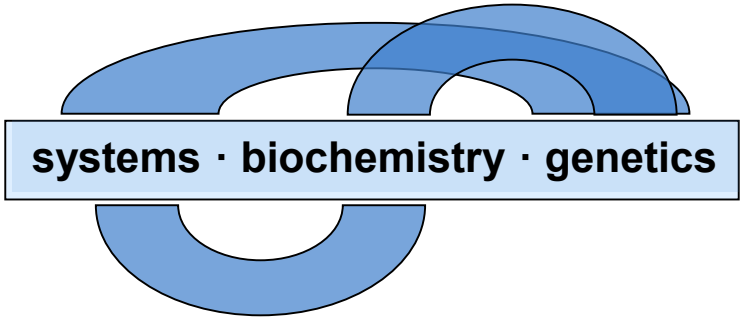
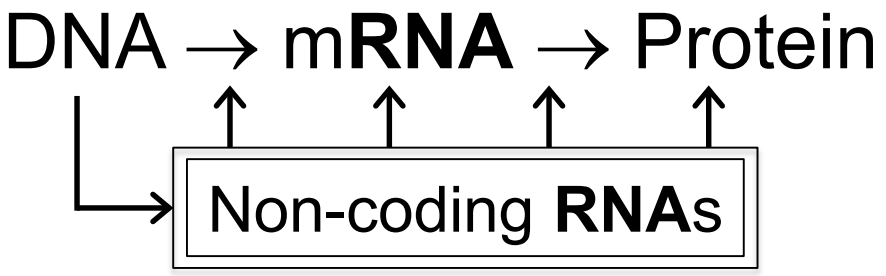
The Gilbert Lab @ Yale

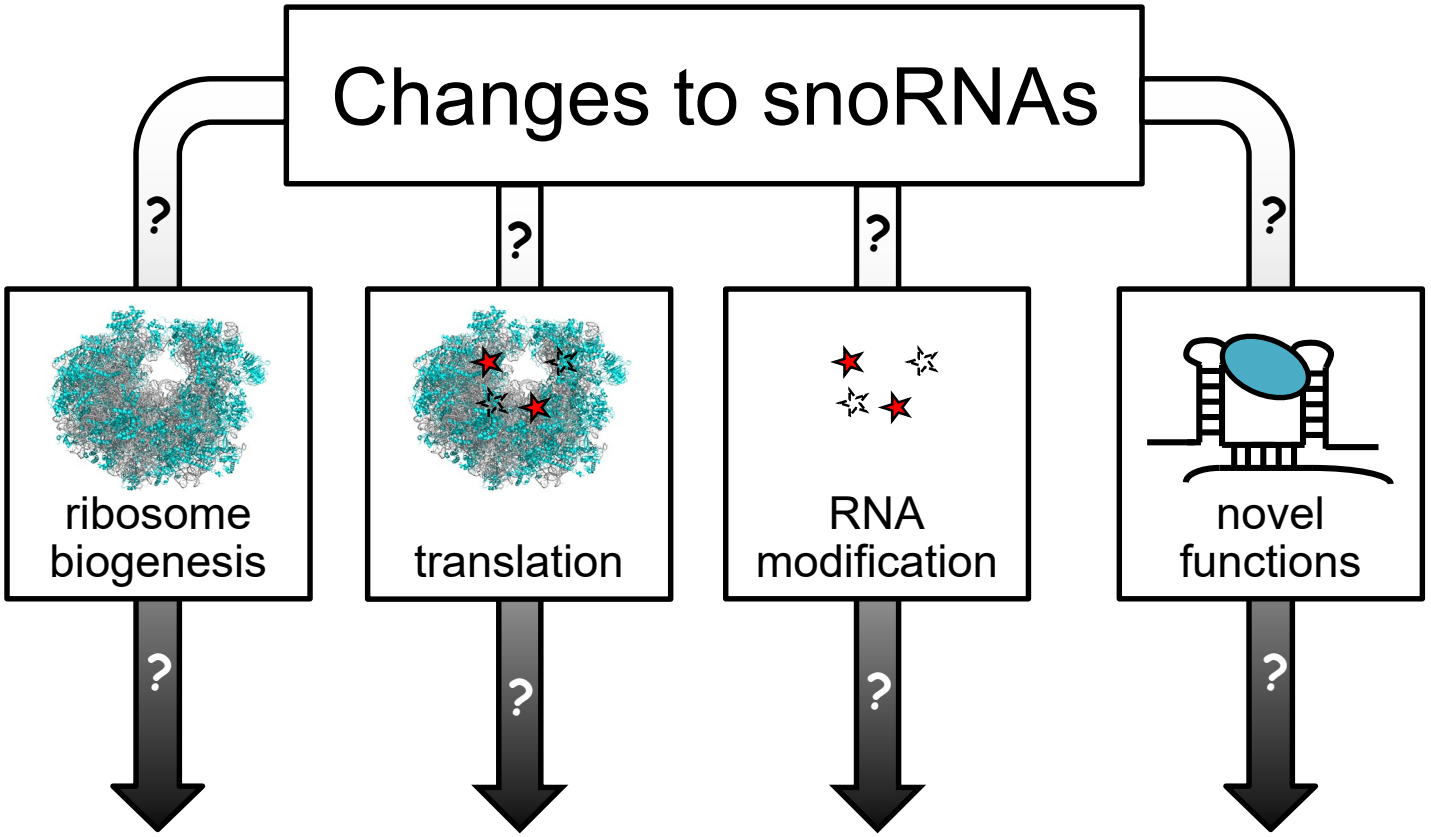
We invent new technology and investigate the ***how*** and ***why*** of post-transcriptional gene regulation





wendy.gilbert@yale.edu Visit us in SHM C129!

snoRNAs are an important class of non-coding RNA recurrently mutated or dysregulated in cancer. ***Why***?



Cancer

Come learn with us!

