BIOGRAPHICAL SKETCH

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NAME: Lucy Erin O'Brien

eRA COMMONS USER NAME (credential, e.g., agency login): lucye2

POSITION TITLE: Assistant Professor of Molecular and Cellular Physiology

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	Completion Date	FIELD OF STUDY
Harvard College, Cambridge, Massachusetts	B.A.	06/1992	Biochemistry
University of California, San Francisco	Ph.D.	08/2001	Biomedical Sciences
University of California, San Francisco	Postdoc	01/2002	Cell Biology
University of California, Berkeley	Postdoc	06/2010	Stem Cells and Organs
University of California, Berkeley	Asst Resrchr	01/2013	Stem Cells and Organs

A. Personal Statement

Scientific training and vision. My lab studies how epithelial stem cells and their differentiated progeny collectively orchestrate cellular turnover at a whole-organ scale. Our testing ground is the midgut of adult *Drosophila*, a stem cell-based digestive organ that undergoes continuous cell turnover. The fly midgut is an archetypical example of an epithelial tube, the most primitive organ form and the form of most organs in our own bodies. At the same time, the midgut's simple anatomy, well-described cell lineages, and tractability—especially for sophisticated genetic and imaging approaches—make it a superlative system for mechanistic research at the interface of stem cell and epithelial tissue biology.

My deep, cross-disciplinary background in epithelial morphogenesis and stem cells provides an ideal foundation for our research program. As a graduate student (UCSF, Keith Mostov), I discovered that epithelial cells polarize by assembling basement membrane fibrils to break spatial symmetry, and I identified that epithelial tubule formation involves a partial epithelial-mesenchymal transition. As a postdoc (UC Berkeley, David Bilder), my excitement about the potential of an emerging stem cell-based epithelium—the *Drosophila* adult midgut—to investigate questions about epithelial organ form in the context of physiological function prompted me to shift to this new system. I discovered that food ingestion triggers the fly gut to grow by activating insulin-controlled symmetric stem cell divisions (O'Brien, *Cell* 2011), one of the first detailed mechanisms of how single-cell behaviors give rise to remodeling in mature organs.

At Stanford, I have built my lab around the question of how single-cell behaviors combine for whole-organ control of healthy renewal and remodeling, developing new methodologies as needed. My lab recently elucidated a novel E-cadherin-EGFR signaling pathway that homeostatically equalizes cell production and loss during steady-state organ turnover (Liang, *Nature* 2017) and determined how disruption of this feedback drives tumor initiation (Ngo, *Current Biology* 2020). Recognizing that the lack of live imaging protocols was a major barrier to progress, we pioneered the first long-term live imaging methodologies for the midgut (Martin, eLife 2018; Koyama, *PLOS Biology* 2020); these have, and will continue to, yield unexpected insights into cell and organ-scale renewal behaviors.

Our MIRA research program positions us to continue this trajectory of significant, innovative contributions to stem cell and epithelial organ biology. We seek to understand the cellular and signaling basis of fundamental, yet still mysterious, features of stem cell-based epithelial organs: how organs measure size and 'count' cells during steady-state turnover, assess what proportion of their cells should be stem cells and where to put them, and how newborn, terminally committed cells integrate into the organ for physiological function. The unique imaging and *in situ* single-cell analytics we have developed exemplify our lab's thrust to bridge single-cell and whole-organ scales, precisely the approach that is needed to understand how single-cell behaviors collectively produce life-long control of organ form and function.

1) Liang, J., Balachandra, S., Ngo, S., & **O'Brien, L.E.** (2017) Feedback control of epithelial turnover and organ size. *Nature* (cover article) **548**:588-591 *PMC5742542*

   • Highlighted in: Principles of Systems Biology, No. 21. Liang, J. & O'Brien, L.E. Organ Size: Act Locally to Control Globally. Cell Systems 5, 158-160 (2017) | Ferrarelli, L.K. A life-death relay in the gut. Science Signaling 10:495 (2017) | Dubnicoff, T. Stories that caught our eye last week: dying cells trigger stem cells, CRISPR videogames and an obesity-stem cell link. CIRM Blog (2017) | Faculty of 1000 *F1000Prime.com/729075065*

2) Ngo, S., Liang, J., Su, Y.H., & **O'Brien, L.E.** (2020) Tumor establishment requires tumor autonomous and non-autonomous decoupling of EGF signaling from apoptosis. *Current Biol* **30**:1539. *PMID32243854*

