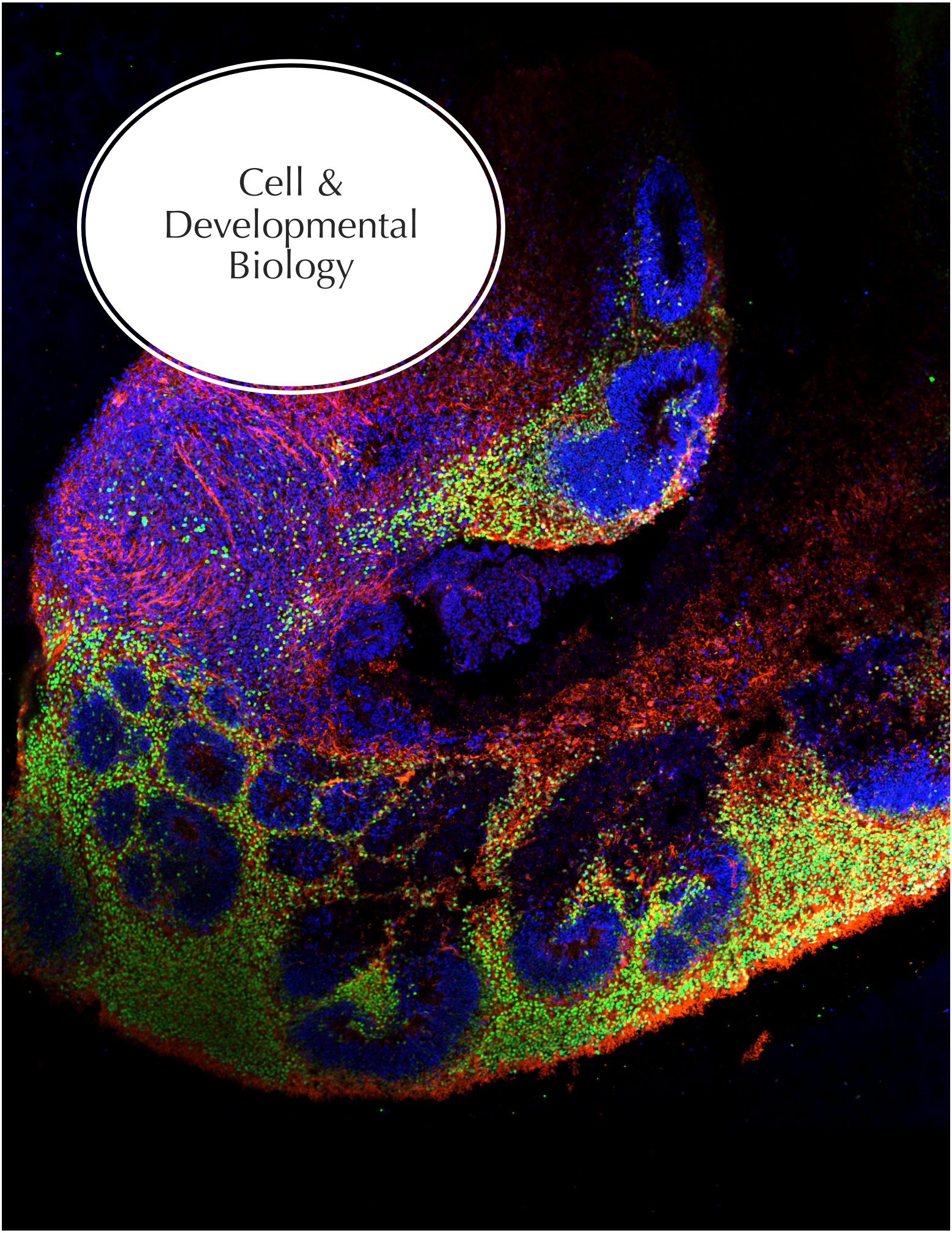
# Cell & Developmental Biology



# Cover Image

The image is a section of a day 60 human cortical brain organoid derived from pluripotent stem cells. Cells within the organoid stain positive for neuronal markers (red: TUJ1 for immature neurons, green: CTIP2 for cortical plate neurons) and neural precursor cell marker (blue: sox2 for neural progenitor cells). It is a Max Intensity Projection from a 4x4 stitched image taken at 20X in the Nikon Center of Excellence spinning disk confocal microscope.

Credit:  Alejandra Romero Morales (Gama lab)

# Introduction to CDB

at the leading edge

**The Department of Cell and Developmental Biology** is a vibrant, interdisciplinary environment for cutting-edge research over a scale that spans seven powers of ten, from single molecules to whole organisms. The difference between a test tube and a cell is spatio-temporal organization, and we study molecular, cellular and tissue organization in many of the laboratories within our department, seeking insights into fundamental biological questions and human disease.

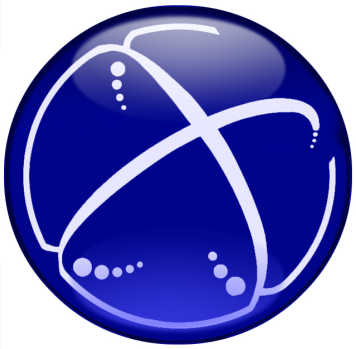
This year we achieved **the #2 ranking** in the nation for funding, as compared with all similar departments around the US. We are an interactive and highly collaborative department, with a strong graduate student association, outstanding core facilities, a top-ranked developmental biology program, and exceptionally strong faculty. Recent faculty recruits are studying cell migration using super-resolution microscopy, single molecule analysis of microtubule dynamics, systems biology of intestinal epithelia, stem cell biology, and the regulation of plasma membrane composition and aging.

As individuals and as a department we strongly support diversity and inclusion. We believe that science is a vocation open to everyone who has an inquiring mind, who wants to learn how the natural world works, and who brings passion to their curiosity.

**https://medschool.vanderbilt.edu/cdb/**

**Vanderbilt University Program in Developmental Biology (PDB)** emerged from CDB as a trans-institutional collective of VU & VUMC laboratories, with inventive trainee activities, courses, annual retreat, and NIH-funded T32 training grant. It provides a stimulating, supportive environment for researchers studying tissue formation, cell differentiation/ reprogramming, morphogenesis, stem & progenitor biology.

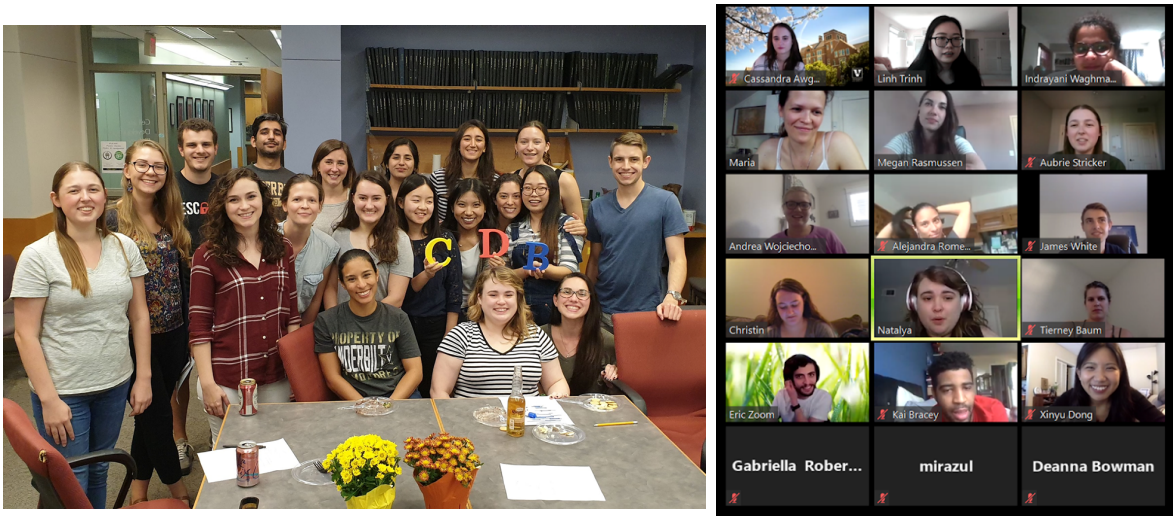
**https://medschool.vanderbilt.edu/pdb/**



# CDB Graduate Student Association

Welcome to Cell and Developmental Biology (CDB) GSA! We hope that you are staying well. Although the start of your graduate training is unusual, we hope that we can give you an idea on how our GSA serves and builds an inviting community for students within CDB.

Despite emerging challenges, CDB GSA has managed to adapt to the new situation and is committed to helping the department become even more inclusive and welcoming for everyone. We are continuing to hold happy hours and provide support to students taking qualification exams. Additionally, GSA has served as a liaison between graduate students and faculty leadership to communicate changes and concerns around the COVID-19 pandemic. Throughout this unprecedented time, we are grateful for CDB's open and supporting environment that allows students to voice our opinions and concerns. In the light of the Black Lives Matter movement, we helped to establish a diversity and inclusion committee that not only initiates important changes within CDB community, but also inspires and supports other GSAs in the combat against racism and social injustice.




CDB rotation parties October 2019 (left) and April 2020 (right)

Although we cannot meet in person with our traditional rotation parties, we would still like to welcome you to our department with online rotation parties. Feel free to contact our incoming and out-going GSA presidents if you have any questions. We look forward to meeting you!

**Mary Chalkley**
Co-President

**Sara Ramirez**
Co-President

**Linh Trinh**
President Emeritus

# CDB Faculty and Leadership

## Program Leadership & Administration

**Ian G. Macara, Ph.D.**
Department Chair
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**Andrea Page-McCaw, Ph.D.**
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## Primary Faculty

**Kristopher J. Burkewitz, Ph.D.**
**Dylan T. Burnette, Ph.D.**
**Chin Chiang, Ph.D.**
**Kathy DelGiorno, Ph.D.**
**Vivian Gama, Ph.D.**
**Kathleen L. Gould, Ph.D.**
**Guoqiang Gu, Ph.D.**
**Rebecca A. Ihrie, Ph.D.**
**Jonathan Irish, Ph.D.**
**Irina N. Kaverina, Ph.D.**
**Ken S. Lau, Ph.D.**
**Ethan Lee, M.D., Ph.D.**
**Ian G. Macara, Ph.D.**
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**David M. Miller, III, Ph.D.**
**Andrea Page-McCaw, Ph.D.**
**William P. Tansey, Ph.D.**
**Matthew J. Tyska, Ph.D.**
**Alissa M. Weaver, M.D., Ph.D.**
**Susan R. Wente, Ph.D.**
**Christopher V. Wright, D. Phil.**
**Marija Zanic, Ph.D.**
**Qiangjun Zhou, Ph.D.**

## Secondary Faculty

**Scott H. Baldwin, M.D.**
**Julie A. Bastarache, M.D.**
**R. Daniel Beauchamp, M.D.**
**Gautam (Jay) Bhave, M.D., Ph.D.**
**Timothy S. Blackwell, M.D.**
**Stephen J. Brandt, M.D.**
**Kendal S. Broadie, Ph.D.**
**Craig R. Brooks, Ph.D.**
**Jin Chen, M.D., Ph.D.**
**Eunyoung Choi, Ph.D.**
**Robert J. Coffey, M.D.**
**Mark P. de Caestecker, MBBS, Ph.D.**
**Kevin C. Ess, M.D., Ph.D.**
**Jeffrey L. Franklin, Ph.D.**
**Sabine Fuhrmann, Ph.D.**
**Maureen A. Gannon, Ph.D.**
**Leslie S. Gewin, M.D.**
**James R. Goldenring, M.D., Ph.D.**
**Todd R. Graham, Ph.D.**
**Antonis K. Hatzopoulos, Ph.D.**
**Patrick J. Hu, M.D., Ph.D.**
**Billy G. Hudson, Ph.D.**
**Ela W. Knapik, M.D.**
**Jonathan A. Kropski, M.D.**
**Deborah A. Lannigan, Ph.D.**
**Edward M. Levine, Ph.D.**
**Mark A. Magnuson, M.D.**
**Robert J. Matusik, Ph.D.**
**Anna L. Means, Ph.D.**
**Young-Jae Nam, M.D.**
**Jared Nordman, Ph.D.**
**Maulik Patel, Ph.D.**
**James G. Patton, Ph.D.**
**John S. Penn, Ph.D.**
**John Jeffrey Reese, M.D.**
**Cynthia Reinhart-King, Ph.D.**
**William E. Russell, M.D.**
**Linda J. Sealy, Ph.D.**
**Michelle Southard-Smith, Ph.D.**
**Roland W. Stein, Ph.D.**
**Jennifer S. Sucre, M.D.**
**Matthew H. Wilson, M.D.,Ph.D.**
**Pampee P. Young, M.D., Ph.D.**
**Roy Zent, M.D., Ph.D.**
**Andries Zijlstra, Ph.D.**
**Sandra S. Zinkel, M.D., Ph.D.**

Vanderbilt University Program in Developmental Biology

Membership in the Vanderbilt University Program in Developmental Biology (PDB) runs deeply throughout the School of Medicine and Arts & Sciences communities, currently comprising more than 250 total faculty members, postdoctoral fellows, graduate students, undergraduates, research staff and other support personnel.

PDB laboratories use many approaches to answer "developmental" questions within an extremely broad spectrum of biomedically relevant research, extending to tissue maintenance/turnover, stress and wound responses, aging, and cancer. The PDB strives for constant application of academic biological discovery towards human health and disease. The rich mixing pot of scientific approaches accesses the most technically sophisticated and ground-breaking technologies (imaging, structure determination, small-molecule screening, various "-omics" data collections). Exciting collaborations have led to many surprisingly novel discoveries that emerged from inter-species approaches. The activities of the PDB are closely aligned with those of the Vanderbilt Center for Stem Cell Biology.

*Fundamental questions addressed by PDB research groups include:*

- How is the basic body plan of an embryo established?
- What factors and cellular interactions drive morphogenetic and developmental processes?
- How are organs formed, and how does the extraordinarily complex brain become correctly wired?
- How does single-cell "-omics" knowledge affect our understanding of cell differentiation and behavior?
- What are the best combinations of model systems to address issues that affect human health and aging?

*PDB activities maintain a vibrant, challenging, and supportive environment, such as:*

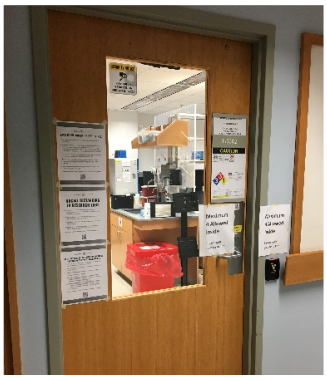
- Didactic Courses focused on most-recent discoveries and concepts, innovative analytical approaches.
- Extramural Guest Speaker Presentations include Trainee Research/Career Discussions, and specific whole-day interactions with student- and postdoc-invited speakers.
- Weekly PDB Journal Club Seminars.
- Annual Boot Camp – an in-depth exposure to the attributes of a range of model organisms, with a focused clinical correlation that elaborates direct connections to human health.
- Twice-monthly Student-Only dbRIC (developmental biology Research in Construction) Meetings.
- Monthly Postdocs-Only Career Development Meetings.
- Student and Postdoctoral Fellow Research Happy Hours.
- Annual Off-Campus PDB Retreat at a State Park location, largely trainee-organized, with stellar extramural keynote speaker.

# CDB Equipment Resource Core

CDB maintains a large and diverse equipment core located throughout the department

We specialize in providing basic services to support a Modern Laboratory's needs

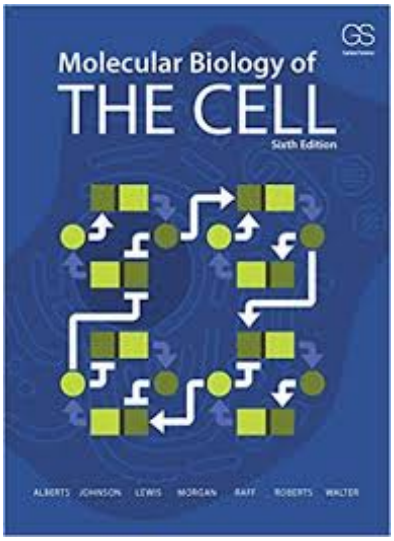
- Autoclaves
- Glasswash & Dry Service – Self Service
- Ultracentrifugation
- High Speed Centrifugation
- Low Speed Centrifugation
- Backup Freezers
- Cryogenic Storage
- Dry Ice
- Freeze Dryer (Lyophilizer)
- Ice Machines
- Incubator Shakers
- Liquid Nitrogen Pay-per-use
- Sonicator
- SpeedVac
- Ultrapure Water Systems
- Chemiluminescent Imager – AI600
- Chemiluminescent and GFP CCD Imager – LAS4000
- Phosphorimager – Typhoon FLA7000IP
- Odyssey CLx Infrared Scanner
- X-Ray Film Processing
- Gel Imaging – GelDoc EZ
- Platereader
- qPCR
- Nanodrops & Spectrophotometers
- TriCarb 2900TR Liquid Scintillation Analyzers
- POLARstar Omega Platereader BMG Labtech
- Cryostat Tissue-Tek's Cryo3 Sakura
- Leica SP5 Scanning Confocal
- EVOS FL Inverted Microscope




# Curriculum Requirements for a PhD in Cell & Developmental Biology

## First year:

Standard IGP or QCB curriculum (16 didactic credits)




## Second year:

Starting in Fall 2020, CDB graduate students are required to take two required classes:

CBIO-GS 8310 – Effective Scientific Communication (3 didactic credits, fall)
CBIO-GS 8315 – Teaching Cell Biology (2 didactic credits, spring)

In addition to these required courses, students entering CDB from the IGP or QCB must earn an additional 3 didactic credits, usually in their second year, from elective courses offered by CDB or by any of the programs within the BRET umbrella; electives from another science department will be considered on a case-by-case basis by the Director of Graduate Studies. CDB offers the following electives for didactic credit:

Summer:
CBIO 8312. Introduction to Developmental Biology (3 didactic credits)

Fall:
CBIO 8331. Current Topics in Stem Cell and Devel. Biology (1 didactic credit)
CBIO 8333. Classic Papers (1 didactic credit)

Spring:
CBIO-GS 8311. Contemporary Technologies and Approaches (1 didactic credit)
CBIO 8313. Introduction to Modern Biological Microscopy (1 didactic credit)
CBIO 8324. Epithelial Pathobiology (offered every other year in even years, 3 didactic credits)
CBIO 8331. Current Topics in Stem Cell and Devel. Biology (1 didactic credit)
CBIO 8338. Nobel Laureates in the Life Sciences (1 didactic credit)
CBIO 8345. Cellular and Molecular Neuroscience (4 didactic credits)

After earning a total of 24 didactic credits, a CDB student is eligible to take the Qualifying Examination, usually between their second and third year.
A second year non-didactic requirements are attendance at CBIO-GS 8339 (Research Exchange, Seminar in Cell Biology) in both spring and fall and laboratory research.

## Third year and beyond:

Most CDB students have completed courses and pursue research exclusively.

# Graduation Requirements for a PhD in Cell & Developmental Biology

- At least 24 didactic credits and 72 total credits (didactic plus research credits).
- An original body of research, comprising at minimum one first-author research manuscript accepted for publication, but often significantly more, including research and/or reviews papers, both candidate-led (first-author) and collaborative.
- At least one presentation to the department at Research Exchange (REx), the department's trainee seminar series, usually in the candidate's fourth year.
- A dissertation written by the candidate.
- A successful thesis defense, including a public presentation and a private defense before the thesis committee made up of four faculty members, at least one of whom is outside the department, and the candidate's thesis advisor.

# Research Areas in CDB

## Biophysics

Dylan Burnette, Ph.D.
Marija Zanic, Ph.D.

## Cancer Biology

Chin Chiang, Ph.D.
Kathy DelGiorno, Ph.D.
Kathy Gould, Ph.D.
Rebecca Ihrie, Ph.D.
Jonathan Irish, Ph.D.
Ken Lau, Ph.D.
Ethan Lee, M.D., Ph.D.
Ian Macara, Ph.D.
Andrea Page-McCaw, Ph.D.
Alissa Weaver, M.D., Ph.D.
Bill. Tansey, Ph.D.

## Cell Cycle Regulation

Kathy Gould, Ph.D.
Andrea Page-McCaw, Ph.D.
Bill Tansey, Ph.D.

## Cell Signaling

Kristopher Burkewitz, Ph.D.
Chin Chiang, Ph.D.
Kathy DelGiorno, Ph.D.
Vivian Gama, Ph.D.
Kathy Gould, Ph.D.
Rebecca Ihrie
Jonathan Irish, Ph.D.
Ken Lau, Ph.D.
Irina Kaverina, Ph.D.
Ethan Lee, M.D., Ph.D.
Ian Macara, Ph.D.
Jason MacGurn, Ph.D.
David M. Miller, Ph.D.
Andrea Page-McCaw, Ph.D.
Bill Tansey, Ph.D.
Alissa Weaver, M.D., Ph.D.
Christopher Wright, D. Phil.

## Cell Motility

Dylan Burnette, Ph.D.
Irina Kaverina, Ph.D.
Alissa Weaver, M.D., Ph.D.

## Chemical Biology

Ethan Lee, M.D., Ph.D.
Bill Tansey, Ph.D.

## Cytoskeleton & Cell Polarity

Dylan Burnette, Ph.D.
Kathy Gould, Ph.D.
Guoqiang Gu, Ph.D.
Irina Kaverina, Ph.D.
Ian Macara, Ph.D.
David Miller, Ph.D.
Matthew Tyska, Ph.D.
Alissa Weaver, M.D., Ph.D.
Marija Zanic, Ph.D.

## Developmental Biology

Kristopher Burkewitz, Ph.D.
Dylan Burnette, Ph.D.
Chin Chiang, Ph.D.
Vivian Gama, Ph.D.
Guoqiang Gu, Ph.D.
Rebecca Ihrie, Ph.D.

Jonathan Irish, Ph.D.
Irina Kaverina, Ph.D.
Ken Lau, Ph.D.
Ethan Lee, M.D., Ph.D.
Ian Macara, Ph.D.
Jason MacGurn, Ph.D.
David Miller, Ph.D.
Andrea Page-McCaw, Ph.D.
Matthew Tyska, Ph.D.
Christopher Wright, D. Phil.

