Jennifer Lippincott-Schwartz, PhD
Senior Group Leader
Janelia Research Campus

Jennifer Lippincott-Schwartz's research uses live cell imaging approaches to analyze the spatio-temporal behavior and dynamic interactions of molecules in cells.

Biography

Not many people can say they've braved Wyoming's wilderness – and even fewer can say they did so when they were teenagers. But as a senior in high school, the idea of scaling boulders, foraging for food, and eluding lumbering grizzly bears captured Jennifer Lippincott-Schwartz's imagination. Her graduation gift was a wilderness training course culminating in a multiday survival test.

"You're basically left in the mountains with three other people – no food – and you have five days to find your way back to the base," Lippincott-Schwartz recalls. The trying excursion fueled her passion for the natural sciences.

Although she loved biology, Lippincott-Schwartz flirted with the humanities, earning degrees in philosophy and psychology at Swarthmore College. After graduating, she took time out to teach science and math in Africa. There, she fell back in love with science.

When Lippincott-Schwartz returned to the United States, she pursued a master's degree in Philip Hanawalt's lab at Stanford University, studying DNA repair. As she dug into the roles of repair enzymes, she couldn't help but think, "I'm breaking cells apart to purify a single enzyme, but what about the entire system – how does the cell, as a whole, function?"

She followed her nose on that question while earning her PhD at Johns Hopkins University, in Douglas Fambrough's lab. Her work focused on lysosomes, organelles responsible for the

breakdown of unwanted proteins in cells. Using antibody targeting and fluorescence microscopy, Lippincott-Schwartz discovered the lysosomal-associated membrane protein, LGP120.

But it was during her postdoctoral work with Richard Klausner, at the National Institutes of Health (NIH), that things really took off. There, she coauthored 19 papers that included the identification of a surprising new protein degradation pathway in which the endoplasmic reticulum (ER) degrades entire proteins, and a retrograde pathway for protein trafficking from the Golgi back to the ER.

Lippincott-Schwartz stayed on at the NIH, as a primary investigator and chief of the Section on Organelle Biology in the Cell Biology and Metabolism Branch. Hoping to expand her research into live-cell imaging, she began searching for a way to tag proteins in live cells. Eventually her group created a photoactivatable form of green fluorescent protein (GFP), which allowed them to switch a tagged protein's green glow on and off using flashes of light.

Her discovery led to a fruitful collaboration with physicists Eric Betzig and Harald Hess (now group leaders at Janelia), who proposed a new function for the photoactivatable protein. The scientists used the protein to generate photoactivatable fluorophores, or dyes, which enabled them to illuminate different sets of molecules sequentially, creating a microscope image far more detailed than previously possible. The method, called super-resolution microscopy, garnered Betzig the 2014 Nobel Prize in Chemistry.

Using super-resolution microscopy and other fluorescence imaging techniques, Lippincott-Schwartz's NIH lab group probed subcellular processes, such as lipid droplet formation and organelle dynamics, for nearly three decades.

In 2016, Lippincott-Schwartz moved her lab to Janelia, where she continues to investigate cell biology, but in the context of the brain. Her group studies neurobiology on a cellular level, looking into processes such as organelle trafficking and metabolism, to better understand how nerve cells communicate and behave in normal and diseased brain function.

David I. Yule, Ph.D.
Louis C. Lasagna, Professor of Experimental Therapeutics,
Director, Physiology Strand of Human Structure and Function,
Professor, Department of Pharmacology and Physiology

"Computational Modeling of Salivary Secretion: Insight from *in vivo* measurements of Intracellular Calcium Signaling Events in Submandibular Glands."

Abstract
Salivary fluid secretion involves an intricate choreography to result in the trans-epithelial transport of NaCl and water into the acinus lumen. Current models are based on experimental observations in enzymatically isolated cells where the Ca^{2+} signal invariably propagates globally and thus appears ideally suited to activate spatially separated Cl and K channels. We monitored Ca^{2+} signals and salivary secretion in live mice expressing GCamp6F, following stimulation of the nerves innervating the submandibular gland. Consistent with *in vitro* studies, Ca^{2+} signals were initiated in the apical endoplasmic reticulum. In marked contrast to *in vitro* data, highly localized trains of Ca^{2+} transients that failed to propagate from the apical region were observed. Following stimuli optimum for secretion, large apical-basal gradients were elicited. Given this incompatibility to the previous model, a new mathematical model was constructed to explain how salivary secretion can be efficiently stimulated by apically localized Ca^{2+} signals.

James McGrath, Ph.D.
Professor of Biomedical Engineering
Department of Biomedical Engineering

"Silicon Nanomembranes as an Enabling Platform for Modeling and Imaging of Barrier Tissues."

Abstract:
Now more than a decade after we first used silicon microfabrication to create free-standing ultrathin nanoporous membranes, the materials are realizing their potential in multiple disciplines. Among these disciplines is the growing field of "Tissue Chips" - in vitro systems that seek to mimic human tissues "on-a-chip" to enable controlled, reductionist experiments with the potential for high throughput discovery. Because the thinness and permeability of our nanomembranes are comparable to natural basement membranes (~100 nm), and because membrane thinness confers glass-like optical transparency, we have discovered their value for the construction and imaging of barrier tissue models. We have developed a highly distributable platform for the construction of barrier mimetics that we call the µSiM (**micro**physiological system enabled by a **si**licon **m**embrane) and are applying the µSiM platform to create vascular mimetics of the blood-brain, blood-lung, and blood-tendon barriers. In our most translational application to date, we have applied the µSiM as a model of the porous osteocanilicular network (OLCN) in bone which is colonized by *S. Aureus* during osteomyelitis. The µSiM-CA (**canalicular a**rray) has been used to demonstrate the ability of *S. Aureus* to invade pores smaller than their nominal size, to identify PBP4 as an essential gene for OLCN invasion, and is now being used to identify small molecule inhibitors of PBP4. The high quality live cell imaging enabled by our vascular mimetics allow unparalleled examination of immune cell trafficking from blood to tissue in applications to inflammation, sepsis, and wound healing. When combined with rapid 3D imaging made possible by spinning disk confocal microscopy and a forthcoming (Rochester-built) light sheet microscope, we anticipate live cell imaging on the µSiM platform will give rise to massive 4D data sets. Capturing and interpreting this data are technical challenges that require both cutting-edge computational power and machine learning algorithms for automation. We will discuss our early progress working with data scientists to takle this formidable bottle-neck so that we can realize the full potential of our platforms to reveal the wonderfully complex dynamics of barrier model microenvironments.

Dan Bergstralh, Ph.D.
Assistant Professor
Department of Biology

“Depth, not Breadth: How Do Epithelial Cells Organize in Z?”

Abstract
Epithelial tissues line the boundaries of organs, where they perform critical functions including secretion, absorption, and protection. These tissues are typically built up from sheets of cells that are one-cell thick, and tissue function requires that the cells that comprise these sheets have a regular, side-by-side organization. How is this organization established and maintained? These questions have interested scientists for decades. Our lab is taking a new approach, combining mesoscale quantitative imaging with *in silico* modeling, to address them. Our results support a model in which uniform architecture emerges from mechanical properties, including cell-cell and cell-substrate adhesions, in combination with densification.