3) Martin, J., Sanders, E.N., Moreno-Roman, P., Balachandra, S., Koyama, L.A.K., & **O'Brien, L.E.** (2018) Long-term live imaging of the *Drosophila* adult midgut reveals real-time dynamics of cell division, differentiation, and loss. *eLife* **7**:e36248. *PMC6277200*

   • Highlighted in: Dye, N. A new method captures the dynamics of tissue homeostasis in the stem-cell based organ of the adult fly midgut. preLights (Company of Biologists preprint reviews) (2018) | Lewis, A. Freshen up: Detailed and direct observation of organ development. MRC Biomedical Picture of the Day (Jan 28, 2019)

4) Koyama, L.A.J., Su, Y.H., Aranda-Diaz, A., Martin, J.L., Balachandra, S., Ludington, W., Huang, K.C., & **O'Brien, L.E.** (2020) Bellymount: A novel method for longitudinal, intravital imaging of abdominal organs in adult *Drosophila*. *PLOS Biology* **18**:e3000567. *PMC7004386*

   • Highlighted in: AAAS EurekaAlert! What can you learn by peering into a fruit fly's gut? It turns out a lot! (Mar 2, 2020) | Medical & Life Science News. New tool allows researchers to peer into live tissue of the fruit fly gut. (Mar 2020) | Carnegie Science. Eavesdropping on "conversations" between gut stem cells and gut bacteria. (Mar 2, 2020)

Mentorship. I have mentored 4 postdocs (3 current) and 4 graduate students (1 current). My approach to mentorship is three-pronged: (1) Empower trainees to devise rigorous and creative approaches to important questions. This latitude led graduate student Jackson Liang to devise an original genetic approach to probe cell equilibrium that ultimately earned him a Harold Weintraub Award, given to ~12 outstanding biosciences Ph.D. theses internationally. (2) Educate trainees to become compelling science communicators. This priority pays large dividends; my trainees have earned 10 fellowships and delivered 15 abstract-selected talks at major conferences. Graduate student Leslie Koyama gave a Plenary talk at the US *Drosophila* Research Conference, and graduate student Paola Moreno-Roman received the Best Student Talk award at the Cell Polarity Gordon Conference. (3) Mentor each lab member as an individual to help them navigate career challenges. I am proud of the research paths taken by our lab alumni; these include a postdoc at Genentech, scientist positions at biotech start-ups; and Staff Scientist at a free-standing research institute.

Diversity and inclusion. Inclusivity is a cornerstone of my lab culture, which I foster by engaging in open dialogue, seeking each person's contributions, and ensuring equity of lab resources and obligations. As a consequence, cumulatively, 85% of my lab members (14 – includes technicians, postdocs, graduate and undergraduate students) have been women; 28% of my trainees have been minorities underrepresented in STEM, one undergraduate is first-in-family to attend college; and our medical student is a Dreamer. Former postdoc, XinXin Du, is the first and only senior woman in her research division. Each person brings a unique perspective that, when combined, boosts creativity, enhances problem solving, and supercharges our science.

Service to the field. My scientific leadership and service synergize with our greater research agenda. My leadership roles in the International Society for Stem Cell Research (ISSCR) have given me a unique vantage from which to perceive and influence trends, opportunities, and challenges in stem cell biology. For instance, as co-chair of the ISSCR Task Force on Annual Meeting Strategy, I led restructuring the ISSCR's flagship conference into five themed tracks encompassing the full scope of this broad field. As co-chair of the Junior Investigators' Committee, I initiated the first Diversity, Equity, and Inclusion Meet-up at the annual meeting. My recent selection as one of ~15 ISSCR Next Generation Leaders will, I expect, open new paths to advocate for one of my passions, which is the vital role of basic science in the increasingly translational stem cell field.

Through professional service, I seek to advance two deeply held scientific goals: supporting exciting work at the nexus of stem cell, tissue, and developmental biology, and building the relatively young community of *Drosophila* midgut researchers. To further our field's impact and visibility, I am a reviewer for general-interest and field-respected journals and will join the *eLife* Board of Reviewing Editors in October 2020. I deliver talks at major symposia and universities, and chair sessions at society meetings, and co-initiated and continue to host

the “Gut PI Dinner” at *Drosophila* Research Conferences. I serve as midgut lead for the Fly Cell Atlas Initiative, an international consortium generating a single-cell expression map for all *Drosophila* organs.