## Epithelial Biology

Ken Lau, Ph.D.
Ian Macara, Ph.D.
Jason MacGurn, Ph.D.
Andrea Page-McCaw, Ph.D.
Matthew Tyska, Ph.D.

## Gene Regulation & Genomics

Ken Lau, Ph.D.
Ethan Lee, M.D., Ph.D.
David Miller, Ph.D.
Bill Tansey, Ph.D.
Chris Wright, D. Phil.

## Intracellular Transport

Kristopher Burkewitz, Ph.D.
Kathy Gould, Ph.D.
Guoqiang Gu, Ph.D.
Irina Kaverina, Ph.D.
Ian Macara, Ph.D.
Jason MacGurn, Ph.D.
David M. Miller, Ph.D.
Matthew Tyska, Ph.D.
Alissa Weaver, M.D., Ph.D.
Susan Wente, Ph.D.
Qiangjun Zhou, Ph.D.

## Imaging

Dylan Burnette, Ph.D.
Kathy Gould, Ph.D.
Irina Kaverina, Ph.D.
Ian G. Macara, Ph.D.
Jason MacGurn, Ph.D.
David Miller, Ph.D.
Andrea Page-McCaw, Ph.D.
Matthew Tyska, Ph.D.
Alissa Weaver, Ph.D.
Christopher Wright, D. Phil.

## Metabolism & Diabetes

Kristopher Burkewitz, Ph.D.
Irina Kaverina, Ph.D.
Guoqiang Gu, Ph.D.
Chris Wright, D. Phil.

## Neurobiology

Kristopher Burkewitz, Ph.D.
Chin Chiang, Ph.D.
Vivian Gama, Ph.D.
Rebecca Ihrie, Ph.D.
David Miller, III, Ph.D.
Alissa Weaver, M.D., Ph.D.
Qiangjun Zhou, Ph.D.

## Proteomics

Kristopher Burkewitz, Ph.D.
Kathy Gould, Ph.D.
Jason MacGurn, Ph.D.

## Stem Cell Biology

Chin Chiang, Ph.D.
Vivian Gama, Ph.D.
Guoqiang Gu, Ph.D.
Rebecca Ihrie, Ph.D.
Jonathan Irish, Ph.D.
Ken Lau, Ph.D.

Ethan Lee, M.D., Ph.D.
Ian Macara, Ph.D.
Christopher Wright, D. Phil.

## Systems & Computational Biology

Rebecca Ihrie, Ph.D.
Jonathan Irish, Ph.D.
Irina Kaverina, Ph.D.
Ken Lau, Ph.D.
Marija Zanic, Ph.D.

# CDB Labs Open to Rotation Students

Julie Bastarache
Timothy Blackwell
Kendal Broadie
Kris Burkewitz
Dylan Burnette
Bob Coffey
Mark deCaestecker
Kathy DelGiorno
Kevin Ess
Sabine Furhmann
Vivian Gama
Jim Goldenring
Kathy Gould
Guoqian Gu
Rebecca Ihrie
Jonathan Irish
Irina Kaverina
Ken Lau
Ethan Lee
Ed Levine
Ela Knapik
Jon Kropski
Ian Macara
Jason Macgurn
David Miller
Young-Jae Nam
Andrea Page-McCaw
John Penn
Michelle Southard-Smith
Roland Stein
Bill Tansey
Matt Tyska
Alissa Weaver
Marija Zanic
QJ Zhou
Sandy Zinkel

# Kendal Broadie

PhD 1994, Cambridge University (England)

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phone: 615-936-3937

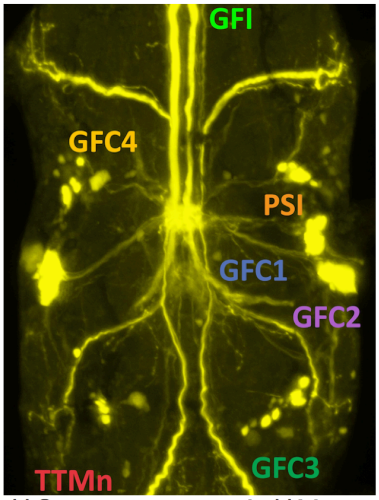
## Research Interests

We employ the immensely powerful *Drosophila* genetic system to study nervous system development, function and plasticity using a combination of forward and reverse genetic approaches. We are interested in both fundamental questions of neurobiology and in the generation of genetic models of heritable neurological disease. Our particular focus is on the synapse, including synaptogenesis, neurotransmission and synaptic plasticity. One foci is activity-dependent synaptic changes and neural circuit remodeling, including connectivity refinement, local translation mechanisms, and the early-life critical periods driving neural circuit optimization. Approaches we use include brain circuit live imaging, optogenetics, transgenic activity reporters, and behavioral studies (learning & memory). A second foci is synapse formation driven by *trans*-synaptic signaling, including synaptic structural and functional differentiation, presynaptic SV cycle, postsynaptic glutamate receptors and extracellular regulation of cell-cell interactions within the synaptomatrix. We study synaptic trafficking, molecular scaffolds, ion channel complexes and binding partners, and developmental calcium signaling. Approaches we use include live imaging at neuromuscular synapses, two-electrode voltage-clamp (TEVC) electrophysiology, transmission electron microscopy (TEM), optogenetics/fluorescent transgenic reports and biochemistry/molecular biology with combined classical and molecular genetics.

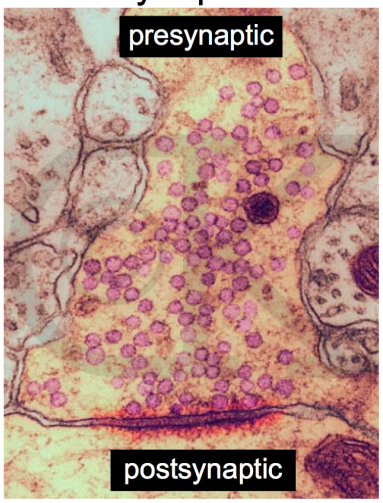
**Core Biology**
Synaptic development
Neurotransmission
Activity-dependent plasticity
Trans-synaptic signaling
Circuit connectivity
Critical period remodeling
Learning and Memory

**Disease Models**
Autism spectrum disorder (ASD)
Intellectual disabilities (ID)
Fragile X syndrome (FXS)
Childhood epilepsies
Congenital Disorders of Glycosylation (CDGs)

Neural Circuits




Synapses




**Synaptogenesis**Neurotransmission**Plasticity**

# Publications: Recent

Vita D.J., Meier C.J. and **Broadie K** (2020). Neuronal Fragile X Mental Retardation Protein regulates glial insulin receptor activation to drive neuron phagocytosis. *Nature Communications* (in revision).

Sears J.C, and **Broadie K** (2020). FMRP-PKA activity negative feedback regulates RNA-binding dependent phase separation in learning and memory circuitry. *Cell Reports* (in revision).

Rushton E, Kopke D.L. and **Broadie K** (2020). Extracellular heparan sulfate proteoglycans and glycan-binding lectins orchestrate *trans*-synaptic signalling. *Journal of Cell Science* (in press).

Kennedy T, Rinker D and **Broadie K** (2020). Genetic background mutations drive neural circuit hyperconnectivity in a Fragile X syndrome model. *BMC Biology* (in press).

Kopke D.L., Leahy S.N., Vita D.J., Lima S.C., Newman Z.L. and **Broadie K** (2020). Carrier of Wingless regulation of *Drosophila* neuromuscular junction development. *eNeuro* 7(2).

# Publications: Older Sampling

Golovin R.M., Vest J, Vita D.J. and **Broadie K** (2019). Activity-dependent remodeling of *Drosophila* olfactory sensory neuron brain innervation during an early-life critical period. *Journal of Neuroscience* 37: 2995-3012.

Kopke D.L., Lima S.C., Alexandre C and **Broadie K** (2018). Notum coordinates synapse development via extracellular regulation of Wingless *trans*-synaptic signalling. *Development* 144: 3499-3510.

Vita D.J. and **Broadie K** (2017). ESCRT-III membrane trafficking misregulation contributes to Fragile X syndrome synaptic defects. *Scientific Reports* 7: 8683.

Parkinson W.M., Dookwah M, Dear M.L., Gatto C.L., Aoki K, Tiemeyer M and **Broadie K** (2016). Synaptic roles of phosphomannomutase type 2 in a new Drosophila congenital disorder of glycosylation disease model. *Disease Models & Mechanisms* 9: 513-527.

Doll C.A. and **Broadie K** (2015). Activity-dependent FMRP requirements in the development of the neural circuitry of learning and memory. *Development* 142: 1346-56.

# Kris Burkewitz

PhD 2012, Vanderbilt University

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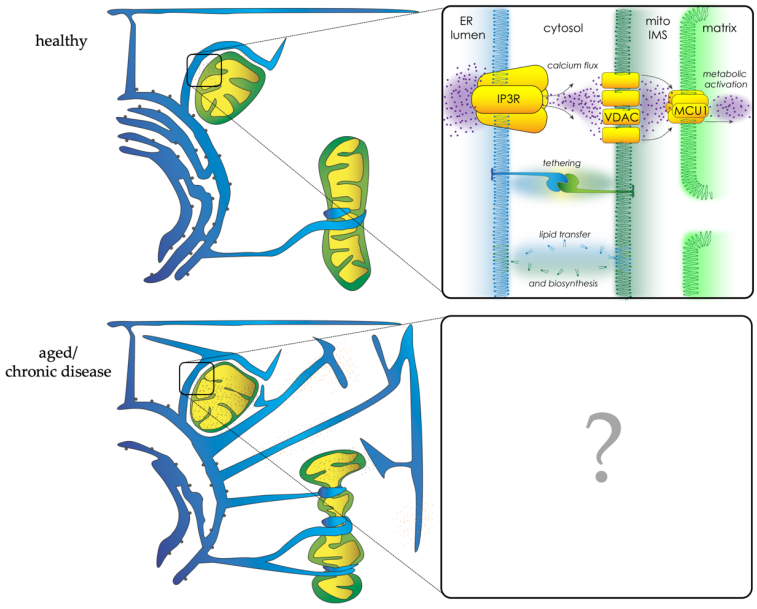
phone: 615-343-6528

## Research Interests

Humans are reaching old age at unprecedented rates, and this has brought to light a new and multi-pronged threat to public health: age-onset diseases, including cardiovascular disease, neurodegeneration, diabetes, and cancer. In recent decades, however, incredible progress has been made in understanding the molecular and genetic basis of aging, revealing that the aging process itself might be targeted therapeutically to simultaneously reduce the risk of ***all*** age-related diseases. Today we have several proof-of-principle interventions capable of extending lifespan in diverse animal models. Among these interventions, a major cluster involves modulating the function of nutrient-sensing and signaling pathways, such as insulin-signaling, mTOR, AMP-activated protein kinase, and the mitochondrial electron transport chain. In all cases, mimicking a starvation-like or nutrient-limited environment promotes healthier aging.

In response to nutrient fluctuations such as those that impact the aging process, some of the most dramatic changes occur at the level of organelles. We are especially interested in mitochondrial and endoplasmic reticulum (ER) networks, the hubs of cellular metabolism, which fuse, fragment, and re-organize their subdomains to adopt or enable alternative functional outputs. Additionally, dysregulation of organelle dynamics is observed in aged animals and in the context of many age-related diseases. Because we are increasingly




**ER and mitochondrial networks are linked.** *Inter-organelle contact sites enable "quasi-synaptic" signaling of ions & metabolites. We now know that ER and mitochondrial morphologies individually are dysregulated in aging and disease contexts: how does this impact their ability to communicate?*

realizing that *organelle form* plays key roles in dictating *organelle function*, we are incredibly excited to understand how organelle dynamics drive outcomes as we age. Broadly, we are interested in questions such as i) how do pro-longevity pathways reprogram ER and mitochondrial form and function, ii) how does remodeling organelle form support the ability of cells to adapt to stress and maintain metabolic homeostasis, iii) how do the observed, age-associated alterations in organelle form and function initiate or exacerbate specific age-related diseases.

Finally, some of our foundational work highlights how important it is that distinct organelles can communicate and coordinate their functions with other compartments in the cell. Specifically, how the ER and mitochondria connect and signal to each other is a major area of exploration (figure), as we find evidence that specific lines of communication (e.g., calcium transfer) are dysregulated in older animals. We strive to use the right experimental model for the question at hand, but rely primarily on *C. elegans* as the foundation for our work because these animals are genetically pliable, transparent throughout life (enabling in vivo imaging of organelles in any tissue), and 'rapid agers.'

# Available Projects

• Genetically interrogate hairpin-domain and other known ER-shaping proteins for roles in mediating the ER remodeling observed in aging animals

• Determine how established pro-longevity interventions (e.g., dietary restriction, reduced insulin/mTOR signaling) protect subcellular architectures from age-related damage

• Develop novel tools and transgenics via CRISPR/Cas9 gene-editing approaches to manipulate and visualize the contacts and communication between organelles in vivo

# Relevant Publications

**Burkewitz K***, **Feng G**, Dutta S, Kelley CA, Steinbaugh M, Cram EJ, Mair WB*. Atf-6 regulates lifespan through ER-mitochondrial calcium homeostasis. *Cell Reports (accepted, 2020). See also BioRxiv pre-print.*
*co-corresponding authors

Weir HJ, Yao P, Huynh FK, Escoubas CE, Goncalves R, **Burkewitz K**, Laboy R, Hirschey MD, Mair WB. Dietary Restriction and AMPK Increase Lifespan via Mitochondrial Network and Peroxisomal Remodeling. *Cell Metabolism* 26(6): 884-96. 2017.

**Burkewitz K***, Weir HJ, Mair WB*. AMPK as a pro-longevity target, In: AMP-activated Protein Kinase, Springer International Publishing, 227-256. 2016.
*co-corresponding authors

Jacobi D, Liu S, **Burkewitz K**, Kory N, Knudsen NH, Alexander RK, Unluturk U, Li X, Kang X, Hyde A, Gangl MR, Farese RV, Walther T, Mair WB, Lee CH. Hepatic Bmal1 regulates rhythmic mitochondrial dynamics and promotes metabolic fitness. *Cell Metabolism* 22(4): 709-720. 2015.

**Burkewitz K,** Morantte I, Weir HJ, Yeo R, Zhang Y, Huynh FK, Ilkayeva OR, Hirschey MD, Grant AR, Mair WB. Neuronal CRTC-1 governs systemic mitochondrial metabolism and lifespan via a catecholamine signal. *Cell* 160(5): 842-55. 2015.

**Burkewitz K,** Zhang Y, Mair WB. AMPK at the nexus of energetics and aging. *Cell Metabolism* 20(1): 10-25. 2014.

# Dylan T. Burnette

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## Research Interests

Using multidisciplinary scientific methodologies, the Burnette lab aspires to understand the forces driving the growth of the human heart on the single cell level and systems level. This requires focusing on the sub-cellular mechanisms controlling contractile system-dynamics, physically coupling these systems between cells, tuning of these systems by extracellular forces (e.g., load), and how these systems switch between driving cell proliferation and cell enlargement.

**Forces driving cell division (hyperplastic growth):** The ability of a cell to divide into two daughter cells is vital for the hyperplastic growth of organs, and the daughter cells must be physically separated. Separation is driven by the ingression of a cleavage furrow, which requires physical forces generated by myosin II-based contractile systems. Experiments using super-resolution microscopy revealed the mechanisms of myosin II assembly and that these coordinate with other cytoskeletal elements during cell shape changes such as cleavage furrow ingression (Fenix et al., 2016, Taneja et al., 2016). There are two different paralogs of myosin II in the cleavage furrow and these were used as tools to reveal an unknown force balance that drives proper cell shape changes during division, as well as, the proper segregation of chromosomes into the resultant daughter cells. (Taneja et al., 2019; Taneja et al., 2020).

**Forces driving cell enlargement (hypertrophic growth).** A large portion of the heart's growth after birth is driven by the enlargement of individual heart muscle cells. Sarcomeres, the contractile units that drive the heartbeat, fill the cytoplasm of a heart muscle cell, and the assembly of new sarcomeres is vital for a cells enlargement. We developed new high-resolution assays that enabled rigorous quantitative analysis of the dynamics of sarcomere assembly in live heart muscle cells derived from iPS cells. The results from these studies supported a unifying model in which sarcomeres arise from precursor structures (i.e., muscle stress fibers) and multiple myosin II paralogs, formin paralogs and substrate adhesion proteins play distinct roles during this transition (Fenix et al., 2018; Neininger et al., 2019; Taneja, Neininger and Burnette, 2020).

**Rotation projects focused on either cell division or cell enlargement are available.**

# Selected Publications


Fenix AM, Taneja N, Buttler CA, Lewis J, Van Engelenburg SB, Ohi R, Burnette DT. (2016) Expansion and concatenation of non-muscle myosin IIA filaments drive cellular contractile system formation during interphase and mitosis. MBoC

Taneja N, Fenix AM, Rathbun L, Millis BA, Tyska MJ, Hehnly H, Burnette DT. (2016) Focal adhesions control cleavage furrow shape and spindle tilt during mitosis. Scientific Reports.

Fenix AM, Neininger AC, Taneja N, Hyde K, Visetsouk MR, Garde RJ, Liu B, Nixon BR, Manalo AE, Becker JR, Crawley SW, Bader DM, Tyska MJ, Liu Q, Gutzman JH, Burnette DT. (2018) Muscle-specific stress fibers give rise to sarcomeres in cardiomyocytes. eLife.

Taneja N and Burnette DT. Myosin IIA drives membrane bleb retraction. (2019) MBoC

Neininger AC, Long JH, Baillargeon SM, Burnette DT. (2019) A simple and flexible high-throughput method for the study of cardiomyocyte proliferation. Scientific Reports.

Taneja N, Bersi MR, Baillargeon SM, Fenix AM, Cooper JA, Ohi R, Gama V, Merryman WD, Burnette DT. (2020) Precise tuning of cortical contractility regulates cell shape during cytokinesis. Cell Reports.

Taneja N*, Neininger AC*, Burnette DT. (2020) Coupling to substrate adhesions drives the maturation of muscle stress fibers into myofibrils within cardiomyocytes. MBoC. * denotes equal contributions


# Graduate student outcomes so far…

*The Burnette lab has had 4 PhD candidates*

**Adian Fenix** (2014-2018)

- 10 papers (2 first authorships); 2 reviews
- Competitive Molecular Biophysics Training Grant
- F31 Predoctoral Fellowship
- AHA Predoctoral Fellowship
- 2019 Steve Hann Outstanding CDB Graduate Student Award
- Currently a postdoc with Charles (Chuck) Murry, University of Washington

**Nilay Taneja** (2015-2020)

- 7 papers (5 first authorships); 1 review
- AHA Predoctoral Fellowship
- 2020 Steve Hann Outstanding CDB Graduate Student Award
- Starting a postdoc with Jennifer Zallen, Memorial Sloan Kettering/HHMI

**Abigail (Abbie) Neininger** (2017-present)

- 6 papers (2 first authorships)
- Competitive Developmental Biology Training Grant
- 2019 Dean's Award for Exceptional Achievement in Graduate Studies.

**James Hayes** (2019-present)

- Competitive Molecular Biophysics Training Grant


# Kathy DelGiorno

PhD 2012, Stony Brook University

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## Research Interests

Pancreatic cancer is the third most deadly cancer in the US and is on course to become second in the near future. This is due to a lack of early diagnostics, as well as a lack of understanding of the steps leading to tumor formation. Pancreatitis is a major risk factor for cancer, and is a serious medical condition in its own right, but how injury leads to tumor formation is incompletely understood. To understand early changes in the pancreas in response to injury or mutation, we use mouse models of pancreas disease in combination with RNA sequencing and different types of microscopy (Figure 1).

By combining these methodologies, we have found that when acinar cells (the major digestive enzyme producing cell type in the pancreas) undergo injury or oncogenic mutation, they become one of a number of different secretory cell types that signal to immune cells, fibroblasts, and other epithelial cells. Our recent work shows that acinar cells can become tuft cells, a chemosensory cell type, which function in tissue healing and inhibit tumor formation by blocking inflammation. We are now exploring how this striking cell type functions in pancreatitis and whether tuft cell secreted products can be co-opted for therapy in patients.

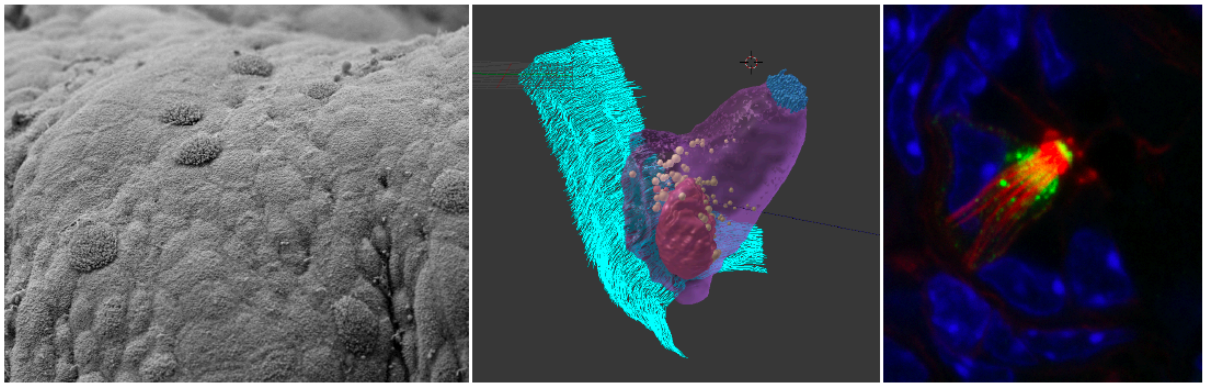

**Figure 1: Imaging modalities used to study pancreatic tuft cells.** Scanning electron microscopy (left), reconstruction of 3D electron microscopy data (middle) and immunofluorescence (right) of pancreatic tuft cells in oncogene-induced lesions.

In addition to tuft cells, acinar cells can become one of a number of different endocrine-like cell types, which have yet to be characterized and studied and could play may major roles in pancreatic injury and tumor formation. Our lab is using single cell RNA sequencing and ultramicroscopy to determine what endocrine-like cell types are present in the diseased pancreas. We use mouse models to genetically eliminate these cells in the context of pancreatitis and/or pancreatic cancer. Based on these results, we evaluate if cells/signaling pathways should be targeted or co-opted for patient benefit.

