cells of the embryonic somatic, visceral and heart musculature. *Mech Dev*. 50(1): 29-41. PMID: 7605749.

In my own lab, we began by defining mechanisms by which transcription factors regulate development. While genetics revealed the participation of these factors, how these factors regulated cell fate choice on a mechanistic level remained unclear. By focusing on Twist, a transcriptional regulator that plays iterative roles in muscle development, we found that dimer partner choices, cooperation with other classes of transcriptional regulators and interactions with chromatin regulators are means by which transcriptional factors selectively drive muscle specification and differentiation.

1. Castanon, I, Von Stetina, S, Kass, J, Baylies, MK. (2001) Dimerization partners determine Twist activity during Drosophila myogenesis. *Development* 2001; 128(16): 3145-3159. PMID: 11688563.

2. Nowak, SJ, Aihara, H, Gonzalez, K, Nibu, Y, Baylies, MK (2012) Akirin links Twist-regulated transcription with Brahman chromatin remodeling complex during embryogenesis. *PloS Genetics* 8(3): e1002547. PMID: 22396663. PMCID: PMC3291577.

3. Wong, M, Dobi, KC, Baylies, MK. (2014) Discrete levels of Twist activity are required to direct multiple cell functions during gastrulation and somatic myogenesis. *PLoS One*. 9(6):e99553. PMID: 24915423. PMCID: PMC4051702.

4. Dobi, KC, Halfon MS, Baylies MK. (2014) Whole-Genome Analysis of Muscle Founder Cells Implicates the Chromatin Regulator Sin3A in Muscle Identity, *Cell Reports.* pii: S2211-1247(14)00572-5. PMID: 25088419. PMCID: PMC4207094.

We understood that signal transduction pathways were important for muscle specification, yet how these pathways interfaced with the tissue specific transcriptional programs remained unknown. Moreover, many of these pathways were used iteratively during muscle development, yet the mechanisms that assured the correct responses in space and time were unclear. Among our achievements in this area, we showed that that the

transcriptional effectors of Notch, RTK, Wnt and BMP pathways collaborate with tissue specific regulators to regulate muscle gene expression, that feed forward mechanisms by Wnt signaling control progression through muscle specification, that RTK and Notch signaling antagonism occurs at certain nodal points, and that muscle progenitors employ a common regulator for RTK, Wnt and Notch signaling to gate specification. Our understanding of signal transduction also allowed us to develop the first transcriptome data sets for Founder Cells, which seed the individual muscles, and the Fusion competent myoblasts, which fuse to Founders to make syncytial myofibers.

1. Halfon MS, Carmena A, Gisselbrecht S, Sackerson CM, Jiménez F, Baylies MK, Michelson AM. (2000) Ras pathway specificity is determined by the integration of multiple signal-activated and tissue restricted transcription factors. *Cell*. 103(1): 63-74. PMID: 11051548.

2. Carmena, A, Buff, E, Halfon, MS, Gisselbrecht, S, Jiménez, F, Baylies, MK*, Michelson AM*. (2002) Reciprocal regulatory interactions between the Notch and Ras signaling pathways in the Drosophila embryonic mesoderm. *Dev Biology*. 244(2): 226-242 (* joint senior authors). PMID: 11944933.

3. Artero, R, Furlong, EM, Beckett, K, Scott, MP, Baylies, MK. (2003) Notch and Ras signaling pathway effector genes expressed in Fusion-competent and Founder Cells during Drosophila myogenesis. *Development*. 130(25): 6257-6272. PMID: 14602676.

4. Cox, V, Baylies, MK. (2005) Specification of individual Slouch muscle progenitors in Drosophila requires sequential Wingless signaling. *Development*. 132(4): 713-724. PMID: 1564732.

Each muscle Founder Cell fuses to a set number of the Fusion Competent Myoblasts to create a muscle fiber. However, the genes and mechanisms required for this cell-cell fusion process, so essential for muscle formation and homeostasis, were unclear. Using genetic and cell biological methods, we identified several essential components in the cell fusion process, including a cell surface recognition and adhesion protein, regulators of branched actin formation, and PI(4,5)P2 signaling. We identified the impact of the spatial arrangement of the muscle cells on myoblast fusion and were the first to live image myoblast fusion *in vivo*. We also extended the *Drosophila* paradigm to mammalian myoblast fusion.

1. Richardson, B, Beckett, K, Nowak, SJ, Baylies, MK. (2007) SCAR/WAVE and Arp2/3 are critical for cytoskeletal remodeling at the site of myoblast fusion. *Development*. 134(24): 4357-4367. Featured article first live imaging of Drosophila myoblasts and myoblast fusion. PMID: 18003739. PMCID: PMC2880884.