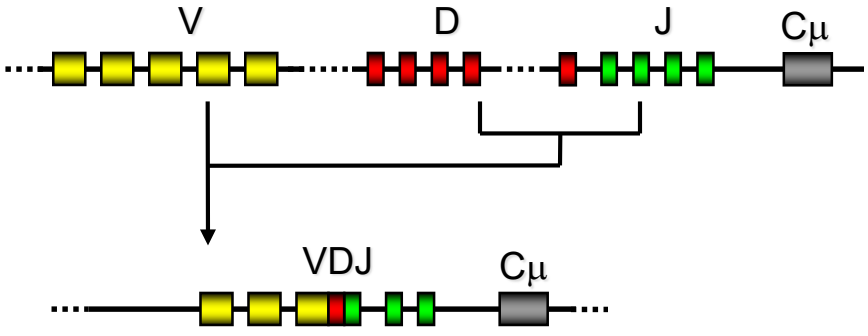
- we're looking for up to 3 students
- weekly lab meetings
- supportive mentoring
- contact me if you are interested!

wendy.gilbert@yale.edu

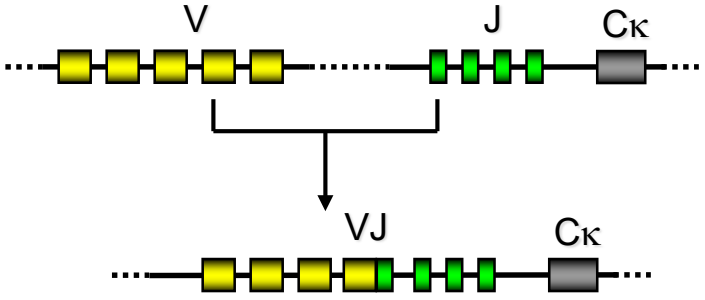
@GilbertLabRNA @WendyGScientist

VDJ Recombination

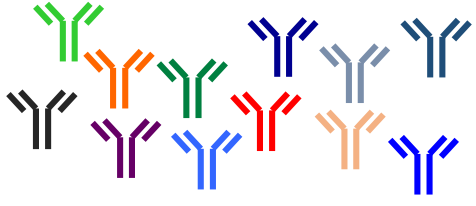
Ig heavy chain gene (Igh)



Ig kappa light chain gene (Igκ)



Billions of antibodies
(B cells)



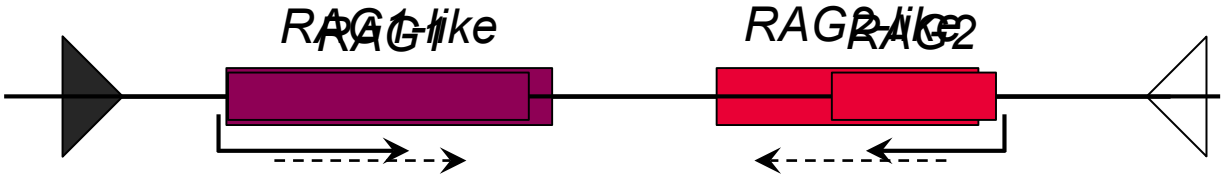
Billions of T cell receptors
(T cells)

What are the evolutionary origins of V(D)J recombination?

Transposon "Molecular Domestication": A pivotal event in the evolution of our adaptive immune system

Selfish

RAG Transposon



RAG Recombinase

Tamed

Major challenge: how to protect our genome from the destructive potential of an active transposase?

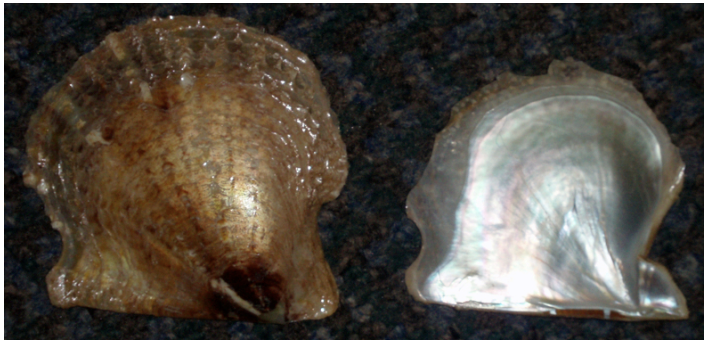
Hundreds of millions of VDJ recombination events each day per person

Species in which RAG-like genes have recently been identified

Mollusca

Eastern oyster
Crassostrea virginica
(fisheries.noaa.gov)

Philippine horse mussel
Modiolus philippinarum
(Hectonicus)



Akoya pearl oyster
Pinctata imbricata
thecephalopodpage.org/MarineInvertebrateZoology/Pinctadaimbricata