# Available Projects

- Ultrastructural heterogeneity of emergent pancreatic tuft cells
- The functional role of chemosensory tuft cells in mouse models of pancreatic injury and regeneration
- How epithelial heterogeneity contributes to pancreatitis and pancreatic tumorigenesis

# Publications

**DelGiorno KE#**, Chung C, Vavinskaya V, Maurer HC, Novak SW, Lytle NK, Ma Z, Giraddi RR, Wang D, Fang L, Naeem RF, Andrade LR, Ali WH, Tseng H, Tsui C, Gubbala VB, Ridinger-Saison M, Ohmoto M, Erikson GA, O'Connor C, Shokhirev MN, Hah N, Urade Y, Matsumoto I, Kaech SM, Singh PK, Manor U, Olive KP, and Wahl GM#. "Tuft Cells Inhibit Pancreatic Tumorigenesis in Mice by Producing Prostaglandin D2". *Gastroenterology,* 2020. **# Co-corresponding author.**

Badgley MA, Kremer D, Maurer HC, **DelGiorno KE**, Lee H, Purohit V, Sagalovskiy I, Ma A, Kapillian J, Firl CEM, Decker AR, Sastra SA, Palermo CF, Andrade LR, Sajjakulnukit P, Zhang L, Tolstyka Z, Hirschorn T, Lamb C, Liu T, Gu W, Seeley ES, Stone E, Georgiou G, Manor U, Iuga A, Wahl GM, Stockwell BR, Lyssiotis CA, and Olive KP. "Cysteine depletion induces pancreatic tumor ferroptosis in mice". *Science*, 2020. 368(6486):85-59.

**DelGiorno KE*# and Naeem RF***, Fang HL, Chung C, Ramos C, Luhtala N, O'Connor C, Hunter T, Manor U, and Wahl G**#**. "Tuft cell formation reflects epithelial plasticity in pancreatic injury; implications for modeling human pancreatitis". *Frontiers in Physiology*, 2020. *** Co-first author. # Co-corresponding author.**

Shi Y, Gao W, Lytle NK, Huang P, Yuan X, Dann A, Ridinger M, **DelGiorno KE**, Antal CE, Liang G, Atkins AR, Erikson G, Sun H, Meisenhelder J, Terenziani E, Woo G, Fang L, Santisakultarm T, Manor U, Xu R, Becerra CR, Borazanci E, Von Hoff DD, Grandgenett PM, Hollingsworth MA, Leblanc M, Umetsu SE, Collisson EA, Scadeng M, Lowy AM, Donahue TR, Tannishtha R, Downes M, Evans RM, Wahl GM, Pawson T, Tian R, and Hunter T. "Targeting LIF-mediated paracrine interaction for pancreatic cancer therapy and monitoring". *Nature*, 2019. 569(7754):131-135.

Bailey JM, **DelGiorno KE**, and Crawford HC. "The Secret Origins and Surprising Fates of Pancreas Tumors". *Carcinogenesis*, 2014. 35: p. 1436-1440.

**DelGiorno KE**, Hall JC, Takeuchi KK, Pan FC, Halbrook CJ, Washington MK, Olive KP, Spence JR, Sipos B, Wright CVE, Wells JM, and Crawford HC. "Identification and manipulation of biliary metaplasia in pancreatic tumors". *Gastroenterology*, 2014. 146: p.233-244 e5.

# Kevin Ess

PhD 1996, MD 1998, University of Cincinnati

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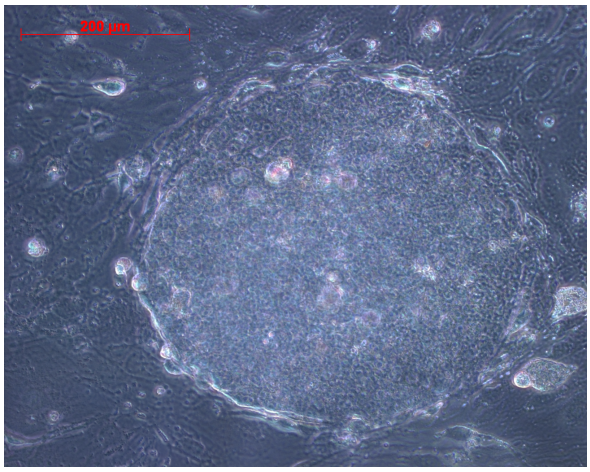
## Research Interests




Our research aims to increase knowledge about the genetic control of brain development and how aberrations in developmental processes lead to neurological disorders including epilepsy, hemiplegia, and autism. Since 2006, the Ess laboratory has focused on tuberous sclerosis complex (TSC) as patients with this disease have prominent brain malformations, white matter disease and a very high prevalence of epilepsy and autism. Resulting from mutations in either the *TSC1* or *TSC2* genes, this disorder involves dysregulation of the mTORC1 and mTORC2 signaling pathways. This has also led to study of *DEPDC5* as this gene also controls mTOR signaling and patients have epilepsy as well as increased risk for SUDEP. Since 2014, we have also been interested in a recently defined disorder, alternating hemiplegia of childhood (AHC), a devastating neurodevelopmental disorder due to mutations in the *ATP1A3* gene.

To study abnormal developmental processes in TSC and AHC, we have utilized diverse model systems including transgenic mice, zebrafish, and human induced pluripotent stem cells (iPSCs). Now principally employing iPSCs from patients with TSC or AHC and employing CRISPR/Cas9 modifications, our basic and translational research approaches should culminate in advanced knowledge about pediatric neurological disorders that hopefully lead to the development of novel and more effective therapies.

## Available Projects

- Study the impact of *ATP1A3* mutations on human neuronal differentiation and function.
    - Genotype/phenotype relationships with different amino acid mutations
    - Response to various drugs including cannabidiol and flunarizine

- Generate *TSC2* mutant human neurons and astrocytes to investigate abnormalities of brain development and hyperexcitability.
    - Differentiate stem cells to glutamatergic and GABAergic neurons, study mechanisms of hyperexcitability
    - Differentiate stem cells to cortical astrocytes, study mechanisms of glia dysfunction

# Select Publications

Simmons C, Thompson C, Cawthon BE, Westlake G, Swoboda KJ, Kiskinis E, **Ess KC**, and George A. Direct Evidence of Impaired Neuronal Na/K-ATPase Pump Function in Alternating Hemiplegia of Childhood. *Neurobiology of Disease*. 2018 Jul;115:29-38. PubMed PMID: 29567111

Darcy A. Krueger, Jamie K. Capal, Paolo Curatolo, Orrin Devinsky, **Ess KC**, Michal Tzadok, Mary K. Koenig, Vinodh Narayanan, Federico Ramos, Sergiusz Jozwiak, Petrus de Vries, Anna C. Jansen, Michael Wong, David Mowat, Stephanie Bruns, David Neal Franz. Safety of mTOR Inhibitors in infants and very young children with Tuberous Sclerosis Complex (TSC): *Eur J Paediatr Neurol.* 2018 Jul 4. pii: S1090-3798(17)31969-4. PMID: 30005812

Rushing, G, Brockman, A, Bollig, M, Leelatian,N, Mobley,B, Irish,J, **Ess,K,** Fu,K, Ihrie, RA. Location-dependent maintenance of an intrinsic susceptibility to mTORC1-driven tumorigenesis. *Life Science Alliance* (2019) PMID: 30910807, PMCID: PMC6435042

Emma H. Neal, Nicholas A. Marinelli, Yajuan Shi, P. Mason McClatchey, Kylie M. Balotin, Dalton R. Gullett, Kameron A. Hagerla, Aaron B. Bowman, Kevin C. **Ess**, John P.6 Wikswo, and Ethan S. Lippmann. A simplified, fully defined differentiation scheme for producing blood-brain barrier endothelial cells from human iPSCs. *Stem Cell Reports.* 2019 Jun 11;12(6):1380-1388. doi: 10.1016/j.stemcr.2019.05.008. PMID: 31189096

Short B, Kozek L, Harmsen H, Zhang B, Wong M, **Ess KC**, Fu C, Nafter R, Pearson M, Carson RP. Cerebral aquaporin-4 expression is independent of seizures in tuberous sclerosis complex. *Neurobiol Dis* 2019 May 9. pii: S0969-9961(19)30118-4. doi: 10.1016/j.nbd.2019.05.003.

Gewin L, Hopp K, Summers M, Harral J, Gaskill C, Nlandu Khodo S, Neelisetty S, Sullivan T, Reese J, Klemm D, Kon V, **Ess K**, Shi W, Majka S. Inactivation of*Tsc2* in Abcg2 Lineage Derived Cells Drives the Appearance of Polycystic Lesions and Fibrosisin the Adult Kidney. *American Journal of Physiology-Renal Physiology* (In Press)

Xie Y, Ng NN, Safrina OS, Ramos CM, **Ess KC**, Schwartz PH, Smith MA, O'Dowd DK. Comparisons of dual isogenic human iPSC pairs identify functional alterations directly caused by an epilepsy associated SCN1A mutation. *Neurobiol Dis*. 2019 Nov 28;134:104627. doi: 10.1016/j.nbd.2019.104627. PMID: 31786370

Klofas L, Short, B, Snow, J, Sinnaeve J, Rushing G, Weinstein W, Westlake, W, Ihrie R, **Ess KC**, Carson, R. DEPDC5 haploinsufficiency drives increased mTORC1 signaling and abnormal morphology in human cortical neurons. *Neurobiology of Disease* (In Press)

Snow, J.P., Westlake, G., Klofas, L.K., Jeon, S., Armstrong, L.C., Swoboda, K.J., George, A.L, Jr., and **Ess, K.C**. Neuronal modeling of alternating hemiplegia of childhood reveals transcriptional compensation and replicates a trigger-induced phenotype. *Neurobiol Dis*, (In Press): https://doi.org/10.1101/2020.04.08.031732

Fu C, Armstrong L, Short B, **Ess KC**. Decreased neocortical interneuron survival and altered growth and behavior in conditional interneuron *Tsc2*-deficient mice. *Neurobiology of Disease* (In Press)

Keller S, Mallack E, Rubin J, Accardo J, Brault J, Corre C, Elizondo C, Garafola J, Jackson-Garcia A, Rhee J, Seeger E, Shullanberger K, Tourjee A, Trovato M, Waldman A, Wallace J, Wallace M, Werner K, White A, **Ess KC**, Becker C, Eichler F. Neurology Care Guidelines for Pediatric Leukodystrophy. *Journal of Child Neurology (In Press).*

# Sabine Fuhrmann

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## Research Interests

The goal of our research is to understand the molecular and cellular mechanisms regulating differentiation, morphogenesis and regeneration of ocular tissues. Questions addressed in our lab include: 1) How is eye development initiated in the anterior neuroepithelium and what factors determine the early steps of eye formation? 2) How is differentiation and morphogenesis of ocular tissues controlled? 3) What are the signals involved in these processes, what are their downstream targets and is there crosstalk between different pathways? 4) How is regeneration of ocular tissues achieved?

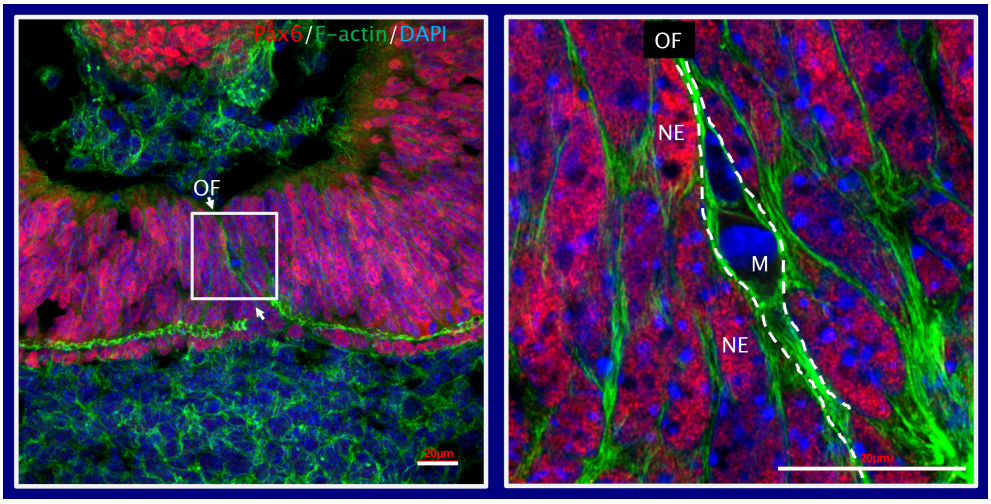


*Figure 1: These images show the optic fissure (OF, between dashed lines on the right image, magnified box from left image). The OF is a transient gap in the ventral eye of the mouse embryo that closes during normal eye development. NE: neuroepithelial cell, labeled for the transcription factor Pax6 in Red, F-actin/Phalloidin in Green, Dapi labeling for nuclei in Blue. M: mesenchymal cell,*

We use conditional inactivation in mice, in combination with tissue culture, molecular, biochemical, and cell biological approaches. We are investigating the function of extracellular signaling pathways (Wnt, Hippo) and intracellular effectors (Cdc42, Nf2) in

ocular morphogenesis and differentiation. Development and adult regeneration of the retinal pigment epithelium (RPE) is another focus in the lab.

## Available Projects

• Analyze differential gene expression of distinct cell populations participating in optic fissure closure.

• Analyze whether Cdc42 is required for normal proliferation in the developing eye.

• Investigate whether pharmacological activation of both Wnt and Hippo signaling stimulates proliferative proliferation.

## Publications

Sun WR, Ramirez S, Spiller KE, Zhao Y, Fuhrmann S. (2020): NF2 fine-tunes proliferation and tissue alignment during closure of the optic fissure in the embryonic mouse eye. BioRxiv 176065 [Preprint]. June 28, 2020. Available from: https://biorxiv.org/cgi/content/short/2020.06.28.176065v1

Pathak A, Stanley EM, Hickman FE, Wallace N, Brewer B, Li D, Gluska S, Perlson E, Fuhrmann S, Akassoglou K, Bronfman F, Casaccia P, Burnette DT, Carter BD. Retrograde Degenerative Signaling Mediated by the p75 Neurotrophin Receptor Requires p150$^{Glued}$ Deacetylation by Axonal HDAC1. Dev Cell. 2018 Aug 6;46(3):376-387.

Yang YP, Ma H, Starchenko A, Huh WJ, Li W, Hickman FE, Zhang Q, Franklin JL, Mortlock DP, Fuhrmann S, Carter BD, Ihrie RA, Coffey RJ. A Chimeric Egfr Protein Reporter Mouse Reveals Egfr Localization and Trafficking In Vivo. Cell Rep. 2017 May 9;19(6):1257-1267.

Alldredge A, Fuhrmann S. Loss of Axin2 Causes Ocular Defects During Mouse Eye Development. Invest Ophthalmol Vis Sci. 2016 Oct 1;57(13):5253-5262.

Bankhead EJ, Colasanto MP, Dyorich KM, Jamrich M, Murtaugh LC, Fuhrmann S. Multiple requirements of the focal dermal hypoplasia gene porcupine during ocular morphogenesis. Am J Pathol. 2015 Jan;185(1):197-213.

Fuhrmann S, Zou C, Levine EM. Retinal pigment epithelium development, plasticity, and tissue homeostasis. Exp Eye Res. 2014 Jun;123:141-50.

# Vivian Gama

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## Research Interests

Our laboratory is investigating the molecular mechanisms by which the dynamic properties of the mitochondria (fission, fusion, motility and mitophagy) affect the most fundamental properties of stem cells – their ability to self-renew or differentiate properly. We are profoundly interested in understanding how "mitochondrial fitness" modulates human brain development (Figure 1).

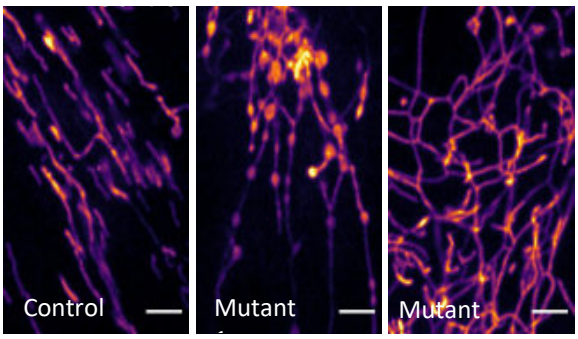



**Figure. 1.** Spinning disk images showing the complexity of the mitochondrial networks in fibroblasts isolated from patients' skin biopsies. Mitochondria were stained using Mitotracker Red. Images show that mitochondria from mutant fibroblasts present with extensive elongation. Scale bar: 5 µm. Patient consent was obtained for the publication of these images.

The underlying mechanisms responsible for the extraordinarily complex cognitive capacity of the human brain remain elusive. A central principle governing brain development is the precise spatiotemporally coordinated birth of, and interactions between, a vast number and types of brain cells. Recent studies from our lab and others, point to a new mechanism – one hinted at previously, but currently poorly understood. We propose that a spectrum of mitochondrial fitness properties could provide internal support to the intrinsic developmental programs of various brain cell types. In humans, defects in mitochondrial homeostasis are linked to conditions such as Leigh syndrome (a neurometabolic disorder), MELAS syndrome (a neurodegenerative disorder), and Autism Spectrum Disorder (a neurodevelopmental disease). But, the mechanisms by which mitochondrial morphology and function influence human brain development are largely unexplored.

A massive challenge in the past has been the lack of appropriate model systems that can reproducibly recapitulate the heterogeneous nature of human brain tissue. Our lab adopted and continues to optimize the long-term culture of neural stem cells, neural progenitor cells, cortical neurons and three-dimensional brain organoids derived from human pluripotent stem cells (Figure 2). Our research program has made advances in modeling complex mitochondrial mechanisms in human systems. We aim to provide new insight into the molecular details underlying neuronal specification, migration and maturation as well as provide new angles to understand developmental brain disorders.

Pluripotent Stem Cell-derived Model Systems

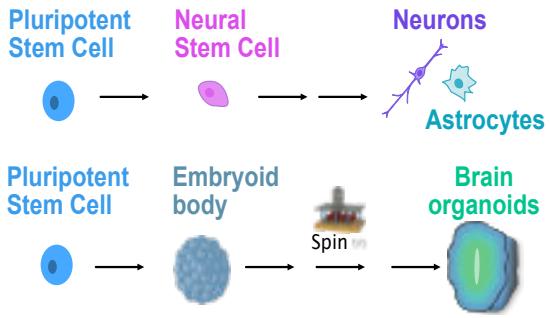
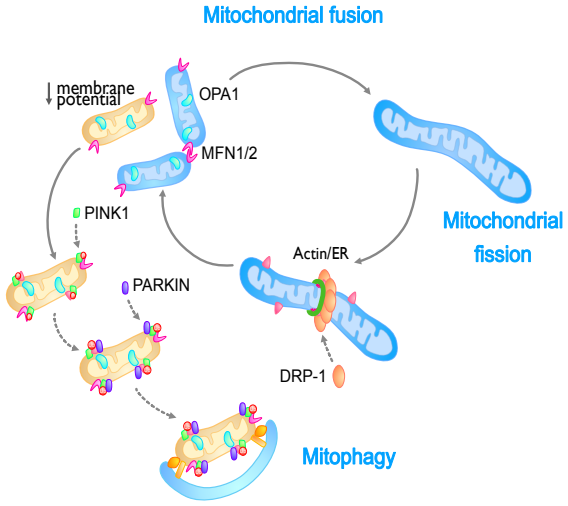



**Figure 2**. The Gama lab uses pluripotent stem cell-derived model systems such as neurons, glia, and brain organoids to reveal the mechanisms by which the dynamic properties of the mitochondria -fusion, fission, mitophagy and motility- impact human brain development.

Dynamic Properties of the mitochondria




# Our Team

Our lab is comprised by a laboratory manager, 6 graduate trainees, and 4 undergraduate students. We are committed to equality, diversity and inclusivity and to create an environment where everyone can thrive and feel welcome.

# Available Projects

Various projects are available based on student's interests. In addition to hPSC-derived models, we use state-of-the-art live imaging, classical biochemistry, proteomics, genetic engineering, and electrophysiological methods. Please contact Vivian.gama@vanderbilt.edu and visit our website to learn more!

# Selected Recent Publications

1. Romero-Morales A., Rastogi A., Temuri H., Rasmussen M., McElroy G., Hsu L., Almonacid P., Millis B., Chandel N.S., Cartailler J-P and Gama V. Human iPSC-derived cerebral organoids model features of Leigh Syndrome and reveal abnormal corticogenesis. bioRxiv: DOI: https://doi.org/10.1101/2020.04.21.054361. In review at Cell Reports.
2. Joshi P., Bodnya C., Rasmussen M., Romero-Morales A.I, Bright A, and Gama V. Modeling the function of BAX and BAK in early human brain development using iPSC-derived systems. Accepted in Cell Death and Disease.
3. Robertson G., Romero-Morales A., Lippmann E., Gama V. 2020. Uncovering cell biology in the third dimension. Mol Biol Cell. Mar 1;31(5):319-323. DOI: 10.1091/mbc.E19-04-0211.
4. Rasmussen M#, Taneja N#, Neininger A, Wang L, Shi L., Robertson G., Knollmann B., Burnette D. and Gama V. MCL-1 inhibition by selective BH3 mimetics disrupts mitochondrial dynamics causing loss of viability and functionality of human cardiomyocytes. iScience. Volume 23, 101015, April 24, 2020. #Co-first authors.
5. Romero-Morales AI#, O'Grady BJ#, Balotin KM, Bellan LM, Lippmann ES*, and Gama V.* 2019. Spin∞ an improved miniaturized spinning bioreactor for the generation of human cerebral organoids from pluripotent stem cells. #Co-first authors. *Co-corresponding authors. HardwareX - Special issue in Neuroscience. Volume 6, October 2019, e00084.
6. Rasmussen M, Kline L.A, Park K.P, Ortolano N.A, Romero-Morales A.I, Anthony C.C, Beckermann K.E, and Gama V. 2018. A non-apoptotic function of MCL-1 in promoting pluripotency and modulating mitochondrial dynamics in stem cells. Stem Cell Reports. 10, Issue 3, p684–692. DOI: 10.1016/j.stemcr.2018.01.005.