2. Nowak, SJ, Nahirney, P, Hadjantonakis, AK, Baylies, MK. (2009) Nap1-Mediated Actin Remodeling is Essential for Mammalian Myoblast Fusion. *Journal of Cell Science* 122: 3282-3293. PMID: 19706686. PMCID: PMC2736864.

3. Bothe, I, Deng, S, Baylies MK (2014) PI(4,5)P2 regulates myoblast fusion through Arp2/3 regulator localization at the fusion site. *Development.* 141(11): 2289-301. PMID: 24821989. PMCID: PMC4034421.

4. Deng, S, Bothe, I, Baylies MK (2015) The Formin Diaphanous Regulates Myoblast Fusion through Actin Polymerization and Arp2/3 Regulation. *PLoS Genet*. 11(8):e1005381. PMID: 26295716. PMCID: PMC4546610.

While mispositioned myonuclei have been used as a diagnostic for muscle disease for over 60 years, how muscle nuclei move and position within the muscle fiber were unclear. Moreover, the contribution of mispositioned myonuclei to disease was unclear. Our genetic screens identified microtubules, microtubule associated proteins, microtubule motor proteins and JNK signaling as critical for myonuclear movement and positioning. Importantly, this work indicated that aberrantly placed nuclei correlated with aberrant muscle function, providing new insights for muscle disease. Using cell biological and imaging assays, we defined a series of nuclear movements during muscle differentiation and identified at least two microtubule-based mechanisms: a cortical pathway that pulls the nuclei along the long axis of the muscle and a nuclear pathway that provides polarity and directional movement for each nucleus. Lastly, we developed techniques that allowed us to introduce drugs used in cell culture to the developing *Drosophila* embryos, thus expanding our array of techniques to investigate muscle cell organization.

1. Metzger T., Gache V., Xu M., Cadot B., Folker ES, Richardson BE., Gomes ER, Baylies, MK. (2012) MAP and Kinesin-Dependent nuclear positioning is required for skeletal muscle function. *Nature.* 484(7392): 120-124. PMID: 22425998. PMCID: PMC3321085.

2. Folker, ES, Schulman, VK, Baylies, MK. (2012) Muscle length and myonuclear position are independently regulated by distinct Dynein pathways. *Development*. 139(20): 3827-3837. PMID: 22951643. PMCID: PMC3445310.

3. Folker, ES, Schulman, VK, Baylies MK. (2014) Translocating myonuclei have distinct leading and lagging edges which require Kinesin and Dynein. *Development*. 141(2):355-66. PMID: 24335254. PMCID: PMC3879816.

4. Schulman, VK, Folker, ES, Rosen, JN, Baylies, MK. (2014) Syd/JIP3 and JNK signaling are required for myonuclear positioning and muscle function. *PLoS Genetics.* 10(12):e1004880. PMID: 25522254. PMCID: PMC4270490.

Complete List of Published Work in PubMed:
http://www.ncbi.nlm.nih.gov/pubmed/?term=bayliesm

D. Research Support
ACTIVE:

NIAMS
1 RO1 GM108981-01A (Baylies) 2014-2019
Role: PI
Mechanisms and Function of Myonuclear Positioning
Our research will significantly impact the knowledge of muscle biology and provide new approaches for human disease treatment. We will identify mechanisms responsible for movement and position of muscle cell nuclei to understand how improper positioning of muscle nuclei can occur, and how improper positioning impacts normal cell function. This grant scored a 4th percentile.

NIAMS 2014-2016
1 R21 AR067361-01 (Baylies)
Role PI
Therapeutic target discovery in Drosophila models of Nemaline Myopathy
Patients diagnosed with Nemaline Myopathy have muscle weakness and decreased mobility and, in some cases, suffer from premature death. No cure exists. Our research will identify FDA approved drugs and novel target genes that slow or inhibit progression of this disease.

Alex's Lemonade Stand Foundation 2015-2017
GC223396 (Baylies)
Identification of Rhabdomyosarcoma therapies using an efficient Mouse and Drosophila Repurposing screen.
Role PI
Based on published and our preliminary data, we hypothesize that an FDA-approved drug repurposing screen, conducted in the aRMS model in *Drosophila*, will identify novel treatments relevant for the human disease.

COMPLETED:
MDA 2012-2015
Muscular Dystrophy Association
Myonuclear Positioning: links to Nuclear structure and Muscle Function (Baylies)
Role PI
The goal of this project is to define the connection between laminC and ensconsin, a known regulator of nuclear movement. Lamin mutants have been linked to several laminopathies that are characterized by aberrant nuclear movement.