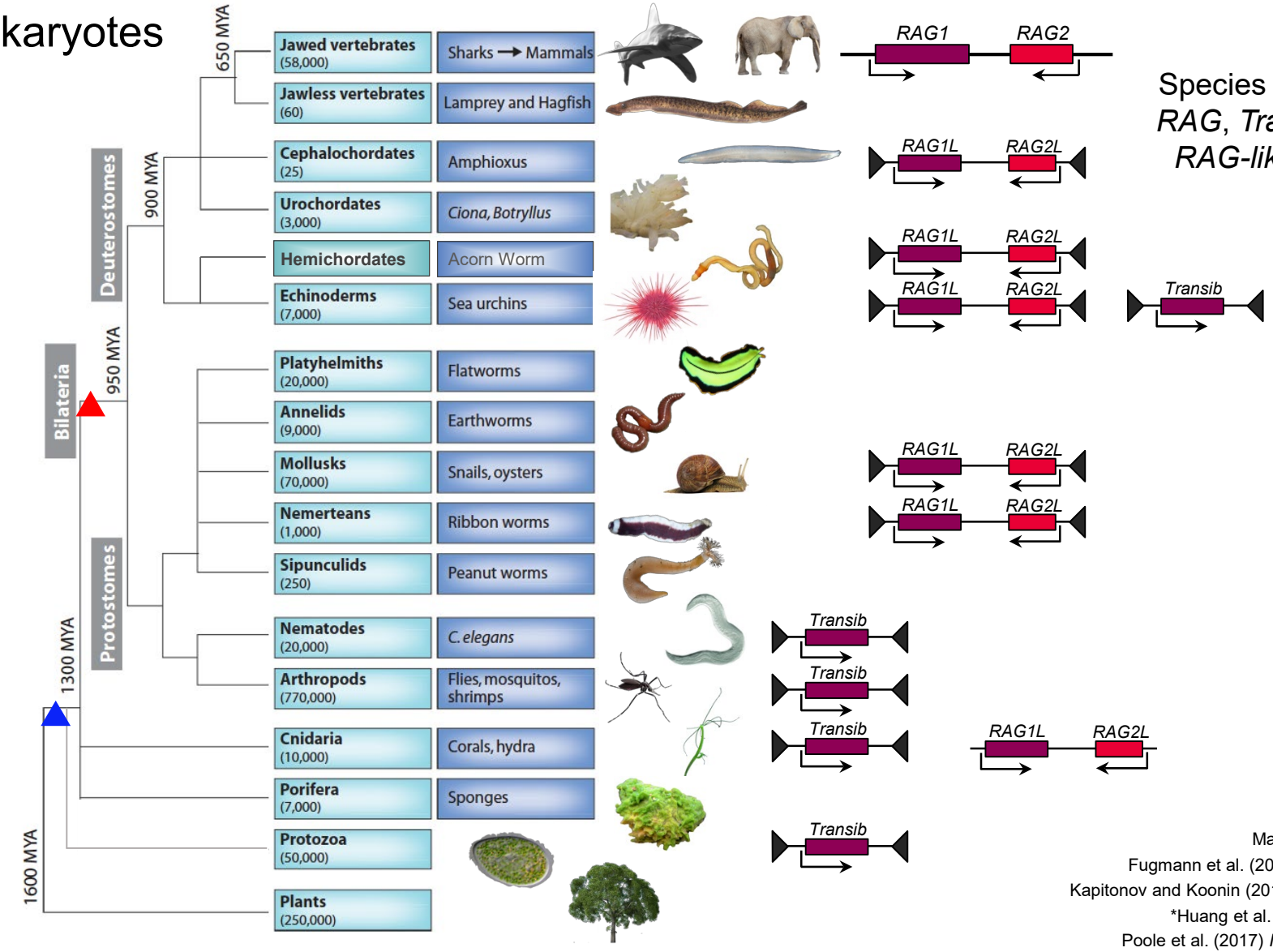
Nemertea

Ribbon worm
Notospermus geniculatus
(Nimrod Shai)

Cnidaria

Moon jellyfish
Aurelia aurita
(Luc Viatour CC BY-SA 3.0)

Eukaryotes

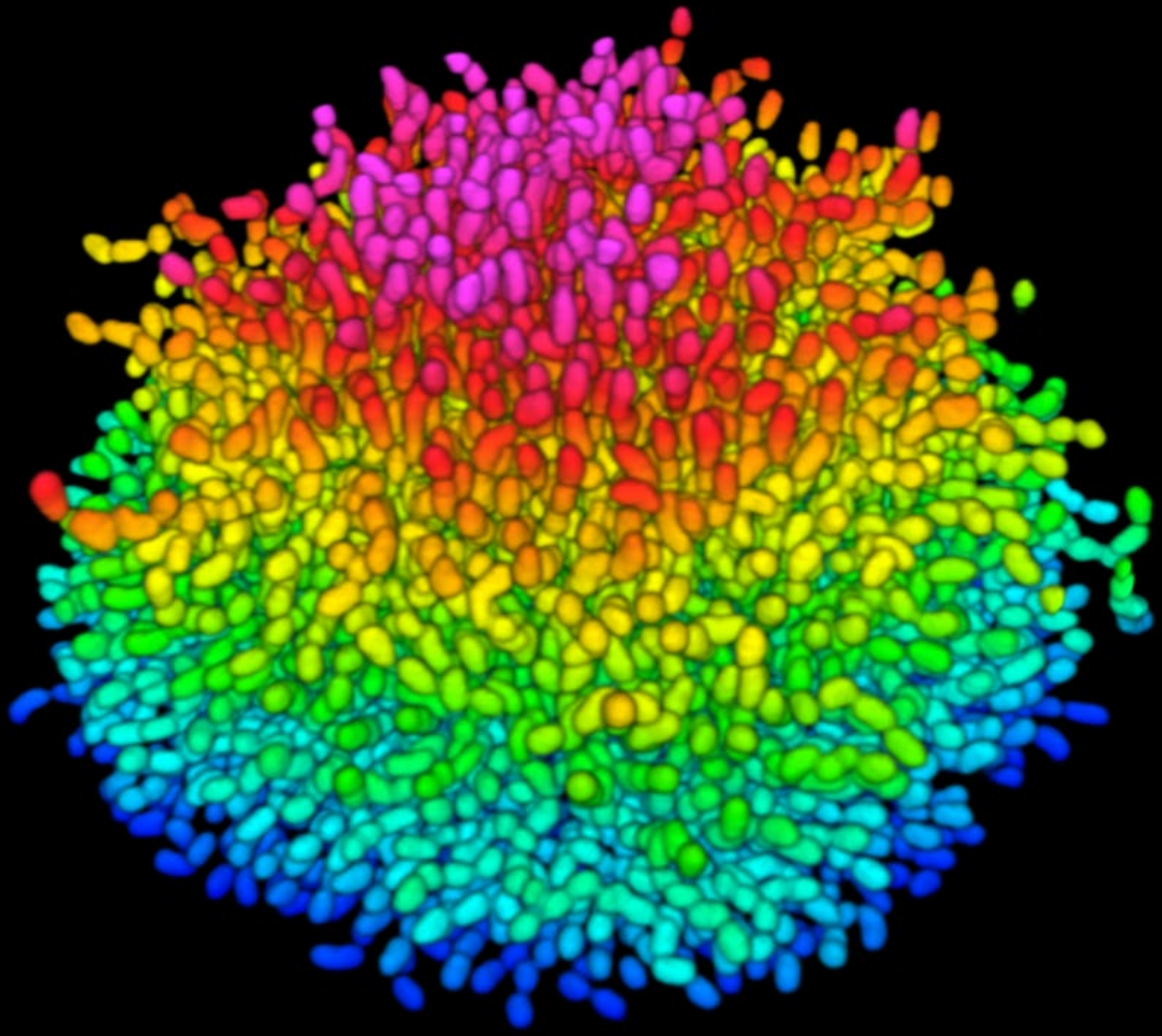


Species harboring *RAG*, *Transib*, and *RAG-like* genes

Martin et al., submitted.
Fugmann et al. (2006) *PNAS 103*:3728.
Kapitonov and Koonin (2015) *Biol Direct 10*:20.
*Huang et al. (2016) *Cell 166*:102.
Poole et al. (2017) *Immunogen. 69*, 391.

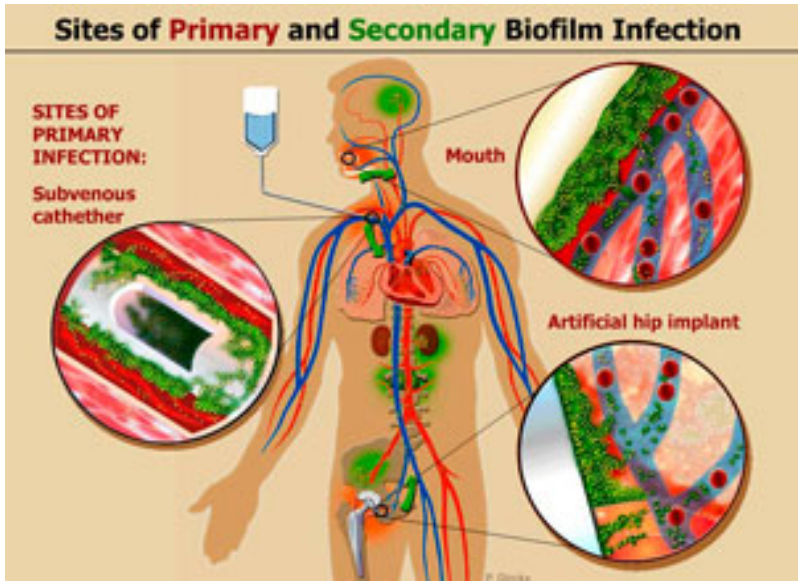
Flajnik and Du Pasquier, Evolution of the Immune System, in Fundamental Immunology, Paul, W. ed. (2013)

How Do Bacteria Build Their Home?