# James R. Goldenring

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## Research Interests

***The origin of pre-neoplastic metaplasia in the stomach***

The Goldenring lab has redefined concepts of the origin of metaplasia in the stomach and altered views of the plasticity of differentiated cells by demonstrating, using lineage mapping techniques, that SPEM arises from transdifferentiation of mature chief cells into mucous cell metaplasia. All of these studies have led to a major change in the paradigm for gastric preneoplasia to recognize a pathway from transdifferentiation of chief cells into SPEM in the presence of parietal cell loss to further progression of metaplasia into a proliferative metaplasia under the influence of inflammatory mediators. Transdifferentiation of chief cells into SPEM is an orderly process, which requires down-regulation of the zymogenic machinery in chief cells, upregulation of mechanisms to deal with oxidative stress, autophagy of zymogen granules, and reprograming of the transcriptome to adopt a mucous cell phenotype. The Goldenring lab defined M2-macrophages, IL-13 and IL-33 as critical inflammatory mediators of induction of metaplasia and progression of metaplasia towards more proliferative and intestinalized pre-neoplastic lineages. Ongoing studies now seek to evaluate the role of ILC2 cells as obligate intramucosal immune cells regulating induction of metaplasia. In the past 4 years, The Goldenring lab has provided evidence that activation of Ras in chief cells (using the Mist1-Kras(G12D) mouse) can lead to all of the metaplastic changes observed in humans, including development of SPEM, followed by evolution of intestinal metaplasia and further development of dysplasia. Just as exciting they have shown that treatment with a MEK inhibitor causes arrest of metaplasia and re-establishment of normal gastric lineages. These findings have major implications for possible reversal of metaplasia in patients at high risk for gastric cancer development.

***Apical membrane recycling, epithelial polarity, congenital diarrheal diseases***

Dr. Goldenring has been a leader in the investigation of the roles of specific roles of Rab small GTPases in regulating vesicle trafficking and membrane recycling in polarized cells. The Goldenring lab established MYO5B as a multifunctional regulator of vesicle

trafficking. They demonstrated that MYO5B can bind all of the Rab11 family members (Rab11a, Rab11b and Rab25) as well Rab8a and Rab10. More recently, the lab has focused on how alterations in regulators of apical membrane recycling system can lead to changes in the integrity of the intestinal enterocyte brush border. Their most recent studies have focused on the pathophysiology of inactivating mutations in MYO5B in Microvillus Inclusion Disease (MVID) and the characterization of novel mouse models of MYO5B deletion. Ongoing studies in mouse models as well as mouse and pig enteroid systems, seek to elucidate the molecular mechanisms of apical bulk endocytosis and the complexity of vesicle trafficking and recycling systems involved in apical membrane transport. Additionally, ongoing investigations seek to identify therapeutic options for bypassing the blockade in apical trafficking in MYO5B-deficient enterocytes and in other congenital enterocyte abnormalities.

## Available Projects

• Investigations into the basic cellular mechanisms responsible for chief cell transdifferentiation into metaplasia

• Studies of the basic vesicle trafficking mechanisms responsible for apical membrane trafficking in enterocytes and their alteration in pathological diarrheal diseases.

## Publications

Petersen, C.P., Weis, V.G., Nam, K.T., Sousa, J.F., Fingleton, B and GOLDENRING, J.R. (2014) Macrophages promote progression of spasmolytic polypeptide expressing metaplasia (SPEM) following acute parietal cell loss. Gastroenterology. 144:1727-38.

Petersen, C.P., Meyer, A.R., De Salvo, C., Choi, E., Schlegel, C., Petersen, A., Prasad, N., Levy, S., Pizarro, T. and GOLDENRING, J.R. (2018) A signaling cascade of IL-33 to IL-13 regulates metaplasia in the mouse stomach. Gut. 67:805-817.

Min, J., Vega, P.N., Engevik, A.C., Williams, J.A., Yang, Q., Patterson, L.M., Simmons, A.J., Bilton, R.J., Betts, J.W., Lau, K.S., Magness, S.T., GOLDENRING, J.R. and Choi, E. (2019) Heterogeneity and dynamics of active Kras-induced dysplastic lineages from mouse corpus stomach. Nature Commun. 10(1):5549.

Engevik, A.C, Kaji, I., Postema, M.M., Faust, J.J. Meyer, A.R., Williams, J.A., Fitz, G.N., Tyska, M.J., Wilson, J.M. and GOLDENRING, J.R. (2019) Loss of Myosin Vb Promotes Apical Bulk Endocytosis in Neonatal Enterocytes. J. Cell Biol. 218(11):3647-3662.

Engevik, A.C., Coutts, A.W., Kaji, I., Saqui-Salces, M., Medida, R.L., Meyer, A.R., Kolobova, E., Williams, J.A., Shub, M.D., Carlson, D.F. Melkamu, T. and GOLDENRING, J.R. (2020) Gene Editing of Swine Myosin Vb Results in Microvillus Inclusion Disease and Loss of Apical Sodium Transporters in Enterocytes. Gastroenterology. 158(8):2236-2249.

Kaji, I., Roland, J.T., Engevik, A.C., Goldstein, A.E. and GOLDENRING, J.R. (2020) Lysophosphatidic acid treatment improves brush border maturation and apical SGLT1 activity in Myo5b deficient mice, a model of MVID. Gastroenterology. In. Press.

# Kathy Gould

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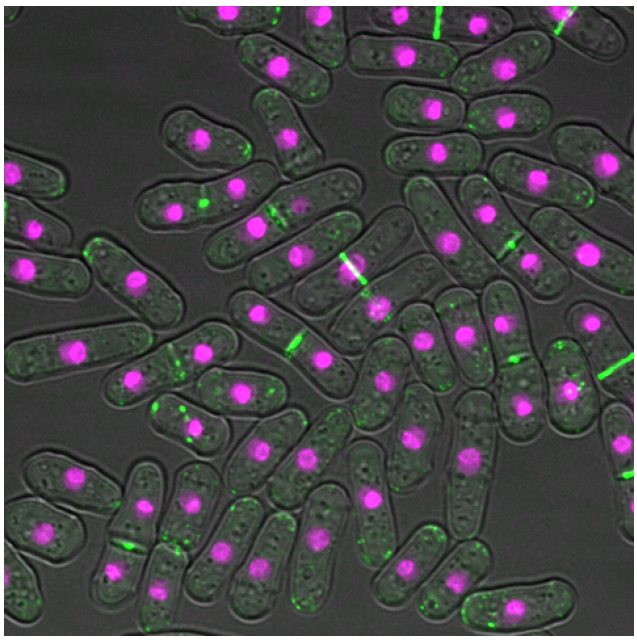
## Research Interests

The Gould laboratory conducts foundational research on the molecular basis of cell division, a highly conserved process central to development and tissue maintenance. Eukaryotic cells accomplish cell division with exquisite spatial and temporal control. A myosin-based cytokinetic ring that constricts to physically separate two new daughter cells. Our lab is fascinated by the question of how the cytokinetic ring is assembled and organized on the plasma membrane. We are also interested in how the assembly and constriction of the cytokinetic ring is coordinated with chromosome segregation to ensure genomic integrity. We have made fundamental, pioneering discoveries in the mechanisms that control cell division using a multi-disciplinary approach that includes super-resolution microscopy, mass spectrometry-based proteomics, genetics, structural biology, biochemistry, and biochemical reconstitution. Our primary model organism is the fission yeast, pictured above, with their nuclei in magenta and a cytokinetic ring protein labeled in green.



## Available Projects

- Analyze how polarity kinases affect the timing of cytokinetic ring assembly and constriction using live cell imaging.
- Determine how myosin II attaches to the plasma membrane for cytokinesis using TurboID coupled to mass spectrometry and other biochemical approaches.
- Learn live cell imaging approaches while contributing to a study of spindle pole body organization critical to mitotic spindle formation.

## Selected Recent Publications

Bhattacharjee, R., Mangione, M.C., Wos., M.P., Chen., J.-S., Snider, C.E., Roberts-Galbraith, R.H., McDonald, NA, Martin, S.G., and Gould, K.L. (2020) DYRK kinase Pom1 drives F-BAR protein Cdc15 from the membrane to promote medial division. *Mol. Biol. Cell.* 31:917-929. DOI: 10.101/mbc.E20-01-0026.

Guillen, R.X., Beckley, J.R., Chen, J.-S., and Gould, K.L. (2020) CRISPR-mediated gene targeting of CK1δ/ε leads to enhanced understanding of their role in endocytosis via phosphoregulation of GAPVD1. *Sci Rep.* 10:6797 doi: 10.1038/s41598-020-63669-2.

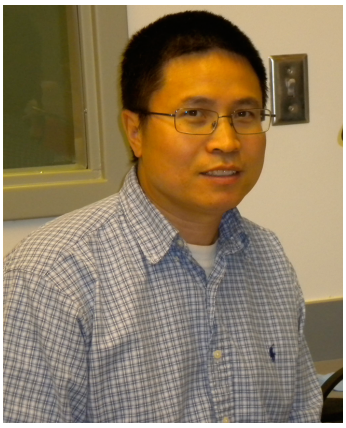
Mangione, M.C., Snider, C.E., and Gould, K.L. (2019) The intrinsically disordered region of the cytokinetic F-BAR protein Cdc15 provides a unique essential function in maintenance of cytokinetic ring integrity. *Mol. Biol. Cell* 30:2790-2801. PMCID:PMC6789166.

Willet, A.H., DeWitt, A.K., Beckley, J.R., Clifford, D.M., and Gould, K.L. (2019) NDR kinase Sid2 drives anillin-like Mid1 from the membrane to promote cytokinesis and medial division site placement. *Curr. Biol.* 29:1055-1063. PMCID:PMC6424596.

Liu, Y.*, McDonald, N.A.*, Naegele, S.M., Gould, K.L.**, and Wu, J.-Q.** (2019) The F-BAR domain of Rga7 relies on a cooperative mechanism of membrane binding with a partner protein during fission yeast cytokinesis. *Cell Reports* 26:2540-2548:e4.*these authors contributed equally to the work, **co-corresponding authors

Snider, C.E., Willet, A.H., Chen, J.-S., Arpağ, G., Zanic, M., and Gould, K.L. (2017) Phosphoinositide-mediated ring anchoring resists perpendicular forces to promote medial cytokinesis. *J. Cell Biol.* 216:3041-3050. PMCID: PMC5626552.*highlighted in JCB special focus on cytokinesis 2017 and 2018

McDonald, N.A., Lind, A.L., Smith, S.E., Li, R., and Gould, K.L. (2017) Nanoscale architecture of the *Schizosaccharomyces pombe* contractile ring. *eLife* 6.:e28865. doi: 10.7554/eLife.28865. PMCID: PMC5779233.



# Guoqiang Gu

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## Research Interests

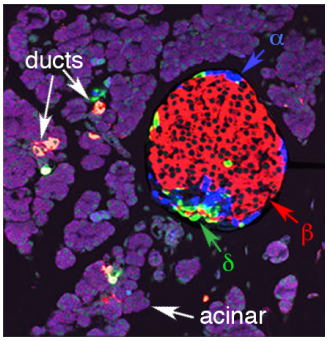


**Figure 1. Tissue/cells in pancreas.** Duct, acinar, α, β, and δ cells are labeled.

We study the mechanisms of pancreas development and function in mouse models and human islets. The pancreas contains exocrine and endocrine islet tissues (Figure 1). The former contains duct and acinar cells that are needed for food digestion. The latter consists of mainly α, β, and δ cells that regulate glucose metabolism. Insufficient number or function of β cells, which secret insulin, results in diabetes. We focused on defining how β cells are made, how they function, and how they stay functional and viable during a long-life span. The post-adolescence islet β cells have poor regenerative activity, underscoring the importance of producing sufficeint number of β cells and maintaining their function and viability. A few questions that we are currently investigting include:

1) *How progenitor cells chose β-cell fate during embryogenesis.* All pancreatic cells in acini, duct, and iselt are derived from a group of seemingly equivalent progenitors. Based on our published studies, we postulate that some unpredictable epigenetic event(s), combined with genetic regulators, can lead to different patterns of DNA methyaltion in some gene enhancers. This creates pools of heterogeneous progenitors with different epigeentic marks that give rise to different cell types, incuding β cells. We are currently examining the lineage of subtypes of progenitors to examine how DNA methylation impacts the production and function of postnatal β cells.
2) *How β cells regulate levels of insulin secretion.* Insulin secretion needs to be tightly regulated for whole-body glucose homeostasis throughout the day, during which multiple blood-glucose surges can occur (after meals). Thus, β cells need to maintain a large storage of insulin vesicles while being able to precisely control of level of secretion. In collaboration with Drs. Kaverina and Jacobson, we have shown that vesicle localization and their sensitivity to intracellular Ca2+, regulated by the microtubule cytoskeleton and Ca2+ sensor proteins, respectively, tune secretion. We are currently testing how glucose stimuli modulate the microtubules and vesicle proteomics to ensure correct dose of insulin secretion.

3) *How $\beta$ cells maintain function and viability.* Insulin secretion is a stressful task. Each β cell synthesizes as high as one million pro-insulin molecules per minute in the ER. Nearly 20% of these are incorrectly folded, which inhibits ER function. Insulin secretion also needs large volume of glucose metabolism, producing reactive oxigen species that damage β cells. Thus β cells constantly activate stress-response to remove the unfolded proinsulin and reactive oxigen species. However, overactivation of stress response will cause β-cell death and dysfunction, subsequently diabetes. We recently showed that a family of transcriptional factors MYTs and co-regulator Sin3 can prevent stress-induced β-cell death/dysfunction. We are currenlty examining the detailed molecular mechanims of this regulation and explore if any chemical activators can target these factors to enhance β-cell function.

# Available Rotation Projects:

**Computational:**

1) Meta analyses of gene expression in islet β cell – identification of alternatively spliced mRNA of key function factors.
2) Pseudo-time ordering of pancreatic progenitor cells along their development to islet cells – identification of feed-forward mechanisms that promote β-cell development.

**Wet lab:**

1) DNA plasmid construction for transgenic mouse production.
2) DNA methylation assays in purified islet cells (DNA fragment cloning followed by sequencing).
3) Islet-isolation from mouse, followed by gene expression assays (immunofluorescence on tissue sections, single cell RNA-sequencing, and cell population RT-PCR).

# Recent Publications:

Ho K et al., Glucose regulates microtubule disassembly and the dose of insulin secretion via tau phosphorylation. Diabetes. 2020; In press.

Yang X et al., Coregulator Sin3a promotes postnatal murine β-cell fitness by regulating genes in $Ca^{2+}$ homeostasis, cell survival, vesicle biosynthesis, glucose metabolism, and stress response. *Diabetes.* 2020; 69, 1219-1231.

Hu R et al., Myt Transcription Factors prevent stress-response gene overactivation to enable postnatal pancreatic β-cell proliferation, function, and survival. *Dev. Cell.* 2020; 53, 754-779.

Liu J et al., Neurog3-Independent Methylation Is the Earliest Detectable Mark Distinguishing Pancreatic Progenitor Identity. *Dev. Cell*. 2019; 48, 49-63.

Huang C et al., Synaptotagmin 4 Regulates Pancreatic β Cell Maturation by Modulating the $Ca^{2+}$ Sensitivity of Insulin Secretion Vesicles. *Dev. Cell*. 2018; 45, 347-361.

Zhu X et al., Microtubules Negatively Regulate Insulin Secretion in Pancreatic β Cells. *Dev. Cell.* 2015; 34, 656-68.

# Rebecca Ihrie

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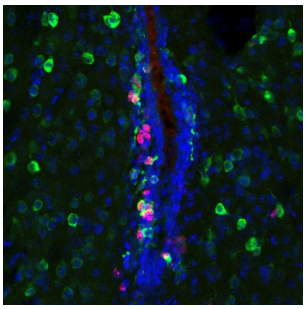
## Research Interests

The Ihrie lab is fascinated by the signals that drive lineage commitment, growth, and differentiation in the largest stem cell niche in the mammalian brain. We are especially interested in how these processes go awry in neurodevelopmental disorders and brain tumors. Using high-dimensional imaging and flow cytometry, we work with collaborators in neurology, neurosurgery, and systems biology to study stem cells, organoids, and tissue from mouse and human brain. For more details and recent lab news, feel free to explore our website and Twitter feed.

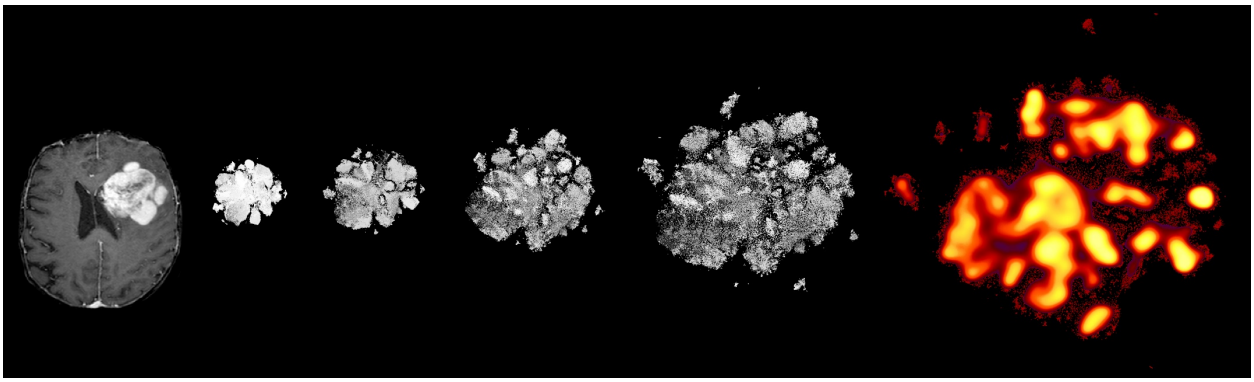
## Available Projects

I work with trainees to craft projects that unite their interests with those of the lab. Current example projects are:

- Dissecting how contact with the stem cell niche results in more aggressive brain tumors using single-cell approaches
- Mapping the effects of mutations in the *TSC1/2* genes on brain development using patient-derived induced pluripotent stem cells and organoid cultures
- Identifying regulators of mTOR in populations of neural stem cells with differing tumor-forming activity.



*Mash1 (progenitors) and p-S6 (mTORC1 activity) in the stem cell niche*



*Banner image from Leelatian and Sinnaeve et al, eLife 2020*

## Lab Environment

*2019 PDB retreat*

The lab is part of the Department of Cell & Developmental Biology, the Program in Developmental Biology, the Program in Cancer Biology, the Vanderbilt Center for Stem Cell Biology, the Vanderbilt Brain Institute, and several other centers. Interested graduate students have also joined the Vanderbilt Program in Molecular Medicine and Clinical Neuroscience Scholars (although neither is required) and completed internships and career training through the ASPIRE program.

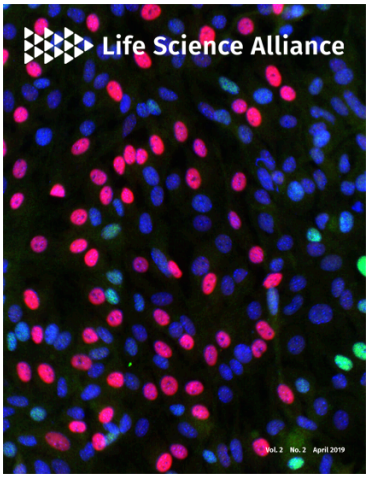
The lab and PI are committed to welcoming and supporting trainees of all genders, races, and groups. Lab members are encouraged to pursue external presentations and travel to relevant conferences is supported. We also build lab community through an annual off-site retreat with a collaborating lab, yearly “state of the lab” lunches, seasonal parties, and happy hour gatherings (currently online).

## Representative Publications

N. Leelatian, J. Sinnaeve, A.M. Mistry, S.M. Barone, K.E. Diggins, A.R. Greenplate, K.D. Weaver, R.C. Thompson, L.B. Chambless, B.C. Mobley, R.A. Ihrie*, J. M. Irish* (* - co-corresponding) (2020). Unsupervised machine learning reveals risk-stratifying glioblastoma cells. *eLife* 9:e56879.

Rushing G.V., A.A. Brockman, M.K. Bollig, N. Leelatian, B.C. Mobley, J.M. Irish, K. C. Ess, C. Fu, R.A. Ihrie (2019). Location-dependent maintenance of an intrinsic susceptibility to mTORC1-driven tumorigenesis. *Life Science Alliance.* 2(2).

Mistry A.M., D. Wooten, T. Davis, B.C. Mobley, V. Quaranta, R.A. Ihrie (2019). Ventricular-Subventricular Zone Contact by Glioblastoma is Not Associated with Molecular Signatures in Bulk Tumor Data. *Scientific Reports* 9(1):1842.




Leelatian N., D.B. Doxie, A.R. Greenplate, B.C. Mobley, J.M. Lehman, J. Sinnaeve, R.M. Kauffman, J. A. Werkhaven, A.M. Mistry, K.D. Weaver, R.C. Thompson, P.P. Massion, M.A. Hooks, M.C. Kelley, L.B. Chambless, R.A. Ihrie, and J.M. Irish (2017). Single cell analysis of human tissues and solid tumors with mass cytometry. *Cytometry B*. 92(1): 68-78.

Mistry A.M.; M. Dewan; G. White-Dzuro; P. Brinson; K.D. Weaver; R.C. Thompson; R.A. Ihrie; L.B. Chambless. Decreased Survival in Glioblastomas is Specific to Contact with the Ventricular-Subventricular Zone, not Subgranular Zone or Corpus Callosum (2017). *J Neurooncol.* 132(2):341-349.