B. Positions and Honors

Positions and Employment

US Fish and Wildlife Service, Moiese, Montana (1992 - 1993)
Field researcher
University of California, San Francisco, Department of Anatomy (1993 - 2002)
Graduate student & Postdoctoral Scholar Mentor: Keith Mostov
Alpine ski mountaineering / Ocean kayaking (2002 - 2005)
Expedition leader; ski and kayak instructor
University of California, Berkeley, Department of Molecular and Cell Biology (2005 - 2013)
Postdoctoral Scholar & Assistant Researcher Mentor: David Bilder
Stanford University, Department of Molecular and Cellular Physiology (Feb 2013 - present)
Assistant Professor

Fellowships and Honors *(selected)*

Westinghouse (now Intel) National Science Talent Search Scholarship *(one of 40 national winners) 1988* | Harvard College Detur Prize *(awarded to the 100 highest freshman GPAs) 1989* | Department of Defense Predoctoral Fellowship, *1993-96* | American Heart Association Predoctoral Fellowship, *1998-2001* | American Society for Cell Biology Worthington Award, *1999* | Life Sciences Research Foundation Genentech Foundation Fellow, *2007-09* | NIH NIDDK Mentored Career Development Award (K01), *2010-2015* | Gabilan Junior Faculty Fellow of Stanford University, *2013* | ISSCR Next Generation Leader, *2020*

Selected Invited Seminars *(since 2015)*

2015: Univ. of Glasgow, Beatson Institute, Imperial College London, Buck Institute for Research on Aging, Univ. of Pennsylvania School of Medicine, Univ. of Southern California; *2016*: National Institute for Biological Sciences (Beijing); *2017*: Univ. of Calgary, San Jose State Univ.; *2019*: Univ. of Chicago; Columbia Univ., Univ. of Utah, M.D. Anderson Cancer Center, NYU/Skirball Institute, Univ. of British Columbia., Stanford Univ., Institut Pasteur, Univ. of Utah; *2020*: Harvard Univ., Hubrecht Institute

Selected Invited Conference and Symposium Talks *(since 2015)*

2015: Cold Spring Harbor Stem Cell Meeting, European Drosophila Research Conference, West Coast Salt and Water Club Meeting *(keynote)*; *2016*: Gordon Conference on Tissue Niches and Resident Stem Cells in Adult Epithelia; *2017*: European Drosophila Research Conference, International Society for Stem Cell Research, US Drosophila Research Conference; *2018*: American Society for Cell Biology Annual Meeting, Society for Developmental Biology Annual Meeting, Santa Cruz Developmental Biology Meeting, Drosophila Crete Meeting, Gordon Conference on Cell Polarity Signaling, Keystone Symposium on Endoderm; *2019*: Champlimaud Symposium on Stem Cells, Gordon Conference on Cell-Cell Contact and Adhesion, UCSF Developmental Biology Symposium, Society for Developmental Biology West Coast Meeting, International Society for Stem Cell Research, European Drosophila Research Conference; *2020*: Society for Developmental Biology Southeast Regional Meeting (*keynote*).

Society Memberships and Service

International Society for Stem Cell Research, 2010-present**:** Annual Meeting Task Force co-chair (*2019*); Junior Investigators’ Committee (*2016-2019*), co-chair (*2017-2019*); Annual Meeting session chair, Tissue Homeostasis (*2019*); Diversity, Equity, & Inclusion Meetup initiator (*2019*)

American Society for Cell Biology, 1994-present**:** *Membership Committee, 2006-2012*; Annual Meeting minisymposium chair, Patterning Tissue Morphogenesis (*2018)*

Genetics Society of America, 2005-present: Annual Drosophila Conference Platform session chair, Stem Cells (*2019*), Intercellular Signaling (*2016*)

Society for Developmental Biology, 2018-present: West Coast Meeting poster judging chair (*2019*); Annual Meeting session chair, Stem Cells (*2018*)

Service as Grant Reviewer

Academy of Medical Science (United Kingdom); Carnegie Trust (Scotland) Medical Research Council (United Kingdom); Henry Dale Fellowship (United Kingdom); German Research Foundation; Human Frontiers in Science Program; Israel Science Foundation

C. Contributions to Science

1. Steady-state and growth regulation of stem cell-based adult organs.

Stem cells ensure lifelong optimization of organ form and function by calibrating their behaviors to meet the changing needs of their resident organ. My work has identified the cellular mechanisms and molecular regulation of these stem cell behaviors. As a postdoc, I discovered that stem cells drive growth of the fly gut upon increased dietary load through symmetric stem cell divisions activated by gut insulin-like peptides. In my lab, we elucidated the feedback mechanism that equalizes stem cell division and differentiated death during midgut renewal—the first such mechanism for any adult organ. In identifying the full molecular axis of homeostatic feedback signaling, we uncovered a novel intercellular signaling pathway linking an epithelial tumor suppressor, E-cadherin, to EGFR, an oncogene activated in many epithelial cancers. We then showed how tumorigenic stem cells subvert this pathway to establish feed-forward signaling that fuels uncontrolled growth.