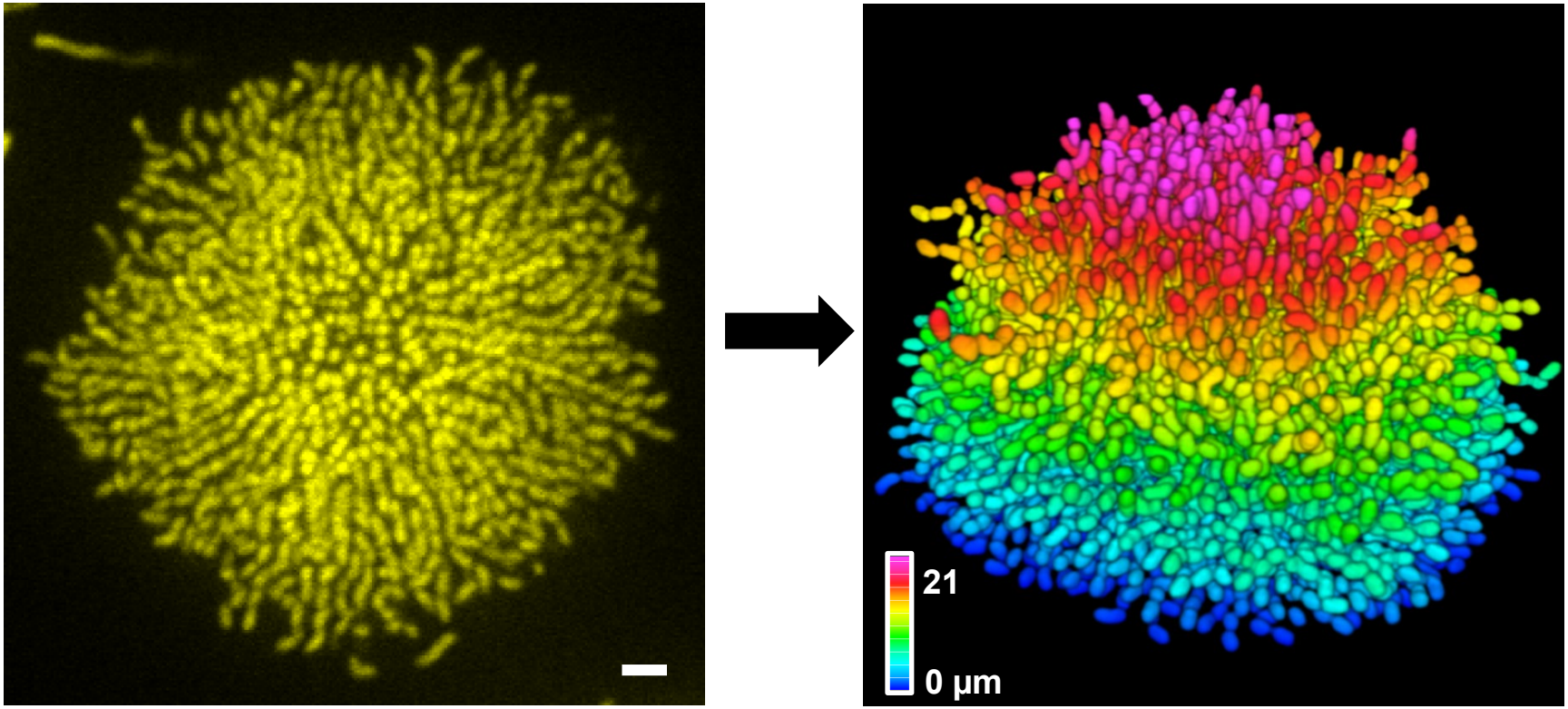


Jing Yan
Quantitative Biology Institute
Department of Molecular, Cellular and Developmental Biology

Bacterial Biofilms Are Everywhere



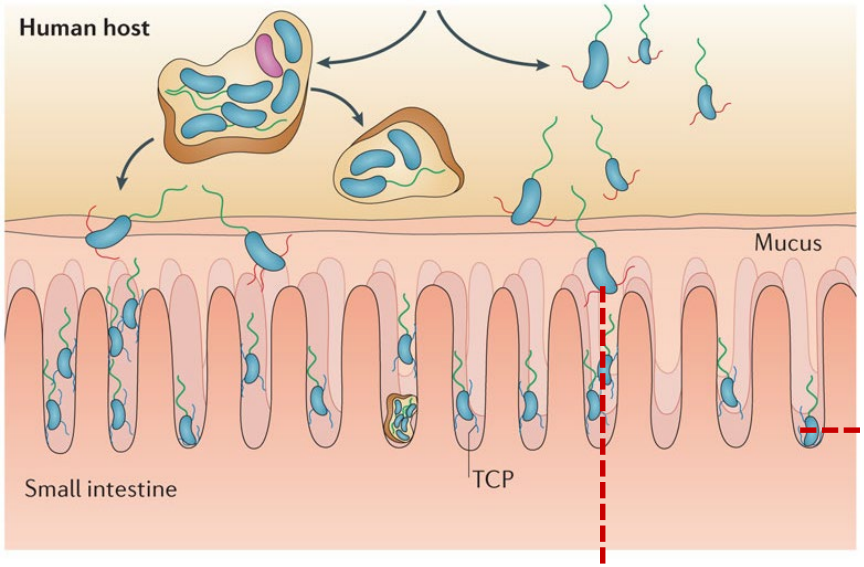
Single-Cell Resolution Imaging of *Vibrio cholerae* Biofilms

