Selected recent publications

Poulton et al. (2017) Journal of Cell Biology, 216, 1255-1265

Choi, W. et al. (2016) Journal of Cell Biology 213, 243-260

Pronobis et al. (2015) eLife 4, e08022

Poulton et al., (2014). Developmental Cell 30, 731-745

Bilancia et al., (2014) Developmental Cell, 28, 394-408

The Peifer lab: Choosing cell fate and assembling the body plan: how it goes right in embryos and wrong in cancer

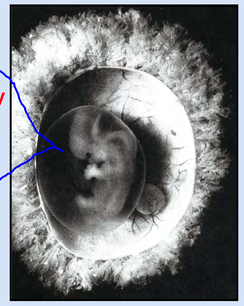
THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

NIGMS

Affiliations: Department of Biology, Lineberger Comprehensive Cancer Center, and Curricula in Genetics and Molecular Biology, Neuroscience, and Cell Biology and Physiology

http://peiferlab.web.unc.edu peifer@unc.edu

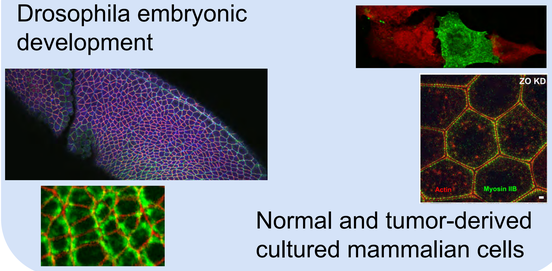
How did my body get built?



Our goal: Define how cells choose fate and assemble tissues and organs, and determine how this goes wrong in cancer

We combine two major model systems:

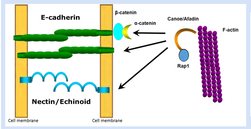
Drosophila embryonic development



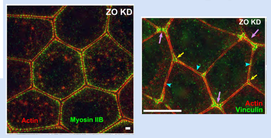
Normal and tumor-derived cultured mammalian cells

How do cells remodel their cytoskeletons and cell-cell junctions so that they can change shape and move during morphogenesis without disrupting epithelial integrity and barrier function?

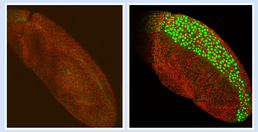
Cadherin-catenin complexes mediate cell adhesion and link junctions to the cytoskeleton

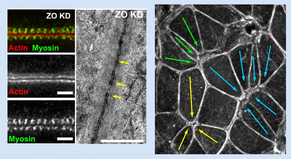


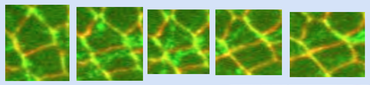
We're also using shRNA knockdown and SIM superresolution microscopy to define how mammalian cells link junctions and the cytoskeleton to maintain tissue integrity

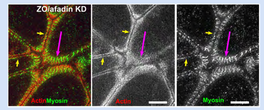


Loss of Canoe in vivo disrupts critical cell shape changes like apical constriction during mesoderm invagination

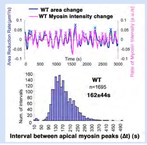


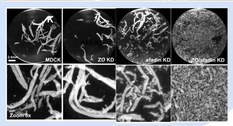






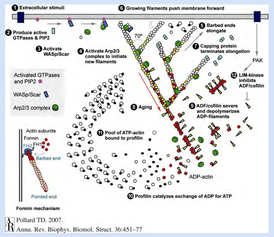
Combining live cell imaging and computational tools allow us to put numbers on dynamic cytoskeletal events revealing new insights





How do cells regulate their actin cytoskeletons during cell migration and shape change and how do oncogenic mutations alter this?

Our challenge: to determine how cells use this complex actin regulatory toolkit during normal development and how it goes wrong in disease



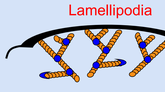
We use Drosophila and cultured cells to explore this at ALL levels of organization

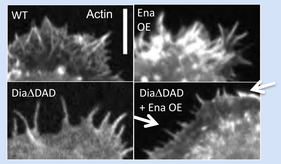
Molecular machines — Cells — Whole animals

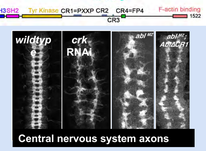
We also explore how the oncogenic kinase Abl regulates the cytoskeleton in both epithelial cells and the nervous system

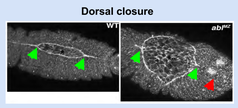
Genetics and live imaging provide insights into how cells make protrusions and thus migrate in a dish and in vivo

Lamellipodia — Filopodia









Current Funding

NIH 1 R35 GM118096 (MIRA Award)
Regulating cell fate and shaping the body plan during morphogenesis and their alteration during oncogenesis July 2016-June 2021

Peifer Lab Trainees

18 Ph.D. Students and 20 postdocs have or are training in our lab. Alumni have gone on to success in diverse careers in science. Examples include:

Tony Harris, Professor, U Toronto

Don Fox, Assistant Professor at Duke

Nasser Rusan, Investigator &Lab Head, NHLBI

Catarina Homem, PI, CEDOC, Lisbon

Karen Hales, Professor, Davidson College

Ed Rogers, Senior Scientist, Janelia

Joe Louriero, Senior Investigator I, Novartis Institutes for Biomedical Research

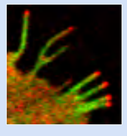
Lizz Grevengoed, Physician Assistant with Western Oncology and Hematology

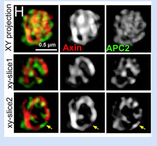
Full list at: http://peiferlab.web.unc.edu/alumni/

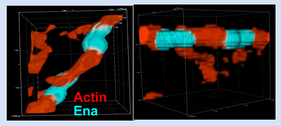
In our own lab and via collaboration we take a very multidisciplinary approach

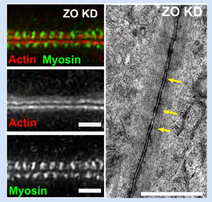
Modern genetic tools including RNAi and CRISPR

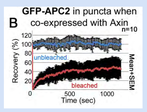
Cutting edge cell biology and microscopy

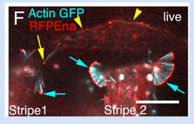




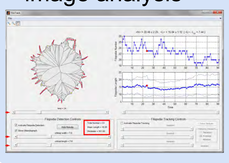








Computational image analysis

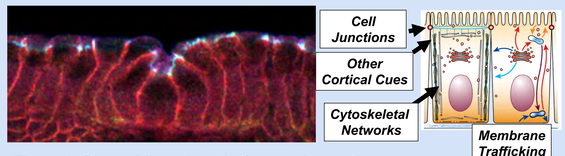


Biochemical approaches including mass spec

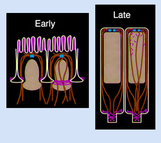
How do cells establish and maintain apical-basal polarity and how does loss of polarity contribute to oncogenesis?

Apical-basal polarity is critical to assemble and maintain the function of all epithelial tissues

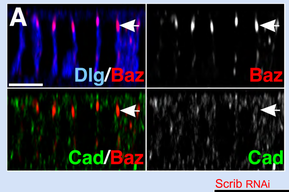
Nelson, 2003

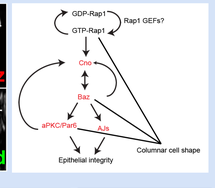


The early Drosophila embryo is the premier system to study establishment of apical-basal polarity

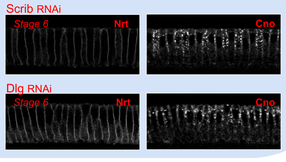


We are defining the network of proteins that act in polarity establishment



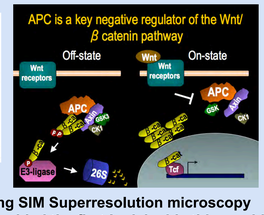


We are continuing to expand this network and define the mechanisms by which proteins act

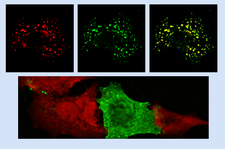


How do tumor suppressors like APC and Axin tightly regulate cell-cell Wnt signaling to allow proper cell fate choices and avoid oncogenic transformation

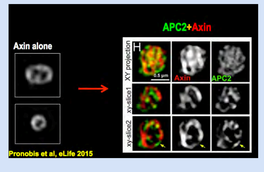
The tumor suppressors APC and Axin, mutated in most colorectal cancers, are negative regulators of the Wnt pathway

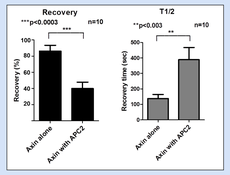


We're using human colorectal cancer cells to define the workings of this megadalton Multiprotein machine



Combining SIM Superresolution microscopy with FRAP provided the first look inside this machine revealing a role for APC in stabilizing Axin polymerization





Functional tests in flies and cultured cells revealed a key role for phosphorylation by GSK3

How do cells maintain genome stability in the face of mutations affecting proteins that help build the mitotic spindle or regulate key cell-cycle checkpoints

Centrioles were thought to be the key organelle that nucleates the mitotic spindle

We found loss of centrosomes slowed but did not prevent Spindle assembly, but many cells lost genome stability and underwent apoptosis

Mutations affecting human Centrosomal proteins are the primary genetic cause of microcephaly

While fly brains can tolerate Centrosome loss, Combined loss of centrosomes plus the spindle assembly checkpoint (SAC) leads to microcephaly

Centrosome plus SAC loss leads to massive aneuploidy and polyploidy, a hallmark of most advanced-stage cancer cells

Genotype	# Normal	# Aneuploid	# Polyploid	% Abnormal
yw	140	4	0	2.8%
mad2	108	7	1	6.9%
sas-4	129	15	0	10.4%
mad2,sas-4	12	34	14	80.0%

p<0.0001