# Jonathan Irish

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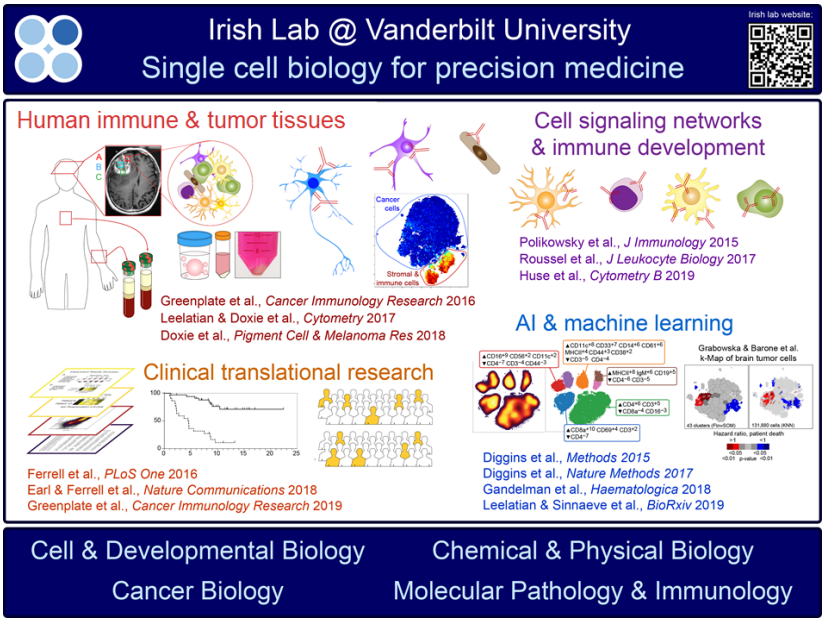
## Research Interests

It is an exciting era for cell biology. Great potential exists to detect diseases earlier and to tailor a patient's therapy to the biological alterations detected in the cells of their disease. By better understanding biological systems which control development and cell-cell interactions in healthy and diseased contexts, we can learn to program cells to become therapeutic agents or target signaling events to specifically kill cancer cells.

A defining feature of our research is the use of primary human tissue as a model system to reveal new cell types and dissect cell signaling mechanisms in healthy development and disease. Prior graduate students have developed single cell functional assays to measure the essential biology of millions of individual cells from patient biopsies and to pinpoint cell subsets that stratify clinical risk. Some graduate students have discovered new types of cells present in human diseases. Others created new machine learning algorithms to teach computers to identify cell types. Our research projects often make use of both experimental bench and computational analysis techniques. Rotation student projects can be 100% wet lab cell biology, 100% dry lab data science, or a mix.

The figure to the right presents four research areas in the lab and notes example publications from each. The bottom notes four graduate programs closely associated with the lab. We collaborate widely with researchers within Vanderbilt and around the world and are used to working remotely with each other and collaborators. We are strongly committed to inclusion and diversity, within our group and beyond.



# Available Projects in Irish Lab

• Dissecting human treatment responses *in vivo*, including COVID-19 and cancer
Related news: https://news.vanderbilt.edu/2020/05/29/artificial-intelligence-offers-a-chance-to-optimize-covid-19-treatment-in-international-partnership/

• Neural stem cell models using primary tissue to target aggressive brain tumor cells
Related news: https://news.vanderbilt.edu/2020/06/24/discovery-of-aggressive-cancer-cell-types-by-vanderbilt-researchers-made-possible-with-machine-learning-techniques/

• Abnormal inflammatory cell signaling in children and adults with immune disorders

• Natural product discovery and classification for translational single cell biology

• Data science approaches for biology and medicine

# Selected Publications (► indicates first author was Irish lab student)

► Leelatian N*, Sinnaeve J*, Mistry AM, Barone SM, Diggins KE, Greenplate AR, Weaver KD, Thompson RC, Chambless LB, Mobley BC, Ihrie RA**, Irish JM**. *Unsupervised machine learning reveals risk stratifying glioblastoma tumor cells*. **eLife** 2020. 10.7554/eLife.56879

► Greenplate AR, McClanahan DD, Oberholtzer BK, Doxie DB, Roe CE, Diggins KE, Leelatian N, Rasmussen ML, Kelley MC, Gama V, Siska PJ, Rathmell JC, Ferrell PB, Johnson DB, Irish JM. *Computational immune monitoring reveals abnormal double negative T cells present across human tumor types*. **Cancer Immunology Research** 2019. 10.1158/2326-6066.CIR-17-069

► Gandelman JS, Byrne MT, Mistry AM, Polikowsky HG, Diggins KE, Chen H, Lee SJ, Arora M, Cutler C, Flowers ME, Pidala J, Irish JM**, Jagasia M**. *Machine Learning Reveals Chronic Graft-Versus-Host Disease Phenotypes and Stratifies Survival After Stem Cell Transplant for Hematologic Malignancies*. ***Haematologica*** 2019 10.3324/haematol.2018.193441

Earl DC*, Ferrell PB*, Leelatian N, Froese J, Reisman B, Irish JM**, Bachmann BO**. *Discovery of human cell selective effector molecules using single cell multiplexed activity metabolomics*. **Nature Communications** 2018. 10.1038/s41467-017-02470-8

► Doxie DB, Greenplate AR, Gandelman JS, Diggins KE, Roe CE, Dahlman KB, Sosman JA, Kelley MC, Irish JM. *BRAF and MEK inhibitor therapy eliminates nestin expressing melanoma cells in human tumors*. **Pigment Cell & Melanoma Research** 2018. 10.1111/pcmr.12712

► Diggins KE, Greenplate AR, Leelatian N, Wogsland CE, Irish JM. *Characterizing cell subsets in heterogeneous tissues using marker enrichment modeling*. **Nature Methods** 2017. 10.1038/nmeth.4149

Irish JM, Myklebust JH, Alizadeh AA, Houot R, Sharman JP, Czerwinski DK, Nolan GP, Levy R. *B-cell signaling networks reveal a negative prognostic human lymphoma cell subset that emerges during tumor progression*. **PNAS** 2010. 10.1073/pnas.1002057107

Irish JM, Hovland R, Krutzik PO, Perez OD, Bruserud Ø, Gjertsen BT, Nolan GP. *Single cell profiling of potentiated phospho-protein networks in cancer cells*. **Cell** 2004. 10.1016/j.cell.2004.06.028

Full List of Publications on Google Scholar

# Irina Kaverina

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## Research Interests

Microtubules (MTs) are dynamic biopolymers, which serve as major trafficking highways in cells. MT-dependent transport is critical for all eukaryotic cell types, and disturbance of MT networks underlies many human diseases, including cancer, neurodegenerative diseases, and diabetes.

In the Kaverina Lab at Vanderbilt, we study the organization and regulation of MT networks and the relevance of their functions to disease. Our overall goal is to learn how interphase MT networks are built to make sure that intracellular cargos are efficiently delivered to their destinations. Because the demands on the intracellular transport vary depending on the cell cycle stage and metabolic context, MT tracks are constantly remodeled to meet specific cellular needs. We study the mechanisms that rule these remodeling processes. One of our favorite models is the motile proliferating cell, where the cytoplasm rapidly adjusts to the cell cycle signaling. Our other fascination is pancreatic beta cells (Figure 1), which are capable to acutely rearrange themselves to achieve an insulin secretion impulse in response to a glucose stimulus, and which we study in the context of the diabetes cause and cure. A variety of experimental and computational rotation projects are available to study either of those models.

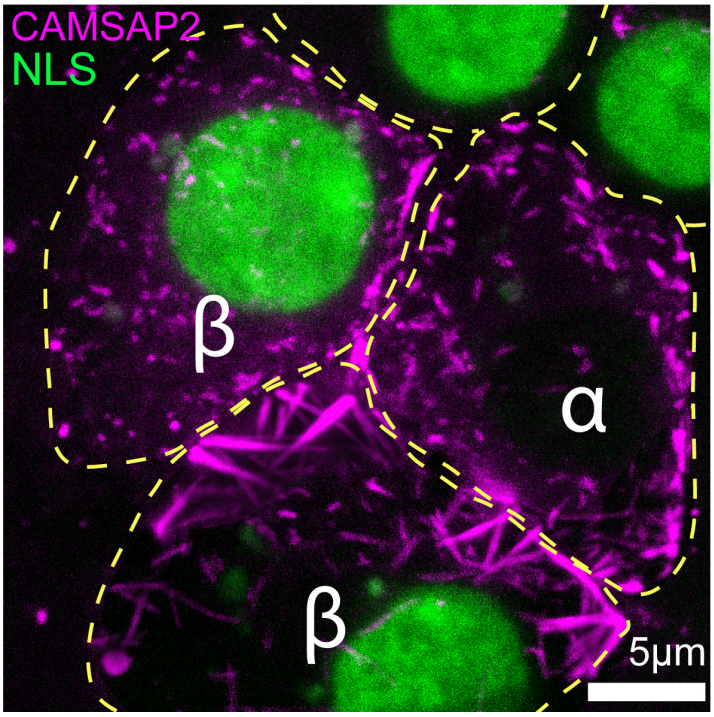


*Figure 1: Pancreatic islet β cells (labelled by a genetically encoded nuclear marker, green) expressing a MT minus end binding protein CAMSAP2 (magenta) at different levels.*

# Available Project Examples

• Analyze which MT-dependent molecular motors drive cell-cycle-dependent Golgi reorganization.

• Analyze how MT-associated proteins regulate transport of secretory insulin vesicles.

# About Us

The Kaverina lab has a history of discovery while challenging dogmas by approaching them from unusual angles and by noting important, previously overlooked phenomena. Our favorite technique is biological light microscopy, which we utilize in a wide range of powerful cutting-edge approaches. We embrace multi-disciplinary approaches and actively collaborate with developmental biologists (Guoqiang Gu lab @ CDB), biophysisists (Marija Zanic lab @ CDB) and computational scientists (William Holmes lab @ Physics&Astronomy). Every Kaverina laboratory trainee over the years has been granted their own independent fellowship(s), because they truly own their beautifully designed projects and publish breakthrough studies. Kaverina laboratory research is generously funded by NIH NIGMS, NIDDK, and AHA.

# Selected Publications

Efimov A., Kharitonov A., Miller P.M., .., Akhmanova A., Kaverina I. Asymmetric CLASP-dependent nucleation of non-centrosomal microtubules at the trans-Golgi network. Dev. Cell. 2007, 12:917-30.

Miller P.M., Folkmann A.W., Maia A.R.R., Efimova N, Efimov A., Kaverina I. Golgi-derived CLASP-dependent Microtubules Control Golgi Organization and Polarized Trafficking in Motile Cells. Nat Cell Biol. 2009, 11:1069-80.

Arnette C*, Efimova N, Zhu X, Clark GJ, Kaverina I. Microtubule segment stabilization by RASSF1A is required for proper microtubule dynamics and Golgi integrity. Mol Biol Cell. 2014, 25:800-10.

Grimaldi AD, Maki T, Fitton BP, Roth D, Yampolsky D, Davidson MW, Svitkina T, Straube A, Hayashi I, Kaverina I. CLASPs are required for proper microtubule localization of End-binding proteins. Dev Cell. 2014, 30:343–352.

Zhu X, Hu R, Brissova M, Stein RW, Powers AC, Gu G, Kaverina I. Microtubules negatively regulate insulin secretion in pancreatic β cells. Dev. Cell. 2015, 34:656-68.

Trogden KP, Zhu X, Lee JS, Wright CVE, Gu G, Kaverina I. Regulation of Glucose-Dependent Golgi-Derived Microtubules by cAMP/EPAC2 Promotes Secretory Vesicle Biogenesis in Pancreatic β Cells. Curr Biol. 2019, 29:2339-2350.

Bracey KM*, Ho KH, Gu G, Kaverina I (co-corr), Holmes WR. Microtubules Regulate Localization and Availability of Insulin Granules in Pancreatic Beta Cells. Biophys J. 2020, 118:193-206.

Frye K*, Renda F, Fomicheva M, Zhu X, Gong L, Khodjakov A, Kaverina I. Cell Cycle-Dependent Dynamics of the Golgi-Centrosome Association in Motile Cells. Cells. 2020 9(5):1069.

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*Underlined, Kaverina lab trainees.*
**, under-represented minorities.*

# Ela W. Knapik

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## Research Interests

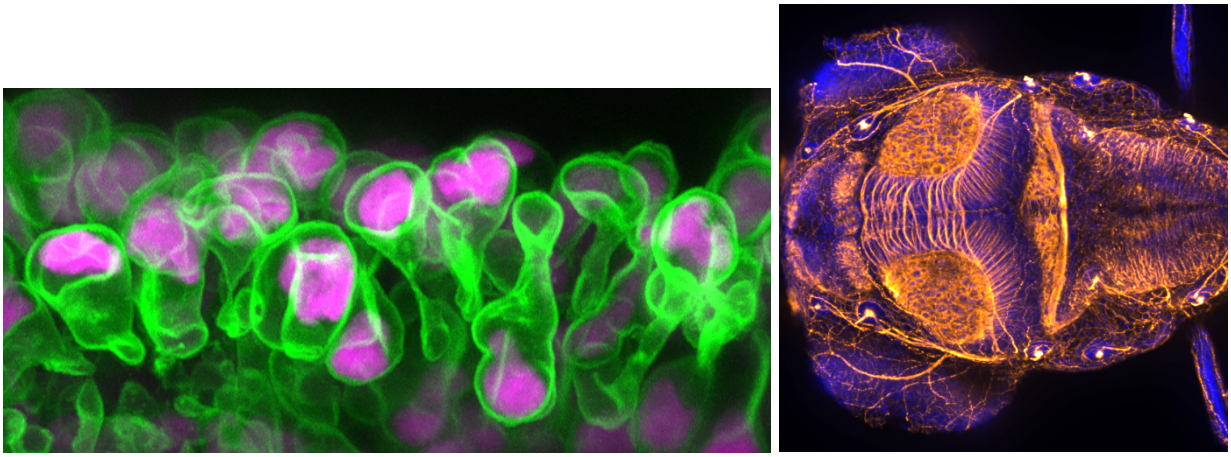


*Figure. Left, Live image of zebrafish chondrocytes in ric1-deficient fish. Right, Axonal projections in zebrafish brain at 5 days post fertilization. (Unlu et al., Nature Medicine 2020).*

The human craniofacial development is affected in many common birth defects and is comorbid with other organs' dysfunction leading to common and rare diseases. Similar to the CATIFA syndrome we have recently described, disruption of other genes contributes to pleiotropic clinical presentation and loss of cellular functions. Our laboratory is interested in understanding basic cellular mechanisms of protein transport and secretion using zebrafish and patients' cells in culture, sophisticated omics sciences and high-resolution in vivo imaging, in order to explain human syndromes ranging from neuropsychiatric and eye disorders to craniofacial dysmorphology.

### Research focuses on:

- Modeling of human disease variants in zebrafish and cell culture (Unlu et al., 2020)
- Extracellular matrix trafficking mechanisms (Cox et al., 2018)
- Evaluations of neuropsychiatric disorders and developmental phenotypes (Levic et al., 2015)
- Modeling of variants in common diseases for drug screening and development (Unlu et al., 2019)

**Methods:**

- CRISPR, (KO, KI),
- Live microscopy and confocal imaging,
- Embryology and Dev. Biology,
- Experimental omics,
- Molecular Biology,
- Zebrafish & Cell culture

## Available Projects

- Phenotypic characterization of the Ric1-deficient brain in transgenic zebrafish
- CRISPR knock in of CATIFA pathogenic variant
- Analysis of the novel craniofacial mutants and chondrocyte cell shape changes

## Publications

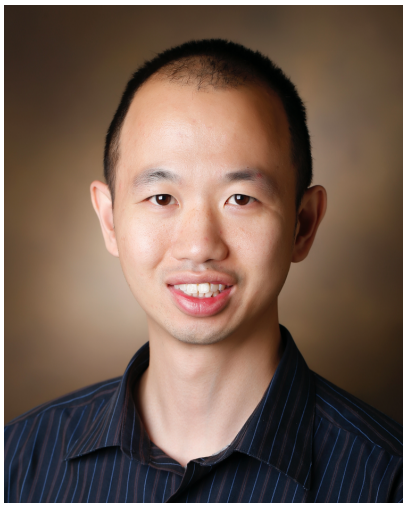
Bayraktar EC, La K, Karpman K, Unlu G, Ozerdem C, Ritter DJ, Alwaseem H, Molina H, Hoffmann H-H, Millner A, Atilla-Gokcumen GE, Gamazon ER, Rushing AR, Knapik EW, Basu S, Birsoy K. Metabolic coessentiality mapping identifies C12orf49 as a regulator of SREBP processing and cholesterol metabolism, ***Nature Metabolism*****,** 2020;2(6):487-498. doi: 10.1038/s42255-020-0206-9

Unlu G, Qi X, Gamazon E, Melville DB, Patel N, Rushing AR, Hashem M, Al-Faifi A, Chen R, Li B, Cox NJ, Alkuraya FA, Knapik EW. Phenome-based approach identifies RIC1-linked Mendelian syndrome through zebrafish models, biobank associations and clinical studies. ***Nature Medicine*** 2020;26(1):98-109. doi:10.1038/s41591-019-0705-y

Unlu G, Gamazon ER, … Knapik EW, and Cox NJ. GRIK5 Genetically Regulated Expression Associated with Eye and Vascular Phenomes: Discovery through Iteration among Biobanks, Electronic Health Records, and Zebrafish. ***Am J Hum Genet*****.** 2019;104(3):503-519. doi:10.1016/j.ajhg.2019.01.017

Cox NJ, Unlu G, … Knapik EW, Boyce M. Dynamic glycosylation governs the vertebrate COPII protein trafficking pathway. ***Biochemistry***. 2018 Jan 9;57(1):91-107. PMID: 29161034; PMCID: PMC5767944; DOI: 10.1021/acs.biochem.7b00870

The Knapik Lab



# Ken Lau

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## Research Interests

We are a lab that utilizes data science approaches to model cell-microbe interaction networks. We consider every one of the 30 plus trillion cells in the body to be unique, and thus, utilize new technologies to profile tissues at single-cell resolution. Resulting data consisting of thousands of data points and measurements are analyzed by data science computational techniques. Our system of study is the mammalian small and large intestine, which are dynamic organs that undergo stem cell-driven renewal of multiple functional cell types every 3-5 days.

We are interested in the following questions: 1) How altering different cell types in the gut affect inflammation, 2) how interactions between the microbiome and epithelial cells contribute to malignant progression of colon cancer, 3) how the origins of colon cancer stem cells affect responses to therapy, 4) how microenvironmental context can dictate outcome given the activation of the same pathways.

## Available Projects

- Mechanisms of inflammation suppression or promotion by microbiome-stimulated cell types
- Cell-of-origins of tumor stem cells as related to metastasis and immunotherapy
- Computation analysis of large single-cell datasets to model human colon cancer progression

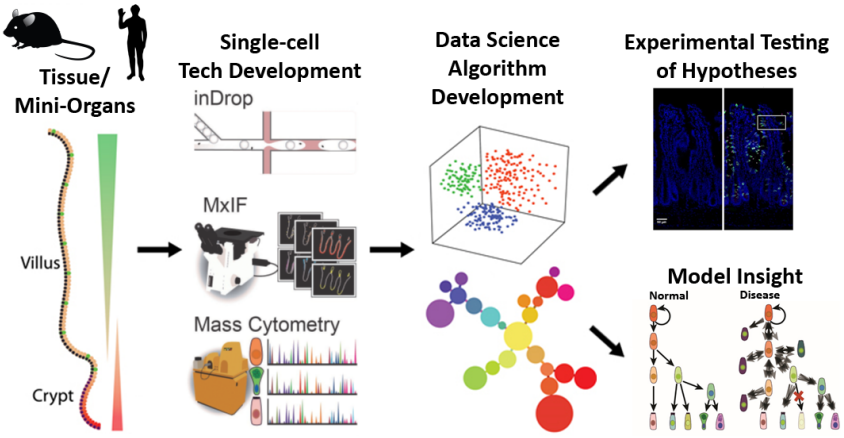


*Figure 1: Integrated dry and wet lab approach for understanding complex tissue composition, architecture, and function.*

# Publications (by students)

Southard-Smith AN, Simmons AJ, Chen B, Jones AL, Ramirez Solano MA, Vega PN, Scurrah CR, Zhao Y, Brenan MJ, Xuan J, Shrubsole MJ, Porter EB, Chen X, Brenan CJH, Liu Q, Quigley LMN, **Lau KS**. Dual indexed library design enables compatibility of in-Drop single-cell RNA-sequencing with exAMP chemistry sequencing platforms. BMC Genomics 21: 456, 2020.

Heiser CN, **Lau KS.** A quantitative framework for evaluating single-cell data structure preservation by dimensionality reduction techniques. Cell Rep 31(5):107576, 2020.

Min J*, Vega PN*, Engevik AC, Williams JA, Yang Q, Patterson LM, Simmons AJ, Bilton RJ, Betts JW, **Lau KS**, Magness ST, Goldenring JR, Choi E. Heterogeneity and dynamics of active Kras-induced pre-neoplastic lineages from mouse stomach. Nat Commun, 10(1): 5549, 2019

Scurrah CR, Simmons AJ, **Lau KS**. Decoding cancer cell signaling pathways by single-cell mass cytometry. Methods Mol Biol, 1884: 215-229, 2019.

Chen B, Herring CA, **Lau KS**. pyNVR: Investigating factors affecting feature selection from scRNA-seq data for lineage reconstruction. Bioinformatics, 35(13): 2335-2337, 2019.

Liu Q, Herring CA, Shen Q, Ping J, Simmons AJ, Chen B, Banerjee A, Gu G, Coffey RJ, Shyr Y, **Lau KS.** Quantitative assessment of cell population diversity in single-cell landscapes. PLoS Biol, 16(10): e2006687, 2018.

Herring CA, Banerjee A, McKinley ET, Simmons AJ, Ping J, Roland JT, Franklin JL, Gerdes MJ, Liu Q, Coffey RJ, **Lau KS**. Unsupervised trajectory analysis of single-cell RNA-seq and imaging data reveals alternative tuft cell origins in the gut. Cell Syst, 6(1): 37-51, 2018.

Kim SW, Ehrman J, Ahn MR, Kondo J, Mancheno Lopez AA, Oh YS, Kim, HX, Crawley SW, Goldenring JR, Tyska MJ, Rericha RC, **Lau KS.** Shear stress induces non-canonical autophagy in intestinal epithelial monolayers. Mol Biol Cell, 28(22): 3034-56, 2017.