These discoveries form two major advances: (1) they revealed unexpected responsiveness of stem cell divisions to the dynamic fluctuations in their signaling environment and (2) they provided first insights into how individual stem cell behaviors give rise to diverse types of organ-scale outcomes. For the midgut field, our identification of the signaling that controls homeostatic, physiological growth, and cancerous states; have since been leveraged by many subsequent midgut studies. For the stem cell field in general, our work has informed investigations of growth and homeostatic behaviors in multiple systems, including mouse intestine, skin, and blood as well as the Drosophila follicle cell epithelium, testis, and immune cells.

a) Liang, J., Balachandra, S., Ngo, S., & **O'Brien, L.E.** (2017) Feedback control of epithelial turnover and organ size. *Nature* (cover article) **548**:588-591 *PMC5742542*

b) Ngo, S., Liang, J., Su, Y.H., & **O'Brien, L.E.** (2020) Tumor establishment requires tumor autonomous and non-autonomous decoupling of EGF signaling from apoptosis. *Current Biol* **30**:1539. *PMID32243854*

c) **O'Brien, L.E.** & Bilder, D. (2013) Beyond the niche: Tissue-wide coordination of stem cell dynamics. *Annu. Rev. Cell Dev. Biol.* **29** 107-136. *PMC3897713*

d) **O'Brien, L.E.**, Soliman, S.S., Li, X., & Bilder, D. (2011) Altered modes of stem cell division drive adaptive intestinal growth. *Cell* **147**:603-614. *PMC3246009*

2. Advanced imaging methodologies for cell- and organ-scale analyses of fixed and live midguts.

Deep understanding of organ-scale cell dynamics requires imaging methodologies for quantitative spatiotemporal analyses from single cell to whole-organ scales. The recent explosion of the midgut as a model stem cell-based organ has created urgent need for such methodologies. We have pioneered several: (1) Semi-automated, *in toto* cell counts of fixed midguts using 3D reconstructions, which remains the field's gold standard. (2) Long-term midgut imaging within live, feeding animals. (3) Longitudinal imaging of the midgut within individual animals over weeks. In addition, we are building novel microfluidic devices to mechanically manipulate and measure forces of live midguts *ex vivo.* Each of these methodologies has delivered new understanding and insights that were not attainable using conventional approaches (please see next Contribution).

a) Koyama, L.A.J., Su, Y.H., Aranda-Diaz, A., Martin, J.L., Balachandra, S., Ludington, W., Huang, K.C., & **O'Brien, L.E.** (2020) Bellymount: A novel method for longitudinal, intravital imaging of abdominal organs in adult *Drosophila*. *PLOS Biology* **18**:e3000567.*PMC7004386*

b) Martin, J., Sanders, E.N., Moreno-Roman, P., Balachandra, S., Koyama, L.A.K., & **O'Brien, L.E.** (2018) Long-term live imaging of the *Drosophila* adult midgut reveals real-time dynamics of cell division, differentiation, and loss. *eLife* **7**:e36248. *PMC6277200*

c) Kim, A.A., Nekimken, A.L., Fechner, S., **O'Brien, L.E.**, & Pruitt, B.L (2018) Microfluidics for mechanobiology of model organisms. *Methods in Cell Biology* **146**:217-259. *PMID30037463*

d) **O'Brien, L.E.**, Soliman, S.S., Li, X., & Bilder, D. (2011) Altered modes of stem cell division drive adaptive intestinal growth. *Cell* **147**:603-614. *PMC3246009*