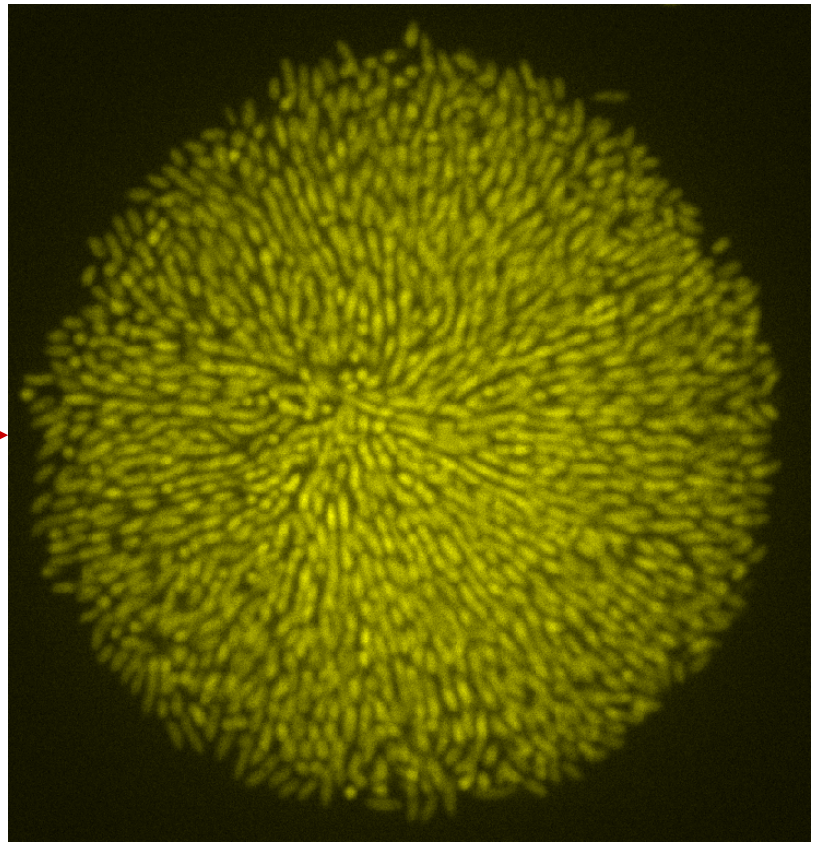


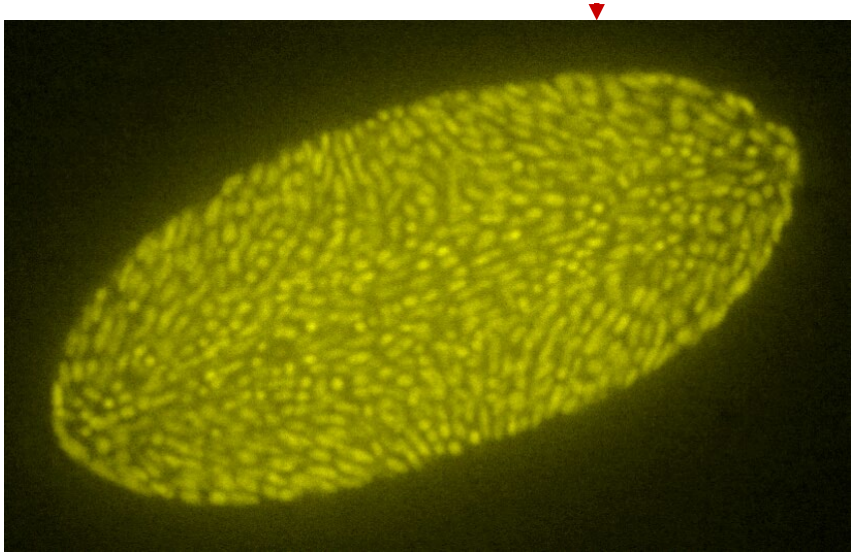
Scale bar: 3 µm

Proc. Natl. Acad. Sci. **113,** E5337 (2016)
Nat. Commun. **8**, 327 (2017)
Nat. Phys. **14**, 954 (2018)

Current Interest: How Do Biofilms Respond to Mechanical Environments?