Simmons AJ, Scurrah CR, McKinley ET, Herring CA, Irish JM, Washington MK, Coffey RJ, **Lau KS**. Impaired coordination between signaling pathways is revealed in human colorectal cancer using single-cell mass cytometry of archival tissue blocks. Sci Signal, 9(449): rs11, 2016.

Simmons AJ*, Banerjee A*, McKinley ET, Scurrah CR, Herring CA, Gewin LS, Masuzaki R, Karp SJ, Franklin JL, Gerdes MJ, Irish JM, Coffey RJ, **Lau KS.** Cytometry-based single cell analysis of intact epithelial signaling reveals MAPK activation divergent from TNF-α-induced apoptosis in vivo. Mol Syst Biol, 11(10):835, 2015.

# Ethan Lee

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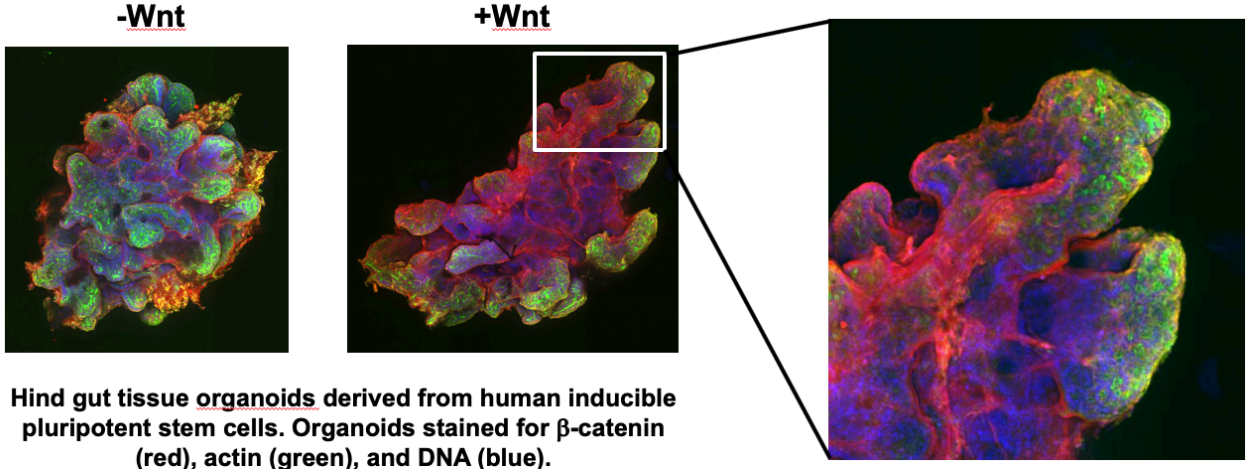
## Research Interests

The Wnt pathway is an evolutionarily conserved signaling pathway present in metazoans from *Drosophila* to humans. Given that the Wnt pathway is involved in the genesis of a wide variety of human diseases (e.g., over 90% of all colorectal cancers), there is an intense effort to develop therapeutics that target this pathway. Unfortunately, in part due to our incomplete understanding of the detailed mechanism of Wnt signal transduction, progress in developing therapeutics that target this pathway has been slow, and no Wnt inhibitors are currently in clinical use. Our lab's overarching goal is to understand the underlying biochemical mechanisms by which a Wnt signal is propagated to ultimately coordinate the formation of tissues, organs, and limbs and to understand how its misregulation can lead to disease states. In over more than a decade, my laboratory has 1) developed the first biochemical system that recapitulated key reactions of the Wnt pathway, 2) developed the first mathematical model (Lee-Heinrich model) of the Wnt pathway, 3) provided evidence for a mechanism involving receptor-mediated signaling to the cytoplasm, and 4) identified a small molecule




**Hind gut tissue organoids derived from human inducible pluripotent stem cells. Organoids stained for β-catenin (red), actin (green), and DNA (blue).**

inhibitor of the Wnt pathway that has been designated by the FDA as an orphan drug for a familial precancerous disease (familial adenomatous polyposis).

Our recent work focuses on 1) dissecting a newly identified mechanism by which loss of the APC tumor suppressor leads to activation of Wnt cell surface receptors and 2) characterization of kinases and ligases and deubiquitinases that regulates receptor activation and nuclear target gene transcription.

## Available Projects

• Develop novel cell lines for studying Wnt signaling using CRISPR-Cas9 editing.

• Analyze and characterize new Wnt genes identified from genome-scale *in vitro* and *in vivo* screens.

## Publications (Select)

Cabel CR, Alizadeh E, Robbins DJ, Ahmed Y*, **Lee E***, and Thorne CA*. (2019) Single-Cell Analyses Confirm the Critical Role of LRP6 for Wnt signaling in APC-Deficient Cells. *Dev Cell* **49,** 827-8. *Co-corresponding authors

Saito-Diaz, K, Benchabane, H, Tiwari, A, Tian, A, Li, B, Thompson, JJ, Hyde, AS, Sawyer, LM, Jodoin, JN, Santos, E, Lee, LA, Coffey, RJ, Beauchamp, RD, Williams, CS, Kenworthy, AK, Robbins, DJ, Ahmed, Y, **Lee, E.** (2018) APC Inhibits Ligand-Independent Wnt Signaling by the Clathrin Endocytic Pathway. *Dev Cell* **44,** 566-581.

Broadus, MR, Chen, TW, Neitzel, LR, Ng, VH, Jodoin, JN, Lee, LA, Salic, A, Robbins, DJ, Capobianco, AJ, Patton, JG, Huppert, SS, and **Lee, E.** (2016) Identification of a paralog-specific Notch1 intracellular domain degron. *Cell Rep **15**, 1920-9.*

Hanson, AJ, Wallace, HA, Freeman, TJ, Beauchamp, RD, Lee, LA, **Lee, E.** (2012) XIAP mono-ubiquitylates Groucho/TLE to promote canonical Wnt signaling. *Mol Cell* **45**, 619-28. PMCID: PMC3299836

Thorne, CA, Hanson, AJ, Schneider, J, Tahinci, E, Orton, D, Cselenyi, CS, Jernigan, KK, Meyers, KC, Hang, BI, Waterson, AG, Kim, K, Melancon, B, Ghidu, VP, Sulikowski, GA, LaFleur, B, Salic, A, Lee, LA, Miller, DM, **Lee, E.** (2010) Small-molecule inhibition of Wnt signaling through activation of casein kinase 1α. *Nat Chem Biol* **6**, 829-36. PMID: 20890287.

*__Lee, E.__, *Salic, A, *Kruger, R, Heinrich, R, Kirschner, MW (2003) The roles of APC and axin derived from experimental and theoretical analysis of the Wnt pathway. *PLoS Biol*. **1**, E10. *Equal Contributors. Reviewed by *Faculty of 1000 Biology*. PMCID: PMC212691

*Coleman, DE, *Berghuis, AM, *__Lee, E.__, Linder, ME, Gilman, AG, Sprang, SR (1994) Structures of active conformations of Giα and the mechanism of GTP hydrolysis. *Science* **265**, 1405-1412. *Equal contributors.

# Ian Macara

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## Research Interests

The Macara laboratory is a wonderfully diverse group of scientists, with students and postdocs from France, Russia, the UK, Ecuador, Bangladesh and Canada, as well as the US. We strongly support racial, gender, and geographic diversity and inclusivity.

We are excited by fundamental questions about **epithelial homeostasis** and **cancer initiation**. Most **human cancers** arise from epithelial tissues. We use the mouse **mammary gland** and **skin**, and **human organoids,** as model systems. Transgenic mice provide powerful tools to probe stem cell plasticity, breast cancer initiation mechanisms, and responses to injury.

We have developed new **genome-wide CRISPR screens** to identify novel genes involved in epithelial homeostasis, cell competition, and apical-basal polarity. We also endogenously tag (with GFP, Halo, etc) proteins involved in epithelial cell polarity and polarized vesicle transport, using **CRISPR gene-editing**, to enable tracking of these proteins with **single molecule sensitivity.** We employ **multi-channel TIRFM** and near-TIRF microscopy, which provides unprecedented spatial and temporal resolution of protein complex dynamics. Finally, we are creating **new mouse models of disease**, using CRISPR technology to

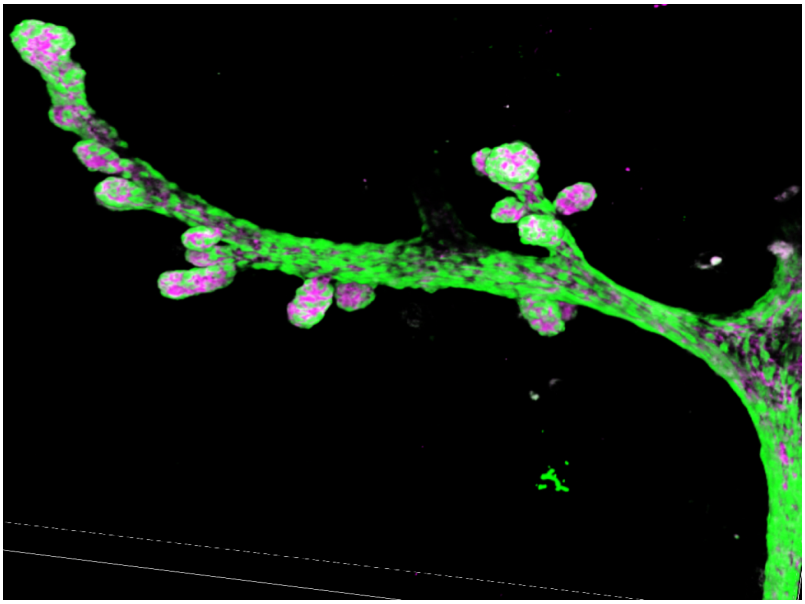


***Figure:*** *3D confocal image of mouse mammary gland duct showing terminal end buds (magenta) and basal cells (green). Armelle LeGuelte.*

introduce fluorescent tags into endogenous alleles, and point mutations in a subunit of the **exocyst**, that correspond to mutations found in a rare human neurological disease.

## Available Projects:

- CRISPR knock-in to tag endogenous proteins
- RNAseq analysis of iPSCs as they transition from an epithelial to mesenchymal phenotype
- Epithelial cell extrusion and re-integration mechanisms.

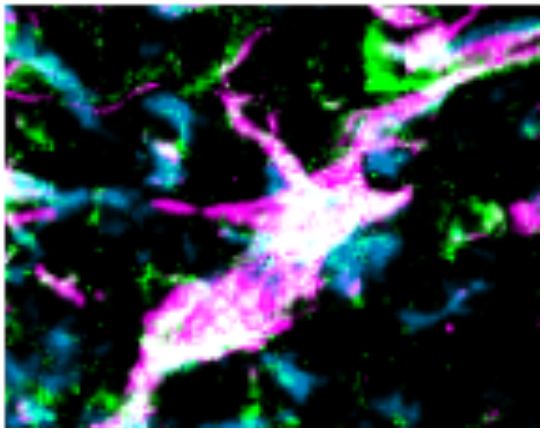
## Recent Publications:

Seldin L, Macara IG, A cell non-autonomous mechanism couples DNA damage to epithelial hyperplasia and stem cell mis-specification. ***Developmental Cell*** (in revision)

Van Bergen J , Ahmed Mukhtar , et al. , **Mutations in the exocyst component EXOC2 cause severe defects in human brain development.** ***Journal of Experimental Medicine.*** 2020 ; 217 (10). e20192040

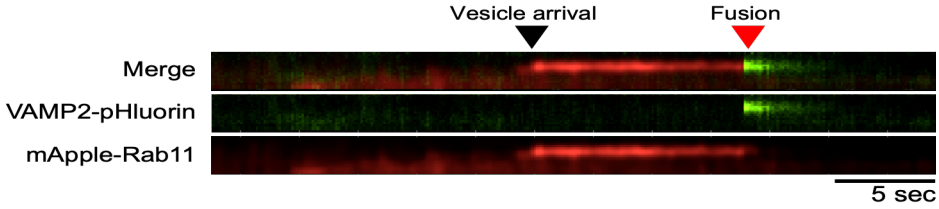
Ahmed Mukhtar , Nishida-Fukuda Hisayo , Li Yuchong , McDonald Hayes , Gradinaru Claudiu C. , Macara Ian G. , , **Exocyst dynamics during vesicle tethering and fusion.** ***Nature Communications.*** 2018 ; 9 5140

Andrews AM , McCartney HJ , Errington TM , D'Andrea AD , Macara IG , **A senataxin-associated exonuclease SAN1 is required for resistance to DNA interstrand cross-links.** ***Nature Communications.*** 2018 Jul 03; 9 (1). 2592



*Left: innate immune response in dermal fibroblasts to DNA damage (Seldin)*

*Below: TIRF timelapse images of vesicle arrival and fusion with the plasma membrane, using pHfluorin to detect the fusion event (Ahmed)*




# Jason MacGurn

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## Research Interests

The MacGurn lab seeks to define basic mechanisms that regulate protein trafficking and degradation in eukaryotic cells. Such mechanisms are critical for maintenance of subcellular organization and proteostasis, especially during adaptation to environmental changes and cellular stress. In both protein trafficking and degradation, the peptide and post-translational modifier ubiquitin plays a fundamental role, yet how ubiquitin governs such a diversity of cellular processes remains incompletely understood. My lab has contributed new paradigms for how ubiquitin function is regulated in eukaryotic cells by focusing on the following questions:

*(1) How does post-translational modification of ubiquitin impact its cellular function?*

*(2) How is cargo specificity achieved in ubiquitin-dependent endocytic trafficking?*

We are discovery-driven in pursuing answers to these questions, challenging existing paradigms and blazing trails into untrodden territory where we feel we can make impactful discoveries, often with high risk-reward activities. We use state-of-the-art methodologies, including genetics, biochemistry, proteomics, and live-cell imaging, with two main experimental models – yeast (*Saccharomyces cerevisiae*) and cultured human cells. Our goal is to leverage mechanistic insights gained from yeast studies to guide our investigations of conserved pathways in human cells. Recent discoveries from our lab have important implications for fundamental biological processes in healthy cells, and insights gained from our studies impact the understanding of human diseases, including cancer and neurodegeneration.

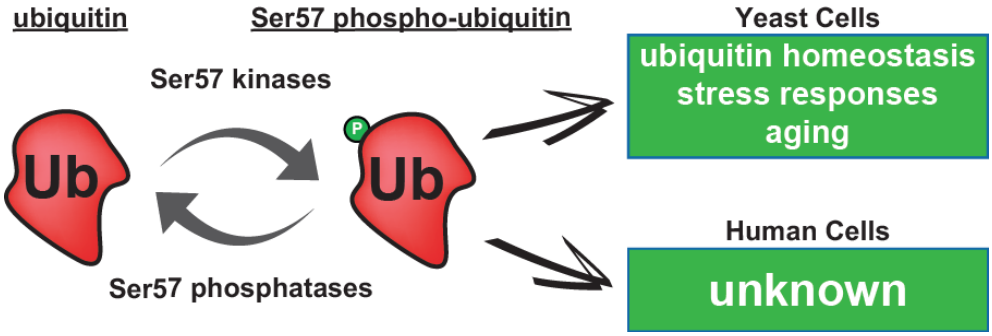



***Figure 1: Learning to read the ubiquitin code 2.0***

# Available Projects

- Investigate the pathways and mechanisms that link ubiquitin phosphorylation to chronological life span in yeast.
- Dissect novel functions of ubiquitin kinases and phospho-ubiquitin in human cells.
- Examining the role of ubiquitin phosphorylation in neurodegenerative disease-related proteinopathies (e.g.,tau aggregation in Alzheimer's Disease, α-synuclein aggregation in Parkinson's Disease).
- Screen for (or characterize) novel ubiquitin binding domains specific for phosphorylated ubiquitin.
- Investigate the role of human arrestin domain-containing proteins (ARRDCs) in the endocytic trafficking of glucose transporters.

# Recent Publications

1. Hepowit NL, Pereira KN, Tumolo JM, Chazin WJ, MacGurn JA. Identification of ubiquitin Ser57 kinases regulating the oxidative stress response in yeast. bioRxiv. 2020:2020.06.20.162883. doi: 10.1101/2020.06.20.162883.

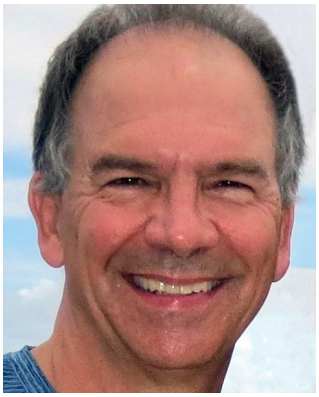
2. Nielsen CP, MacGurn JA. Coupling Conjugation and Deconjugation Activities to Achieve Cellular Ubiquitin Dynamics. Trends Biochem Sci. 2020;45(5):427-39. Epub 2020/02/28. doi: 10.1016/j.tibs.2020.01.008. PubMed PMID: 32311336; PMCID: PMC7176742.

3. Tumolo JM, Hepowit NL, Joshi SS, MacGurn JA. A Snf1-related nutrient-responsive kinase antagonizes endocytosis in yeast. PLoS Genet. 2020;16(3):e1008677. Epub 2020/03/19. doi: 10.1371/journal.pgen.1008677. PubMed PMID: 32191698.

4. Lee S, Ho HC, Tumolo JM, Hsu PC, MacGurn JA. Methionine triggers Ppz-mediated dephosphorylation of Art1 to promote cargo-specific endocytosis. J Cell Biol. 2019. Epub 2019/01/04. doi: 10.1083/jcb.201712144. PubMed PMID: 30610170.

5. Nielsen CP, Jernigan KK, Diggins NL, Webb DJ, MacGurn JA. USP9X Deubiquitylates DVL2 to Regulate WNT Pathway Specification. Cell Rep. 2019;28(4):1074-89.e5. doi: 10.1016/j.celrep.2019.06.083. PubMed PMID: 31340145.

6. Lee S, Tumolo JM, Ehlinger AC, Jernigan KK, Qualls-Histed SJ, Hsu PC, McDonald WH, Chazin WJ, MacGurn JA. Ubiquitin turnover and endocytic trafficking in yeast are regulated by Ser57 phosphorylation of ubiquitin. Elife. 2017;6. Epub 2017/11/13. doi: 10.7554/eLife.29176. PubMed PMID: 29130884.



# David M. Miller

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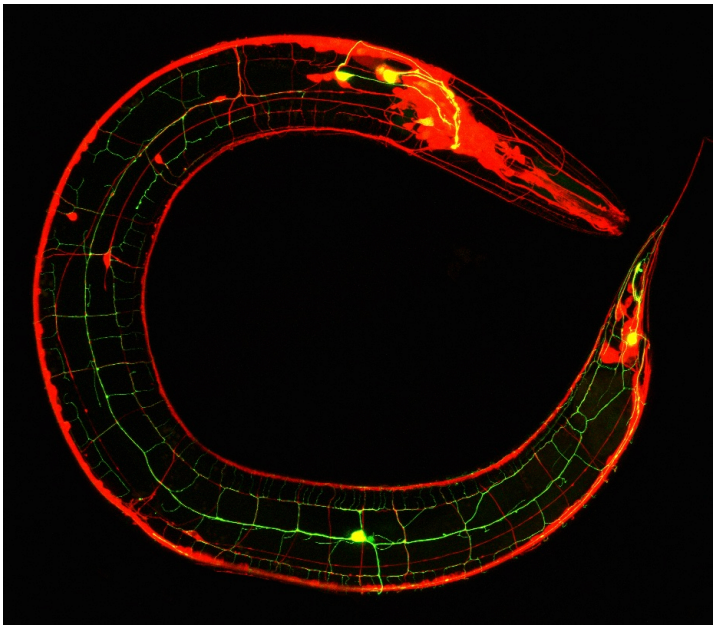
## Research Interests

The human brain embodies the most complex and functionally remarkable tissue in biology. These attributes are defined by elaborate, highly connected networks in which myriad types of neurons are linked together in circuits with discrete physiological roles. I am interested in fundamental mechanisms that drive the creation and maintenance of this intricate structure. To obviate the need to study the brain directly, we are using the model organism, *C. elegans*, to reveal the underlying programs that specify neural architecture. With its simple, well-defined nervous system and facile genetics, *C. elegans*, is especially well-suited to this approach. For example, the phenomenon of synaptic specificity is readily evident in the wiring diagram of the *C. elegans* nervous system which catalogs synaptic partners for all 302 neurons in the circuit.



*Live image of C. elegans nervous system (red) and highly branched PVD sensory neuron (green)*

We have exploited this resource to identify genetic mutants that alter connectivity and thus define pathways that are normally required for directing the creation of synapses between specific neurons. The execution of these developmental programs depends on expression of unique combinations of genes in different types of neurons. With the goal of identifying these genetic signatures, the Miller lab has pioneered the development of robust methods for generating neuron-specific gene expression profiles. Reverse genetic strategies (e.g., RNAi) are then employed to test candidate genes from these lists for key roles in circuit architecture. Perturbations are readily detected in this small, transparent organism with high-resolution light microscopy of neurons and synapses marked with fluorescent proteins (e.g., GFP).

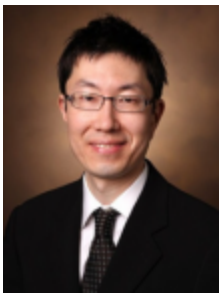
In addition to investigating the mechanisms that direct the formation of synapses, we are also studying pathways that remodel synaptic structure and function, an active but poorly understood feature of the developing brain. In a collaborative project with investigators at Yale and Columbia (CeNGEN.org), we have produced a gene expression atlas of the entire *C. elegans* nervous system to serve as a unique resource for delineating the role of cell-specific gene expression in neural fate determination and connectivity.