3. Spatial-temporal dynamics of cell behaviors during organ renewal *in vivo*

Our work has unearthed a dynamic picture of the defining cell behaviors of adult organs: stem cell division, daughter cell differentiation, and differentiated cell loss. *In toto* cellular analyses revealed key cell and organ scale features, such as predominantly symmetric stem cell divisions during growth and conservation of total cell numbers when cell death is blocked, that would have been obscured by examining only population averages or small tissue fields. Live imaging demonstrated dynamic re-orientation of the stem cell mitotic spindle and showed that the switch from stem to enteroblast identity is quantitatively thresholded. Longitudinal imaging revealed startling differences in differentiation rates; spatial modelling suggests that differentiation kinetics may distinguish growth versus homeostasis. The overarching theme is that cellular 'life cycles' show huge variation in nearly every cellular parameter we have measured, yet give rise to organ states that are precise and robust. Given that these cell behaviors are general to most stem cell-based organs, we believe that these emergent mechanisms in the midgut provide a template to decipher more complex systems.

a) Liang, J., Balachandra, S., Ngo, S., & **O'Brien, L.E.** (2017) Feedback control of epithelial turnover and organ size. *Nature* (cover article) **548**:588-591 *PMC5742542*

c) Martin, J., Sanders, E.N., Moreno-Roman, P., Balachandra, S., Koyama, L.A.K., & **O'Brien, L.E.** (2018) Long-term live imaging of the *Drosophila* adult midgut reveals real-time dynamics of cell division, differentiation, and loss. *eLife* **7**:e36248. *PMC6277200*

c) Du, X., **O'Brien, L.E.***, and Riedel-Kruse, I.* (*co-corresponding) (2017) A model for adult organ resizing demonstrates stem cell scaling through a tunable commitment rate. *Biophys. J.* **113**:174-184. *PMC5510814*

d) Koyama, L.A.J., Su, Y.H., Aranda-Diaz, A., Martin, J.L., Balachandra, S., Ludington, W., Huang, K.C., & **O'Brien, L.E.** (2020) Bellymount: A novel method for longitudinal, intravital imaging of abdominal organs in adult *Drosophila*. *PLOS Biology* **18**:e3000567. *PMC7004386*

4. Self-organization of epithelial tissues through collective cell behaviors.

Individual epithelial cells form multicellular organoids when cultured in a three-dimensional matrix. My early graduate work showed that coordinated orientation of epithelial polarity relies on cross talk between intracellular signals and the extracellular matrix, a mechanism since found to direct polarized morphogenesis *in vivo* in the post-implantation mouse embryo, mammary terminal end buds, and the zebrafish optic cup. It was also a featured case study in the Alberts Molecular Biology of the Cell textbook (*5th ed., p. 1155*). My later graduate work examined how epithelial tissues convert from spheroids to tubes by two sequential, opposing processes, partial epithelial-mesenchymal transition and redifferentiation. Analogous mechanisms are now known to control mammary and endothelial tubulogenesis and become deregulated in non-small cell lung cancer. This led me to posit that diverse types of epithelial organogenesis can be deconstructed as a 'three-surfaces pursuit' plus varying degrees of epithelial-mesenchymal transition, a hypothesis that has influenced the field, led to the development of mathematical models, and framed research studies in organoid culture and *in vivo*.

a) **O'Brien, L.E.**, Jou, T.S., Hansen, S.H., Pollack, A.L., Zhang, Q., Yurchenco, P.D. & Mostov, K.E. (2001) Rac1 orients epithelial apical polarity through effects on basolateral laminin assembly. *Nature Cell Biol*. **3**:831-838. *PMID11533663*

b) **O'Brien, L.E.**, Tang, K., Kats, E.S., Schutz-Geschwender, A., Lipschutz, J.H., & Mostov, K.E. (2004) ERK and MMPs sequentially regulate distinct stages of epithelial tubule development. *Dev. Cell* **7**:21-32. *PMID15239951*

c) **O'Brien, L.E.**, Zegers, M.M.P., & Mostov, K.E. (2002) Opinion: Building epithelial architecture: Insights from three-dimensional culture models. *Nat. Rev. Mol. Cell. Biol.* **3**:531-537. *PMID12094219*

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/lucy.o'brien.1/bibliography/40022200/public/

D. Current Research Support *(Please see Current and Pending Support for detailed description.)*

1R21 OD028273 NIH/OD *O'Brien (PI)* 03/15/2020-02/28/2022
Bellymount: A platform for ultra-long term imaging of abdominal organs in live adult Drosophila

Research Scholar Grant 17-167-01 American Cancer Society *O'Brien (PI)* 01/01/2018-12/31/2021
Niche control of stem cell-driven epithelial tumorigenesis

1R01 GM116100 NIH/NIGMS *O'Brien (PI)* 04/01/2016-03/31/2021
Dynamic mechanisms of fate control during epithelial organ renewal