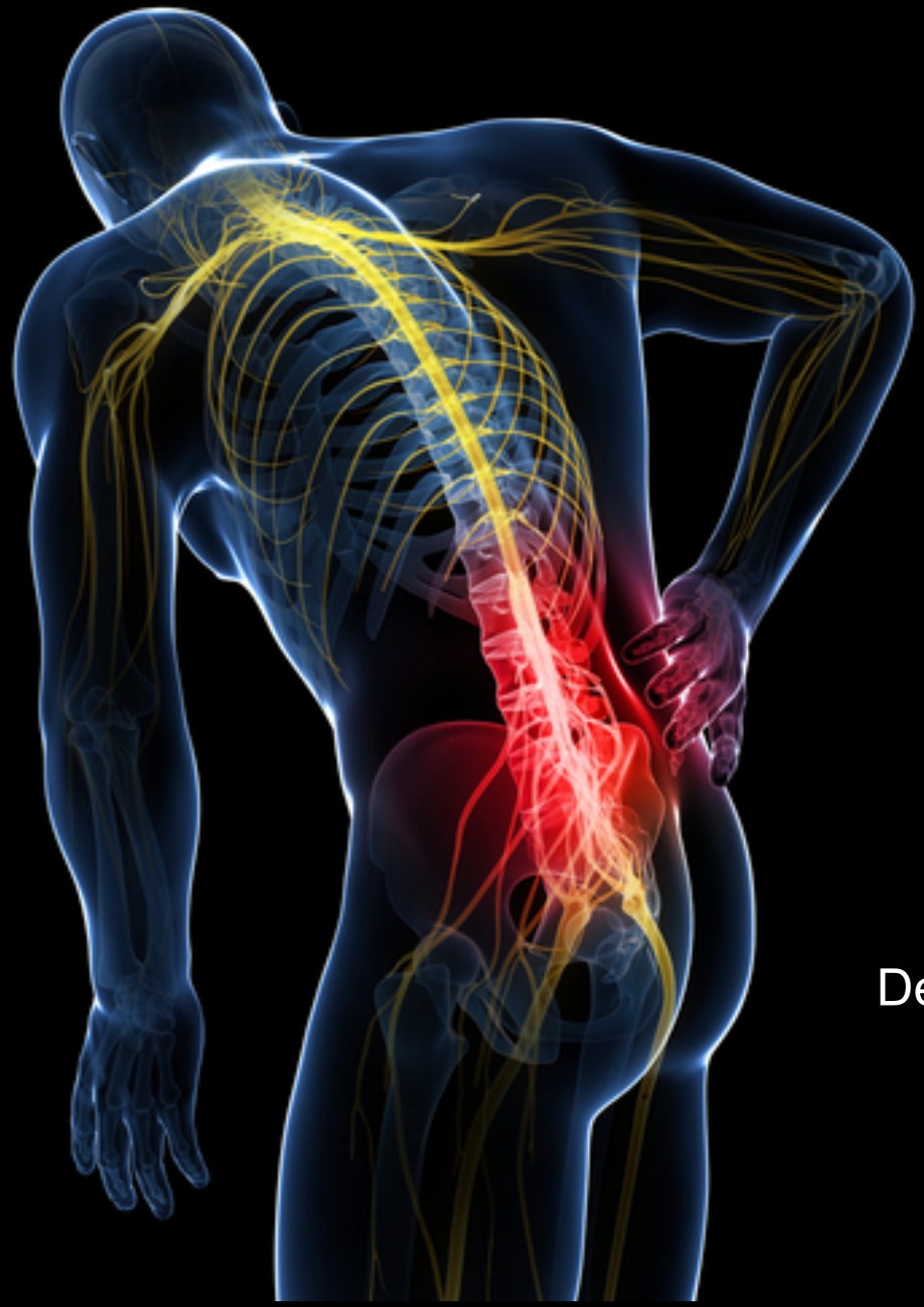






Check https://yanbiofilmlab.yale.edu/ for more information!
Or email jing.yan@yale.edu

Functional plasticity after CNS injury



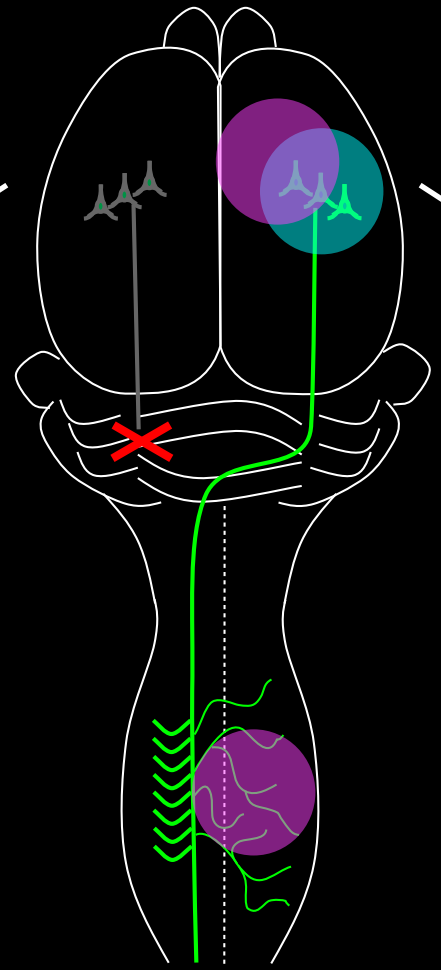
William Cafferty Ph.D
Depts of Neurology and Neuroscience
Yale School of Medicine
#Associate Professor
#Immigrant Scientist
#LGBTQI+ Scientist
william.cafferty@yale.edu

CAFFERTY LAB

Identify and exploit the anatomical and molecular pathways that drive spontaneous recovery of function

Structural / Functional imaging

Chronic *in vivo* 2-photon imaging (GECIs, GEVIs) of soma, spines, dendrites, axons of lesioned and intact neurons in cortex and spinal cord of awake behaving mice.



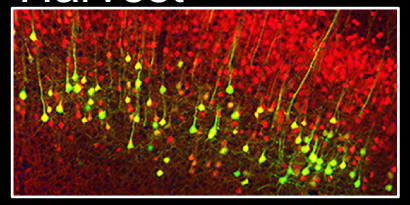
Molecular Profiling / exploitation

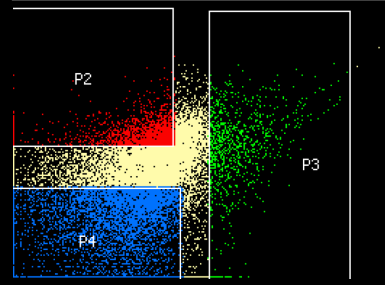
Laser capture microdissection/ FACS of homogenous cell types in an active and quiescent growth mode, RNAseq, *in vivo* exploitation, functional recovery.

CAFFERTY LAB

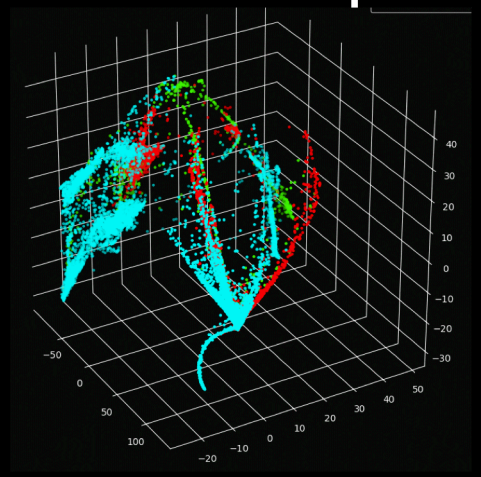
Identify and exploit the anatomical and molecular pathways that drive spontaneous recovery of function