## Available Projects

- Mechanisms that direct the formation of synapses between specific neurons
- Molecular genetic analysis of synaptic remodeling
- Dendrite morphogenesis
- Neuron-specific gene expression profiling by single-cell RNA-Seq

## Publications


1. ***Tyne W. Miller-Fleming, *Sarah C. Petersen**, Laura Manning, Cristina Matthewman, **Megan Gornet, Allison Beers,** Sayaki Hori, Shohei Mitani, Laura Bianchi, Janet Richmond, **David M. Miller, III**. (2016) The DEG/ENaC channel protein UNC-8 drives activity-dependent synapse removal in remodeling GABAergic neurons. *eLife 5, e14599.* *These authors contributed equally. PMID: 27403890.
2. Marc Hammarlund, Oliver Hobert, **David M. Miller, III,** Nenad Sestan (2018) The CeNGEN Project: The Complete Gene Expression Map of an Entire Nervous System. *Neuron 99, 430-433*.
3. **Siwei He, Andrea Cuentas Condori, David M. Miller, III.** (2019) NATF (Native And Tissue-specific Fluorescence): A strategy for bright, tissue-specific GFP labeling of native proteins in *Caenorhabditis elegans*. *Genetics 212, 387-395, PMID 30952669*.
4. **Lakshmi Sundararajan**, **Cody J. Smith**, Joseph D. Watson, Bryan A. Millis, Matthew J. Tyska, **David. M. Miller, III** (2019) Actin assembly and non-muscle myosin activity drive dendritic retraction in an UNC-6/Netrin-dependent self-avoidance response. *PLoS Genetics 15, e1008228, PMID:31220078*.
5. **Seth R Taylor**, Gabriel Santpere, Molly Reilly, Lori Glenwinkel, **Abigail Poff, Rebecca McWhirter**, Chuan Xu, Alexis Weinreb, Manasa Basavaraju, Steven J Cook, Alec Barrett, Alexander Abrams, Berta Vidal, Cyril Cros, Ibnul Rafi, Nenad Sestan, Marc Hammarlund, Oliver Hobert, **David M. Miller, III** (2019) Expression profiling of the mature *C. elegans* nervous system by single-cell RNA-Sequencing. *bioRxiv, August 17, 2019.* doi:https://doi.org/10.1101/737577.
6. **Andrea Cuentas-Condori,** Ben Mulcahy, **Siwei He, Sierra Palumbos,** Mei Zhen, **David M. Miller, III** (2019). *C. elegans* neurons have functional dendritic spines. *eLife, DOI 10.7554/eLife.47918, PMID: 31584430.*



# Young-Jae Nam

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## Research interests

The fundamental problem in heart diseases is the myocardium's failure to repair itself by rebuilding cardiac muscle. Therefore, to convert cardiac fibroblasts, one of the most abundant cell types in the heart, into cardiomyocytes after injury is a particularly attractive heart repair strategy. Over the last several years, we have made several important contributions toward this goal: 1) in vitro reprogramming of adult mouse fibroblasts into beating cardiomyocytes by forced expression of four cardiogenic transcription factors (*Nature* 2012; 485: 599-604), 2) developing in vivo reprogramming strategy targeting resident cardiac fibroblasts after myocardial infarction which improved heart function and reduced scar formation *(Nature* 2012; 485: 599-604, *Nature Medicine* 2013;19: 413-415), 3) identifying the optimal combination of factors that is necessary and sufficient to induce a contractile phenotype in adult human fibroblasts (*PNAS* 2013;110(14):5588-5593), 4) defining the requirement of sarcomere assembly and subtype specification for functional reprogrammed cardiomyocytes (*Development* 2014;141(22):4267-78), and 5) developing an effective gene delivery system for cardiac reprogramming (*Scientific Reports* 2019;9(1):6362, and *Scientific Reports* 2019; 9(1):14970). Based on these progresses, our long-term scientific goals are to understand the mechanistic basis of heart repair processes and to develop clinically applicable heart repair strategies. Currently, we are working on the following projects.

1. **Defining the lineage paths toward induced cardiomyocytes (iCMs) during cardiac reprogramming**: The goal of this project is to define the lineage paths from cardiac fibroblasts to iCMs. In vivo reprogramming has to take place not only within rapidly progressing infarct healing cascades, but also in a complex mixture of many different cell types, each of which plays an important role in a given temporal phase of infarct healing. Using Cre-LoxP fate mapping studies, we will determine how resident cardiac fibroblasts can be coaxed away from their default pro-fibrogenic path, and instead induced to become new cardiomyocytes following cardiac injury. We will also determine if non-fibroblast cell types involving infarct healing processes can be reprogrammed.

2. **Re-defining in vivo cardiac reprogramming:** The goal of this project is to define 1) optimal timing of cardiac reprogramming post-injury, 2) optimal injury type (permanent LAD ligation vs ischemia-reperfusion), and 3) minimal combination of cardiogenic transcription factors that is necessary and sufficient to induce new cardiomyocytes in vivo. Using the new reprogramming tool that we recently generated (*Scientific*

*Reports* 2019;9(1):6362, and *Scientific Reports* 2019; 9(1):14970), we will re-reconstruct in vivo cardiac reprogramming, which has been remain "a proof-of-concept" approach.

3. **Subtype specification of pluripotent stem cell (PSC)-derived and reprogrammed cardiomyocytes**: New cardiomyocytes generated by reprogramming or PSC differentiation demonstrate high heterogeneity of cardiac subtypes, which prevents any clinical use of newly generated cardiomyocytes. We have generated a unique genetic tool to label each subtype of cardiomyocytes (i.e. atrial, ventricular, and pacemaker). Using this genetic tool, we are studying subtype specification processes during cardiac reprogramming and PSC differentiation toward cardiomyocytes.

4. **Regulation of myofibroblast senescence for heart repair:** The goal of this project is to define the role of myofibroblast senescence after cardiac injury and elucidate the mechanisms underlying this process. Cellular senescence is a programmed cellular response to injury or stress. It locks the cells into a cell-cycle arrest that prevents the proliferation of old, damaged and potentially tumorigenic cells. As such, cellular senescence was initially recognized as a potent tumor-suppressive mechanism that arrests the growth of cells at risk for malignant transformation. However, numerous recent studies identified more diverse roles of cellular senescence in physiological and pathological processes beyond tumor suppression or aging. We are studying how myofibroblast senescence regulates cardiac fibrogenesis after cardiac injury.

# Recent Publications

Cadar AG, Feaster TK, Bersell KR, Wang L, Hong T, Balsamo JA, Zhang Z, Chun YW, Nam YJ, Gotthardt M, Knollmann BC, Roden DM, Lim CC, Hong CC. Real-time visualization of titin dynamics reveals extensive reversible photobleaching in human induced pluripotent stem cell-derived cardiomyocytes. American journal of physiology. Cell physiology. 2019 Nov 11.PMID: 31747312 [PubMed].

Zhang Z, Zhang W, Nam YJ. Stoichiometric optimization of Gata4, Hand2, Mef2c, and Tbx5 expression for contractile cardiomyocyte reprogramming. Scientific reports. 2019 Oct 10;9(1). 14970 p.PMID: 31628386 [PubMed].

Guo Y, Sui JY, Kim K, Zhang Z, Qu XA, Nam YJ, Willette RN, Barnett JV, Knollmann BC, Force T, Lal H. Cardiomyocyte HIPK2 Maintains Basal Cardiac Function via ERK Signaling. Circulation. 2019 Oct 10.PMID: 31581792 [PubMed].

Zhang Z, Zhang Q, Lal H, Nam YJ. Generation of Nppa-tagBFP reporter knock-in mouse line for studying cardiac chamber specification.Genesis (New York, N.Y. : 2000). 2019 Jun 6;57(6). e23294.PMID: 30920727 [PubMed].

Zhang Z, Zhang AD, Kim LJ, Nam YJ. Ensuring expression of four core cardiogenic transcription factors enhances cardiac reprogramming.Scientific reports. 2019 Apr 4;9(1). 6362 p.PMID: 31019236 [PubMed]. PMCID: PMC6482135.

Zhang Z, Nam YJ. Analysis of Cardiac Chamber Development During Mouse Embryogenesis Using Whole Mount Epifluorescence. Journal of visualized experiments : JoVE. 2019 Apr 4;PMID: 31058904 [PubMed]

# Andrea Page-McCaw

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## Research Interests

My lab focuses on understanding how tissues repair after damage. One area of interest is how epithelial wounds trigger the cells around them to engage in repair behaviors. To close the wound, surrounding cells migrate, proliferate, and invade – the same behaviors that epithelial cells adopt in carcinomas, the most common type of human cancer. To understand how epithelial cells adopt these behaviors, we analyze signals derived from the wound and signaling pathways that interpret them in the surrounding epithelial cells (Fig. 1). These studies are performed in living fruit flies, imaged live, using powerful genetic techniques to analyze gene function. We have a vibrant collaboration with Shane Hutson's physics lab to measure and analyze the data quantitatively, and Shane acts as a co-advisor to my students working in this area. Excitingly, the NIH R01 grant that funds this work recently purchased a new spinning disc laser-ablation microscope dedicated to this work. (Fig. 1 is from an older scope.)

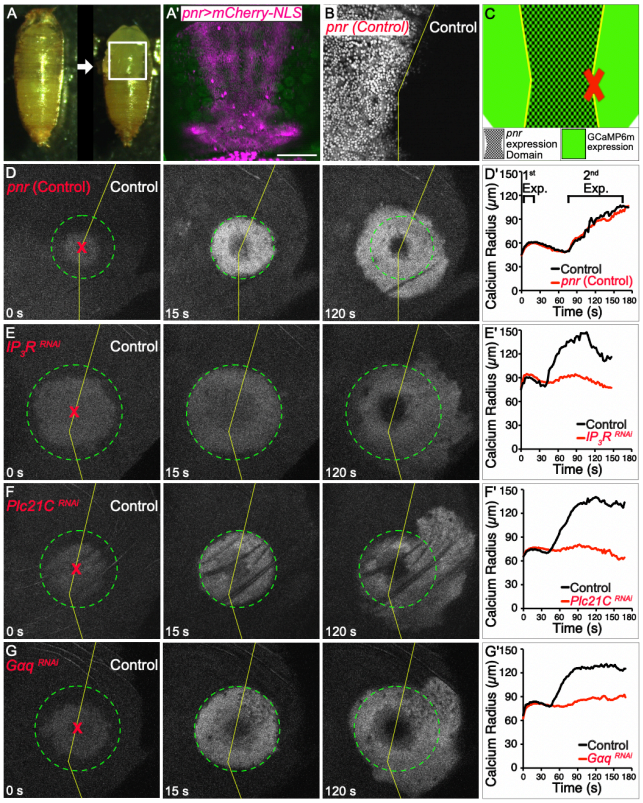


*Figure 1: Wounds trigger delayed calcium release via the Gq pathway.* ***(A–C)*** *Experiments are conducted on live Drosophila pupae with case removed. Gene manipulations are performed in the domain of* pnr *expression (magenta, A', bar=200 μm), and wounds (red X) are targeted at the* pnr *domain boundary (yellow line, B,C).* ***(D-H)*** *GCaMP6m calcium reporter.* ***(D)*** *In control pupae, calcium response is symmetric on* pnr *and control sides of a wound, for both the rapid 1st expansion (max extent marked by green circle) and the delayed 2nd expansion, typically beginning 30–80 seconds after wounding.* ***(E–H)*** *The 2nd expansion is absent in knockdowns of Gq-pathway components (E–G).*

Another area of interest is in how extracellular matrix repairs after damage. We focus on the basement membrane, a thin sheet-like matrix that is essential for epithelial tissue organization. Recent studies have shown that basement membrane is considerably more dynamic than previously appreciated, and we are asking how repair dynamics differ from normal homeostasis

dynamics. We collaborate with physicians and mechanical engineers to understand the function and mechanics of basement membranes in vivo, asking about the relationship between dynamics and mechanics. We engage the larger basement membrane community in weekly (remote) meetings with a basement membrane lab at Duke University.

My lab members and I are committed to promoting racial and other types of diversity in our local research environment and in the larger scientific enterprise. I aim to provide rigorous training in a supportive and inclusive environment.

# Available Projects

- *Epithelial wound repair*: Analyze how microtubule cytoskeleton is reorganized around wounds in vivo.
- *Basement membrane repair*: Analyze the dynamics of laminin and perlecan during homeostasis and matrix repair.
- *Combination*: Analyze the formation of basement membrane and its repair after laser ablation using live imaging in pupae.

# Selected Publications

## Epithelial Wound Repair

1. J. O'Connor, A.S. Stevens, E.K. Shannon, B. Akbar, M.S. Hutson*, A. Page-McCaw*. A protease-bait model of epithelial wound detection. Under review.
2. E.K. Shannon, A.S. Stevens, W. Edrington, Y. Zhao, A.K. Jayasinghe, A. Page-McCaw*, and M.S. Hutson*. Multiple Mechanisms Drive Calcium Signal Dynamics around Laser-Induced Epithelial Wounds. *Biophysical Journal 113*, 1623-1635 (2017).
3. L. J. Stevens and A. Page-McCaw. A secreted MMP is required for re-epithelialization during wound healing. *Molecular Biology of the Cell 23*, 1068-1079. (2012)

## Basement Membrane

1. A. M. Howard, K. S. LaFever, A. M. Fenix, C. R. Scurrah, K. S, Lau, D. T. Burnette, G. Bhave, N. Ferrell, and A. Page-McCaw. DSS-induced damage to basement membranes is repaired by matrix replacement and crosslinking. *Journal of Cell Science 132:* jcs22686 (2019).
2. W. Ramos-Lewis and A. Page-McCaw. Basement membrane mechanics shape development: Lessons from the fly. *Matrix Biology 75-76*, 72-81 (2019).
3. W. Ramos-Lewis, K.S. LaFever, and A. Page-McCaw. A scar-like lesion is apparent in basement membrane after wound repair *in vivo*. *Matrix Biology 74*, 101-120 (2018).
4. A.S. McCall, C.F. Cummings, G. Bhave, R. Vanacore, A. Page-McCaw, and B.G. Hudson. Bromine is an essential trace element for assembly of collagen IV scaffolds in tissue development and architecture. *Cell 157*, 1380-1392 (2014).

# John S. Penn

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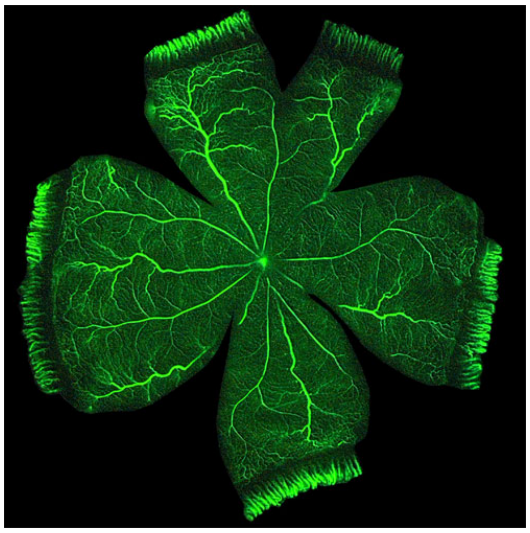
## Research Interests



*This image illustrates the retinal vasculature of a 20-day old rat using isolectin staining. The method allows for high resolution study of vascular architecture.*

The large majority of irreversible blindness in the US is caused by pathology of the blood vessels of the eye. Penn's long-standing interest is in the molecular basis of retinal vascular disease. The over-arching goal of his research is to characterize the processes involved in retinal vascular inflammation and angiogenesis, and to begin to develop preventive strategies based on understanding gained from *in vitro* and *in vivo* studies. The Penn lab has the capability to isolate and culture a variety of primary cells from retinal tissue of several species, including retinal vascular endothelial cells, choroidal endothelial cells, retinal Müller glia, retinal pericytes, retinal microglia and retinal pigment epithelial cells – all of which are involved in vascular diseases of the retina. In addition, the lab uses a battery of *in vivo* models of vascular diseases of the eye including rodent models of retinopathy of prematurity, neovascular age-related degeneration and diabetic retinopathy. Using these *in vitro* and *in vivo* tools, Penn's research program focuses on pro-inflammatory and pro-angiogenic molecular signaling in the retina. In his research, Penn places an emphasis on both drug target identification and on development of novel pharmacotherapeutics and methods of drug delivery to the eye.

Penn has been continuously funded by the National Eye Institute of NIH for 33 years. He currently serves on the advisory boards of three prominent foundations supporting eye research, and he is President of the International Society for Eye Research. Penn's lab currently holds 18 contracts with pharmaceutical companies to develop novel drugs for eye diseases.

**NFAT and retinal vascular homeostasis:** The Penn lab currently has multiple projects directed at understanding the role of the transcription factor, NFAT, in diabetic retinopathy pathogenesis. First, we are investigating NFAT's regulation of extracellular matrix expression in the development of basement membrane thickening – a hallmark of diabetic retinopathy. Second, we are characterizing the role of NFAT in the response of photoreceptors to diabetes-relevant stimuli.

Finally, we are determining NFAT isoform specificity in early pathogenic events related to retinal cytokine induction under diabetic conditions.

**Epoxygenated lipids and their products in retinal vascular inflammation:** Epoxide lipids generated by Cytochrome P450 epoxygenases are anti-inflammatory, but their levels are limited by the soluble epoxide hydrolase enzyme. We are testing the hypothesis that epoxide levels are decreased in the diabetic retina due to altered expression of the enzymes that regulate them, and therefore elevating their levels would be beneficial for the early treatment of diabetic retinopathy. Similarly, the lipid epoxide-derived endocannabinoids that are selective for cannabinoid receptor 2 (CB2) binding are also potently anti-inflammatory. We are characterizing their roles in diabetic retinopathy and the efficacy associated with elevating their endogenous levels.

**Novel biomarker imaging and drug delivery methods:** The properties of the eye allow for unique opportunities to image biomarkers *in vivo.* We are designing novel RNA-based molecular beacons and contrast agents to better understand early disease processes, and as a first step in developing targeted strategies for delivery of novel therapeutic agents.

# Available Projects

- Characterize the specific mechanisms by which NFAT-c2 exerts its anti-inflammatory bioactivity in retinal disease
- Characterize the efficacy and mechanism of action of endocannabinoids in inflammatory retinal disease
- Define the role of photoreceptors in promoting vascular inflammation in the diabetic retina
- Determine the utility of hypoxia probes RNA-based molecular beacons for ophthalmic use

# Publications

Uddin, M.I., Jayagopal, A., Wong, A., McCollum, G.W., Wright, D.W. and **Penn, J.S.** (2018) Real-time imaging of VCAM-1 mRNA in TNF-α activated retinal microvascular endothelial cells using antisense hairpin-DNA functionalized gold nanoparticles. *Nanomed.* 14(1):63-71.

Capozzi, M.E. and **Penn, J.S.** (2018) Palmitic acid induces Müller cell inflammation that is potentiated by co-treatment with glucose. *Nature Sci Rep.* 2018 Apr 3;8(1):5459.

Uddin, M.I., Kilburn, T.C., Yang, R., McCollum, G.W., Wright, D.W. and **Penn, J.S.** (2018) Targeted imaging of VCAM-1 mRNA in a mouse model of laser-induced choroidal neovascularization using antisense hairpin DNA-functionalized gold nanoparticles. *ACS Mol Pharm.* 3;15(12):5514-5520.

Cao, J., Yang, R., Smith, T.E., Evans, S., McCollum, G.W., Pomerantz, S.C., Petley, T., Harris, I.R. and **Penn, J.S.** (2019) Human umbilical tissue-derived cells secrete soluble VEGFR1 and inhibit choroidal neovascularization. *Mol Ther Meth Clin Dev.* 2019 May 22(14):37-46.

Capozzi, M.E., Savage, S.R., McCollum, G.W., Hammer, S.S., Yang, R., Bretz, C.A. and **Penn, J.S.** (2020) Peroxisome proliferator-activated receptor-β/δ mediates retinal leukostasis via CCL8 and CXCL10. *Exp Eye Res.* 2020 Jan;190:107885.

# Bill Tansey

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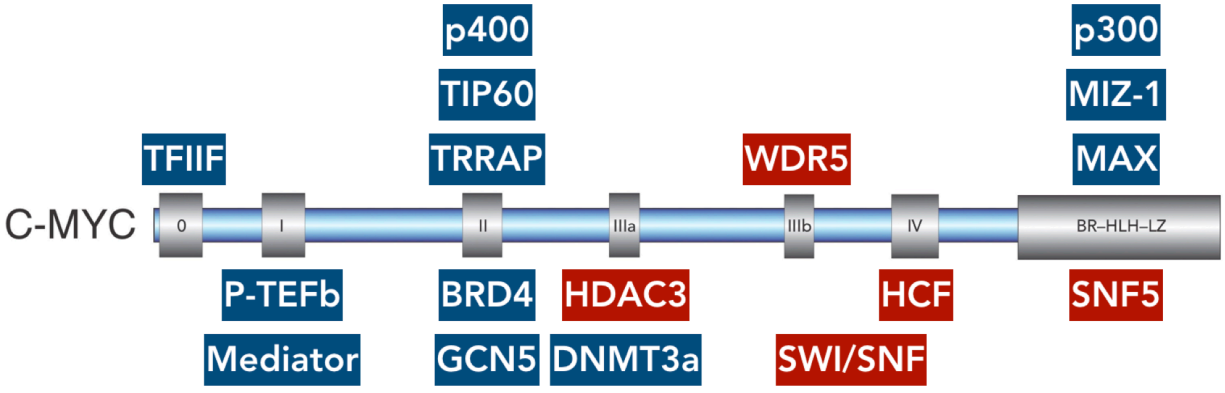
## Research Interests

We study the MYC family of oncoprotein transcription factors. MYC proteins are overexpressed in the majority of cancers, and are responsible for ~100,000 cancer related deaths each year in the USA—and millions worldwide. There is universal agreement that drugs targeting MYC could transform the way we treat and cure cancers, but MYC proteins are “undruggable”, and so some of the best prospects for broadly impactful, targeted, anti-cancer therapies remain out of reach.

Fortunately, MYC does not work alone. Its actions depend on interaction with a host of co-factors that descend on conserved regions of MYC (shown as silver boxes) to execute its pro-tumorigenic transcriptional program. Our thesis is that one or more of these co-factors can be drugged, and that by studying how they interact with MYC, what they do, and how they contribute to oncogenesis, we can find new ways to block MYC function in cancer cells. We study the co-factors we identified as important for MYC function (shown in red).




We use a lot of different approaches—whatever it takes to get the job done. Genetics, genome engineering, genomics, proteomics, metabolomics, biochemistry, even the occasional cell biology. And we have an active drug discovery program ongoing, in

collaboration with Dr. Stephen Fesik (BCHM), to target WDR5. We hope to select a clinical candidate WDR5 inhibitor in late 2020 and then begin IND enabling studies.