Harvest

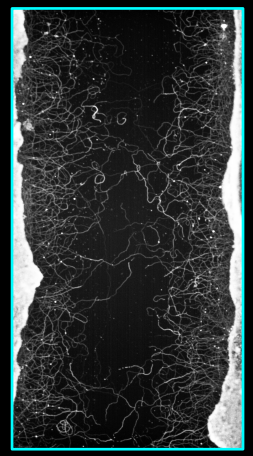


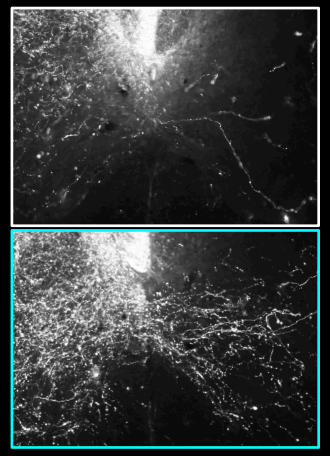


FACS

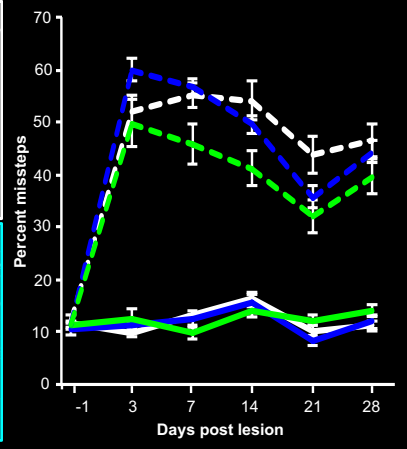


Single cell RNAseq

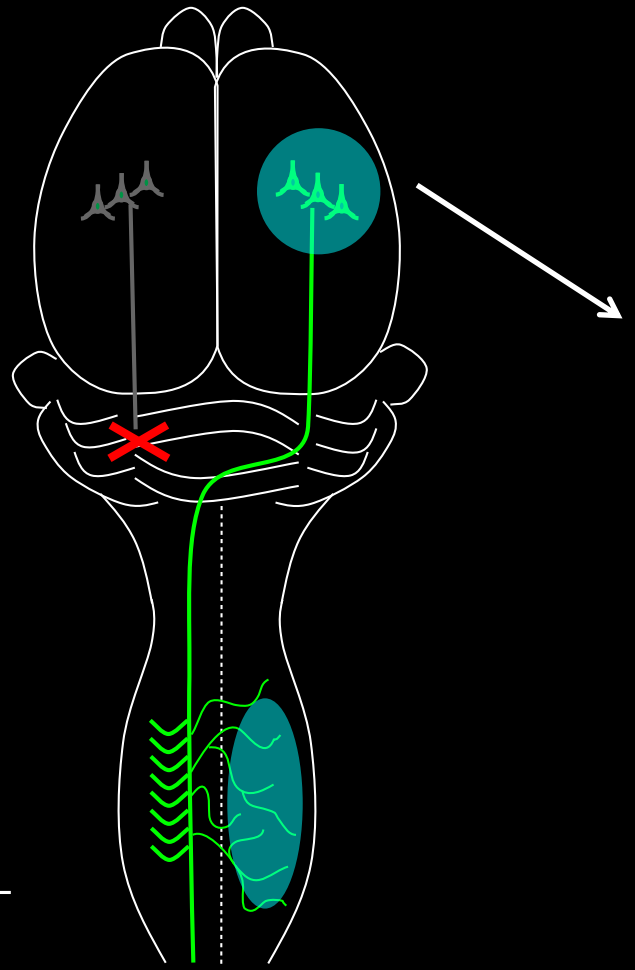




In vitro *In vivo*



Function



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Profiling / exploitation

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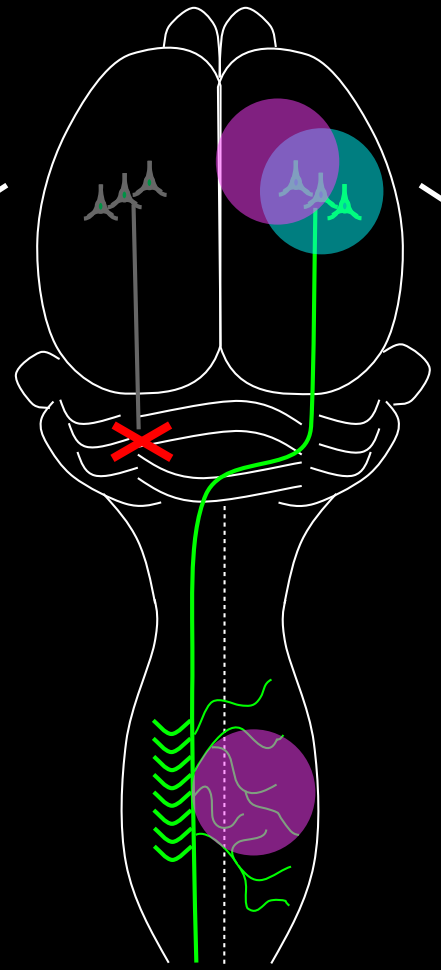
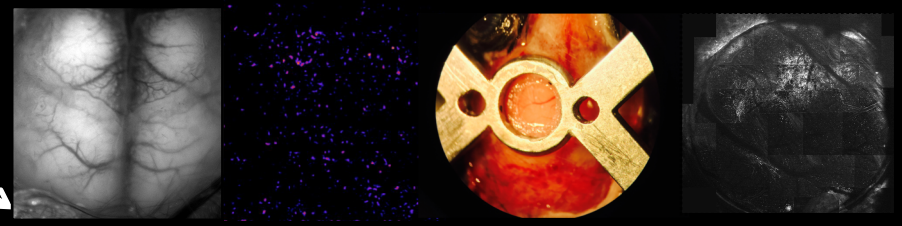


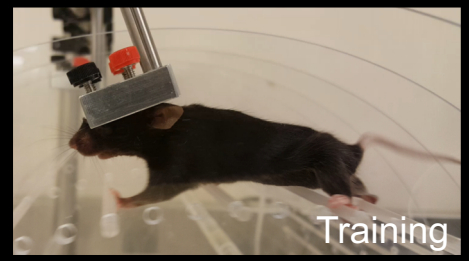
Trans cranial

Meso scale

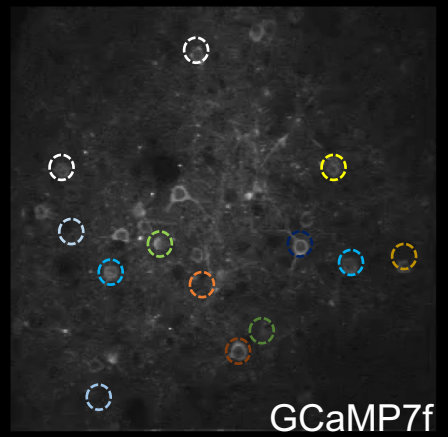
Cranial window

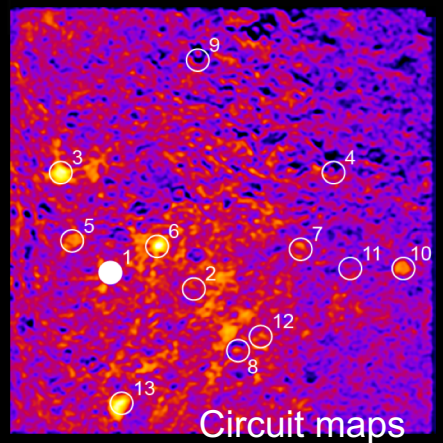
Intersectional GCaMP6





Function

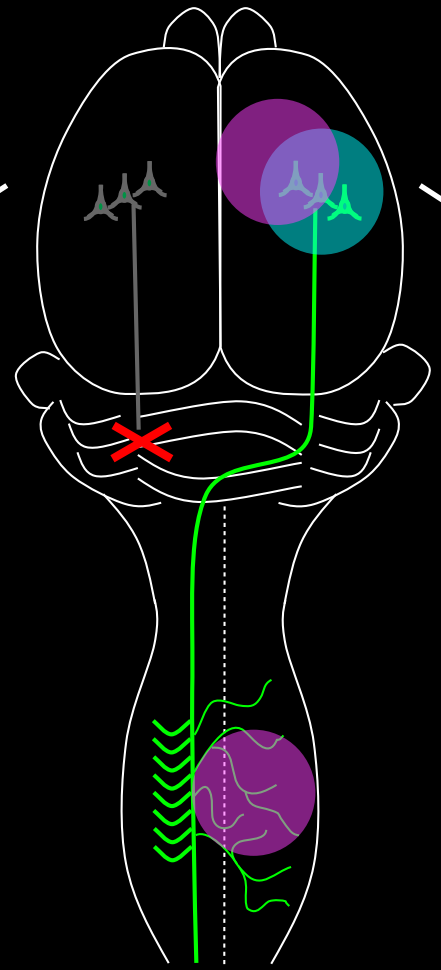




Cafferty lab projects

Structural / Functional imaging

- Layer 2/3 vs. 5?
- Intra/inter hemisphere dynamics after SCI/TBI – therapy?
- Confirm intact functional mapping and plasticity induced recovery with opto/chemogenetics?