## Projects

Our work at the moment can be divided into five areas: (i) Understanding the mechanisms and significance of the MYC–WDR5 interaction, (ii) understanding how WDR5 links to the growth factor signaling machinery, (iii) understanding how MYC and HCF work together to promote ribosome biogenesis, (iv) understanding the MYC–SWI/SNF connection and its role in development of rare pediatric cancers, and (v) drugging WDR5 and figuring out how to drug HCF. There is plenty to do!

## Training History

Including current trainees, I have mentored 18 graduate students over the last 22 years. All of my former trainees have stayed in science, and have gone to successful careers in industry, as postdocs, and in academia.

## Recent Publications

Bryan, A. F., Wang, J., Howard, G. C., Guarnaccia, A. D., Woodley, C. M., Aho, E. R., Rellinger, E. J., Matlock, B. K., Flaherty, D. K., Lorey, S. L., Chung, D. H., Fesik, S. W., Liu, Q., Weissmiller, A. M., and Tansey, W. P. (2020). WDR5 is a conserved regulator of protein synthesis gene expression. *Nucleic Acids Research.* **48:** 2924–2941. doi: 10.1093/nar/gkaa051.

Simon, S. C., Wang, F., Thomas, L. R., Phan, J., Zhao, B., Olejniczak, E. T., MacDonald, J. D., Shaw, J. G., Schlund, C., Payne, W. G., Creighton, J., Stauffer, S., Waterson, A. G., Tansey, W. P., and Fesik, S. W. (2020). Discovery of WD Repeat-Containing Protein 5 (WDR5)-MYC inhibitors using fragment-based methods and structure-based design. *J. Med. Chem.* doi: 10.1021/acs.jmedchem.0c00224. Epub 2020 April 9.

Thomas, L. R., Adams, C. M., Wang, J., Weissmiller, A. M., Creighton, J., Lorey, S. L., Liu, Q., Fesik, S. W., Eischen, C. M., and Tansey, W. P. (2019). Interaction of the oncoprotein transcription factor MYC with its chromatin co-factor WDR5 is essential for tumor maintenance. *Proc. Natl. Acad. Sci. USA.* **116:** 25260–25268. doi: 10.1073/pnas.1910391116.

Weissmiller, A. W., Wang, J., Lorey. S. L., Howard, G. C., Martinez, E., Liu, Q., and Tansey, W. P. (2019). Inhibition of MYC by the SMARCB1 tumor suppressor. *Nature Communications.* **10:** 2014. doi: 10.1038/s41467-019-10022-5.

Aho, E. R., Wang, J., Gogliotti, R. D., Howard, G. C., Phan, J, Acharya, P., Macdonald, J. D., Cheng, K., Lorey, S. L., Lu, B., Wenzel, S., Foshage, A. M., Alvarado, J., Wang, F., Shaw, J. G., Zhao, B., Weissmiller, A. M., Thomas, L. R., Vakoc, C. R., Hall, M., Hiebert, S. W., Liu, Q., Stauffer, S. R., Fesik, S. W., and Tansey, W. P. (2019). Displacement of WDR5 from chromatin by a WIN site inhibitor with picomolar affinity. *Cell Reports.* **26:** 2916–2928.


# Matthew J. Tyska

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## Research Interests

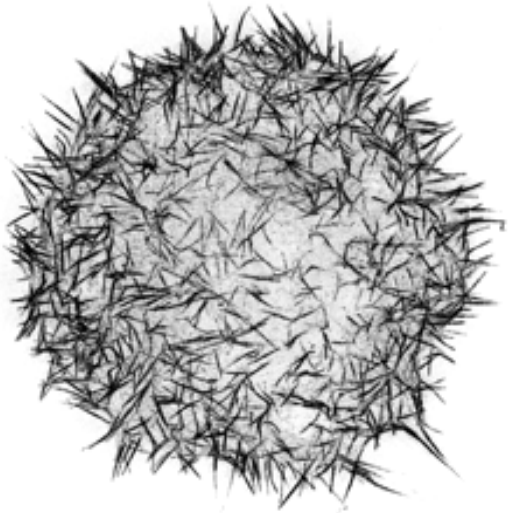

Fig. 1 – A melanoma cell induced to assemble microvillus-like surface protrusions. Image acquired using super-resolution structured illumination microscopy.

The human body is composed of hundreds of different cell types, each one adopting a unique morphology (i.e. shape) optimized for its tissue-specific function. Understanding this ancient and fundamental relationship between cell morphology and function is a central goal our research program. As our primary model for investigating this problem, we focus on the nutrient-absorbing epithelial cells of the intestinal tract. These highly polarized cells assemble a massive array of microvilli – a 'brush border' – which provides the sole surface for nutrient uptake from the gut lumen and a barrier to microbes that reside in this space. Current projects seek to identify molecules and define mechanisms that control the number, size, and organization of apical microvilli. Because microvilli are supported by the actin cytoskeleton, a major emphasis is on understanding how actin filaments are assembled into the networks and bundles that shape the epithelial apical surface. Although state-of-the-art light and electron microscopy serve as our principal discovery tools, investigations are decidedly broad in scale and scope, ranging from physiological experiments in mouse model systems, to live imaging of organoid dynamics, to super-resolution imaging of cell structure (Fig. 1). Importantly, the critical physiological role of the brush border means that many of our basic science discoveries hold direct relevance for understanding human disease. Indeed, a general long-term goal is to develop insight on molecules and pathways that may be perturbed in GI diseases characterized by loss of the brush border, such as enteropathogenic *E. coli* infection, celiac disease, IBD, and microvillus inclusion disease.

## Available Projects

Rotation projects typically branch from ongoing funded investigations, which currently include studies on: (i) mechanisms and function of novel actin bundling proteins, (ii) the

role of cadherin-based adhesion complexes in brush border assembly and organization, and (iii) the function of myosin motors in cell surface protrusion formation and apical actin dynamics. Interested students are encouraged to contact Dr. Tyska to brainstorm ideas for projects in these or related areas.

## Recent Publications


1. Meenderink LM, Gaeta IM, Postema MM, Cencer CS, Chinowsky CR, Krystofiak ES, Millis BA, **Tyska MJ**. Actin dynamics drive microvillar motility and clustering during brush border assembly. *Dev Cell*. 2019 Jul 30. pii: S1534-5807(19)30580-5. doi: 10.1016/j.devcel.2019.07.008.
   **Featured as cover image*

2. Sundararajan L, Smith CJ, Watson JD, Millis BA, **Tyska MJ**, Miller DM 3rd. Actin assembly and non-muscle myosin activity drive dendrite retraction in an UNC-6/Netrin dependent self-avoidance response. *PLoS Genet.* 2019 Jun 20;15(6):e1008228.

3. Postema MM, Grega-Larson NE, Neininger AC, and **Tyska MJ**. PACSIN-2 dependent endocytosis controls the morphology of epithelial microvilli. *Mol Biol Cell*. 2019 Aug 7:mbcE19060352. doi: 10.1091/mbc.E19-06-0352.
   **Featured as cover image*

4. Engevik A, Kaji I, Faust J, Meyer AR, Williams JA, **Tyska MJ**, Wilson J, Goldenring JR. Loss of Myosin Vb Promotes Apical Bulk Endocytosis in Neonatal Enterocytes. *J Cell Biol.* 2019 Sep 27. pii: jcb.201902063.
   **Featured as cover image*

5. Faust JJ, Millis BA and **Tyska MJ**. Profilin-mediated actin allocation regulates the growth of epithelial microvilli. *Curr Biol.* 2019 Oct 21;29(20):3457-3465.e3.

6. Choi MS, Graves MJ, Matoo S, Storad ZA, Idris RA, Weck ML, Smith ZB, **Tyska MJ**, Crawley SW. The Small EF-hand Protein CALML4 Functions as a Critical Myosin Light Chain Within the Intermicrovillar Adhesion Complex. *J Biol Chem*, 2020 Mar 24;jbc.RA120.012820. doi: 10.1074/jbc.RA120.012820.
   **Featured as cover image.*

7. Seervai RNH, Jangid RK, Park I-Y, Karki M, Tripathi DN, Dere R, Jung SY, Kearns SE, Verhey KJ, Cianfrocco MA Millis BA, **Tyska MJ**, Mason FM, Rathmell WK, and Walker CW. The Huntingtin-interacting protein SETD2 is an actin lysine methyltransferase. In press at *Science Advances*. March 2020.

# Alissa Weaver

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## Research Interests

Extracellular vesicles (EVs) are a newly recognized and evolutionarily conserved mechanism of cell-cell communication. EVs drive a variety of cell and tissue processes, including cancer progression and metastasis, brain development and function, and immune function. This is a very new field with many outstanding major questions – many of which we are pursuing. We are particularly focused on how secretion of small extracellular vesicles called exosomes from cancer cells promotes aggressive, invasive behavior and facilitates tumor growth and metastasis. We also have projects related to neuroscience and heart disease. Current projects include: 1) Function of exosomes in cell migration, invasion, and cancer metastasis; 2) The role of exosome secretion in additional tumor-associated phenotypes, such as fibrosis and immune evasion; 3) How RNAs are trafficked to EVs and what is the function of RNA-containing EVs; 4) Development of EV-based biomarkers in blood for detection and prognostication of cancer; 5) Role of EVs in neuronal synapse formation. Students use a variety of approaches in their research, including live imaging and other microscopy approaches, in vivo tumor studies, biochemical purification and analysis, and bioinformatics/systems approaches. Our goal is to train students to become rigorous scientists while making important and novel discoveries in a collaborative environment.

## Available Projects

Projects relate to the 5 areas listed above and the student's interest, please contact Dr. Weaver for more information!

## Publications

### Original Data Articles:

Sung BH, Von Iersner A, Guerrero J, et al. A live cell reporter of exosome secretion and uptake reveals pathfinding behavior of migrating cells. Nat Commun. 2020;11(1):2092. PMCID: 31661464

Sato S, Vasaikar S, Eskaros A, et al. EPHB2 carried on small extracellular vesicles induces tumor angiogenesis via activation of ephrin reverse signaling. JCI Insight. 2019;4(23) PMCID: 31661464

Jimenez L, Yu H, Mckenzie A, Franklin JL, Patton JG, Liu Q, and Weaver AM "Quantitative proteomic analysis of small and large extracellular vesicles (EVs) reveals enrichment of adhesion proteins in small EVs." J Proteome Res. 2019; PMCID: 30608700

Sung, BH and AM Weaver, "Exosome secretion promotes chemotaxis of cancer cells" Cell Adhesion & Migration, 11:187-195, 2017. PMCID: 5351719

Sinha, S, Hoshino, D, Hong, NH, Kirkbride, KC, Grega-Larson, N, Seiki, M, Tyska, MJ, and Weaver AM, "Cortactin promotes exosome secretion by controlling branched actin dynamics." J. Cell Biol., 214:197-213,2016. PMCID: PMC4949450

McKenzie, AJ, Hoshino, D, Hong, NH, Cha, DJ, Franklin, JL, Coffey, RJ, Patton, JG, and Weaver AM, "Kras-Mek signaling controls ago2 sorting into exosomes", Cell Reports, 15:978-987, 2016. PMCID: PMC4857875

## Review Articles:

Sato, S, and AM Weaver, "Extracellular vesicles: important collaborators in cancer progression.", Essays in Biochemistry, 62(2) 149-163, 2018. PMCID: PMC6377252

Maas, N, Breakefield, X, and AM Weaver, "Extracellular vesicles – unique intercellular delivery vehicles", Trends in Cell Biology, 27:172-188, 2017. PMCID: PMC5318253

# Marija Zanic

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## Research Interests

A look inside of every living cell reveals an intricate world of dynamic intracellular structures. Among them are structures made of microtubule polymers, which play essential roles in the fundamental processes of life. For a cell to divide, microtubules form the mitotic spindle, a complex molecular machine that captures chromosomes and pulls them apart. For a sperm to swim, microtubules slide against each other in a highly coordinated manner within a precisely organized bundle to generate the bending motion of the sperm tail. For a neuron to grow and survive, microtubules build an elaborate roadmap for directed long-range transport of intracellular cargos. Our research unites the tools of biology and physics to uncover the molecular rules governing the dynamic microtubule architecture.

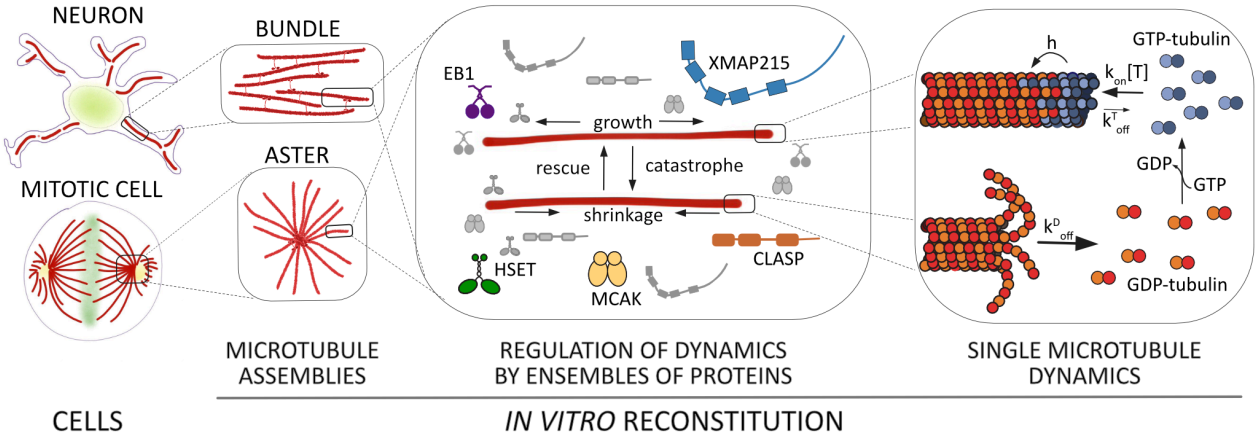


*Figure: Molecular regulation of microtubule dynamics underlies cellular microtubule architecture.*

Microtubules are biological polymers found in all eukaryotic cells. The microtubule network is highly dynamic, rapidly remodeling to realize its essential functions in cell division, motility and differentiation. The reshaping of this network is achieved through precisely regulated switching between growth and shrinkage of individual microtubules, a behavior known as dynamic instability. Even though dynamic instability plays a central role in cellular organization, the underlying molecular mechanisms and their regulation by complexes of microtubule-associated proteins remain poorly understood. We are investigating microtubule dynamics by combining biochemical *in vitro* reconstitution, single-molecule microscopy, quantitative image analysis and theoretical modeling. Our studies range from investigations of dynamics of individual microtubules with tubulin alone, to ensembles of regulators and multi-polymer assemblies (Figure). We are especially interested in emergent behaviors that arise through the collective effects of groups of proteins that regulate microtubule dynamics. By developing predictive models of molecular-level polymer dynamics and testing them in controllable *in vitro* reconstitution assays, we take a bottom-up approach towards a comprehensive understanding of large-scale, dynamic cellular structures essential for life. Because microtubules are a common target for chemotherapeutic agents and many of their regulating proteins are implicated in cancer and neurodegenerative diseases, quantitative and predictive models of microtubule regulation not only provide fundamental insight, but also have important medical relevance.

## Our Team

Our lab is currently comprised of two postdoctoral researchers, five graduate students and several undergrads. The members of our lab come from five different countries (Croatia, Peru, Turkey, UK and USA) and span a range of disciplines (cell biology, biochemistry, physics and engineering). We are deeply committed to inclusion across race, ethnicity, gender, age, religion and identity. We believe that uniting our diverse perspectives enriches our lives and makes us better scientists.

## Available Projects

Our investigations of microtubule dynamics are highly multidisciplinary, and our rotation projects involve any desired combination of protein biochemistry, fluorescence microscopy and computational modeling. No previous experience necessary!

## Selected Recent Publications

Arpag G*, Lawrence EJ*, Farmer VJ, Hall SL, **Zanic M**. “Collective effects of XMAP215, EB1, CLASP2 and MCAK lead to robust microtubule treadmilling”, *PNAS, 117(23):12847-12855.* (2020)

Strothman C, Farmer V, Arpağ G, Rodgers N, Podolski M, Norris S, Ohi R, **Zanic M.** “Microtubule minus-end stability is dictated by the tubulin off-rate”, *JCB, 218 (9) 2841-2853.* (2019), ***Journal Cover***

Norris SR, Jung S, Singh P, Strothman CE, Erwin AL, Ohi MD, **Zanic M***, Ohi R*. “Microtubule minus-end aster organization is driven by processive HSET-tubulin clusters”, *Nature Comm, 9(1):2659.* (2018)


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## Research Interests

Cell-to-cell communication is essential for the development and function of multicellular organisms. We focus on two types of intercellular communication: synaptic transmission and exosome-based cell-to-cell communication. Similar to other biological activities, they are highly complex and tightly regulated processes by a large number of proteins. The function of almost all proteins is dependent on their higher-order assembly into nanoscale molecular machines with its biological membrane. However, defining molecular assembly, spatial organization and dynamics of these nanoscale molecular machines is a daunting task largely because of the technical challenges imposed by the cellular and molecular complexity.

Cryogenic electron tomography (cryo-ET) can provide 3D images (tomograms) of nanoscale molecular machines or cellular landscapes in their near-native states. Subtomogram averaging and classification allow any repetitive structures to be averaged to improve and achieve close-to-nanometer resolution or better (3-20 Å). Moreover, cryogenic focused ion beam (cryo-FIB) milling has been developed to create a 150-250 nm thick cell lamella for overcoming the limitation of sample thickness for cryo-ET imaging of large eukaryotic cells *in situ*. To target areas of interest in the cell, cryogenic correlative light and electron microscopy (cryo-CLEM) has become a powerful and broadly available tool owing to the combined advantages of both imaging techniques. We combine these techniques to bridge the gap and link high resolution (sub-3 Å) structural information with physiological functions at the molecular and cellular levels.

## Available Projects

1. ***In situ* molecular architecture and nanoscale organization of synaptic protein super-complexes**

Different modes of synaptic transmission play distinct roles in encoding and transmitting information in brain circuits, which is essential for perception, decision making, learning and memory formation. However, it remains unclear how these modes of synaptic transmission regulate neural circuit activity and how the molecular mechanisms differ between these modes. Synapses constitute the most complex cell-cell junctions in the body with more than 2,000 different synaptic proteins. Especially, the presynaptic active zone, the postsynaptic density (PSD) and the synaptic cleft are membrane-protein

specializations, each containing protein complexes unique to their function. Recent studies also revealed that supramolecular assembly is likely to be a general property of synaptic proteins, but defining the assembly and nanoscale organization of these synaptic protein super-complexes remains elusive.

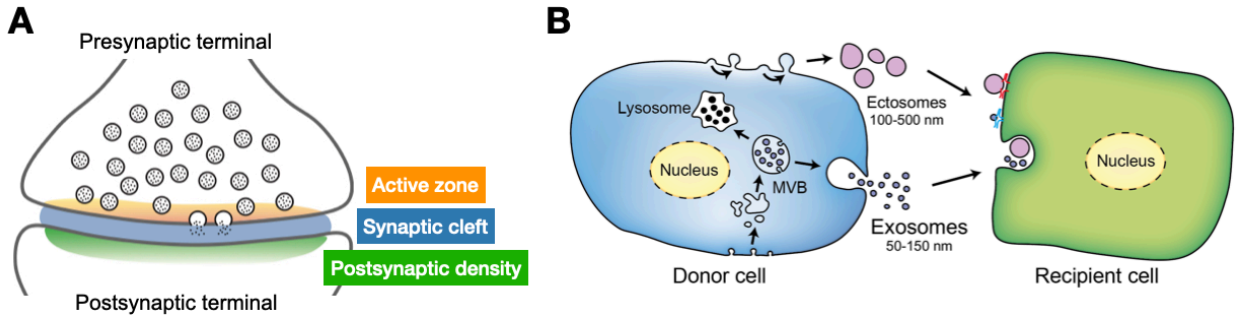


*Figure: Schematic diagrams of a synapse (A) and exosome biogenesis & release (B).*

**2. Molecular mechanism and regulation of exosome secretion in cancer and central nervous system**

Nano-sized vesicles called “exosomes” which contain genetic material, proteins and lipids are released upon exocytic fusion of multivesicular bodies (MVBs) with the plasma membrane (PM). They are found to be particularly involved in various stages of tumor and cell-to-cell communication in the brain. However, the molecular mechanisms and regulation of exosome secretion are poorly understood.

## Select Publications

1. **Zhou Q.**, Zhou P., Wang A.L., Wu D., Zhao M., Südhof T.C., Brunger A.T., (2017) The Primed SNARE-Complexin-Synaptotagmin Complex for Neuronal Exocytosis. *Nature* 548:420-425.
2. **Zhou Q.**, Lai Y., Bacaj T., Zhao M., Lyubimov A.Y., Uervirojnangkoorn M., Zeldin O.B., Brewster A.S., Sauter N.K., Cohen A.E., Soltis S.M., Alonso-Mori R., Chollet M., Lemke H.T., Pfuetzner R.A., Choi U.B., Weis W.I., Diao J., Südhof T.C., Brunger A.T., (2015) Architecture of the Synaptotagmin-SNARE Machinery for Neuronal Exocytosis. *Nature* 525:62-67
3. Zhao M., Wu S., **Zhou Q.**, Vivona S., Cipriano D.J., Cheng Y., Brunger A.T., (2015) Mechanistic insights into the recycling machine of the SNARE complex. Nature 518:61-67
4. **Zhou Q**., Li J., Yu H., Zhai Y., Gao Z., Liu Y., Pang X., Zhang L., Schulten K., Sun F., Chen C., (2014) Molecular insights into the membrane-associated phosphatidylinositol 4-kinase IIα. *Nature Communication* 5:3552.
5. **Zhou Q.**, Zhai Y., Lou J., Liu M., Pang X. and Sun F., (2011) Thiabendazole inhibits ubiquinone reduction activity of mitochondrial respiratory complex II via a water molecule mediated binding feature. Protein & Cell, 2(7):531-542.