Molecular Profiling / exploitation

- Explore CST adult plasticity genes.
- Development (P5) targets?
- Critical period (P28) targets?
- Axotomy genes?
- Rubrospinal, Reticulopspinal?
- Ascending sensory?

(william.cafferty@yale.edu, 300 George street)

Bergwitz Lab information

Lab Head (top photo third from left):

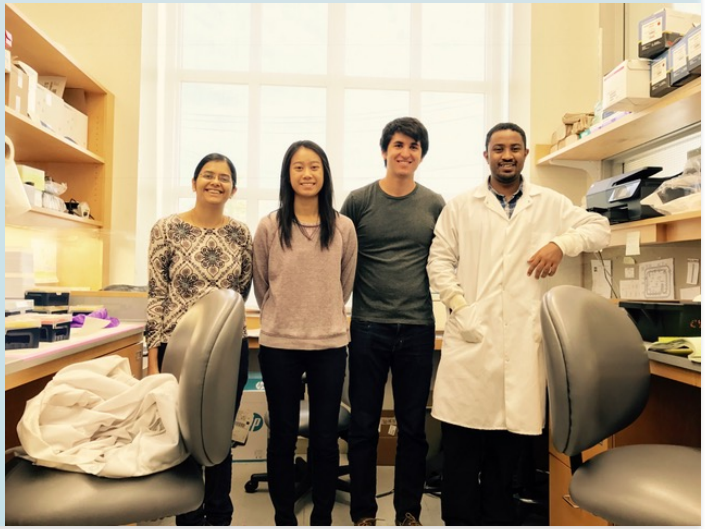
Clemens Bergwitz, M.D.

website:

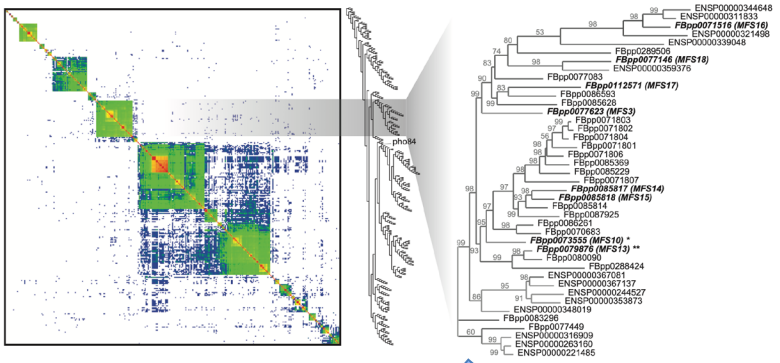
http://medicine.yale.edu/lab/bergwitz/

Associate Professor of Medicine
Yale University School of Medicine
Section Endocrinology and Metabolism
Anlyan Center (TAC), Office S117, Lab S110
1 Gilbert Street
New Haven, CT06519

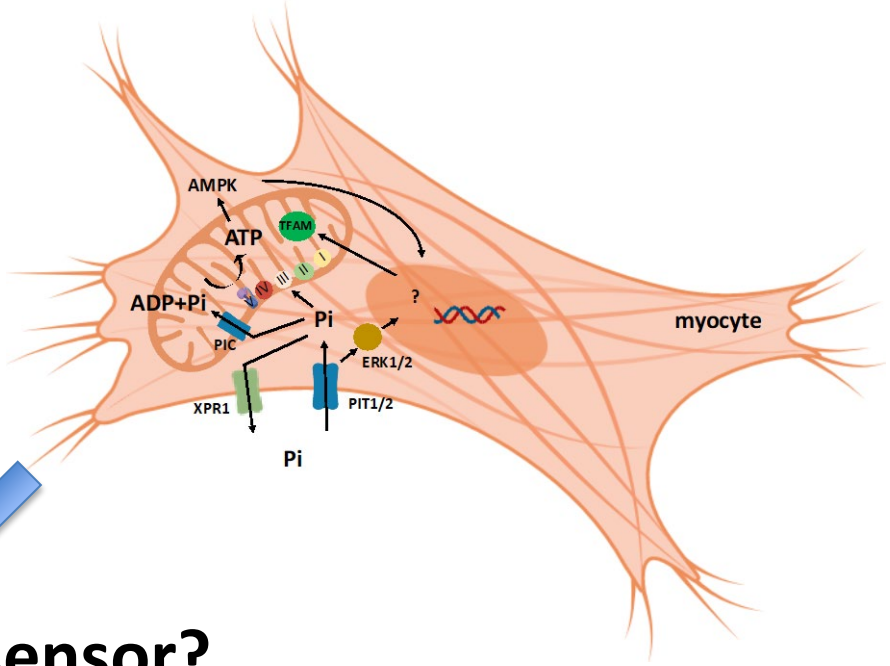
Work Phone: 203-737-5450
Work Fax: 203-785-5535
email: clemens.bergwitz@yale.edu



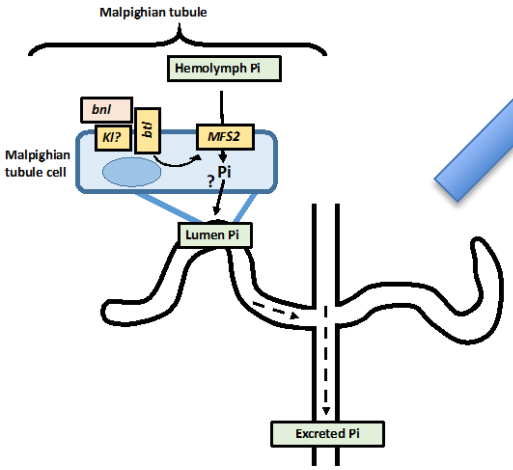
Homologs of bacterial and yeast Pi sensors

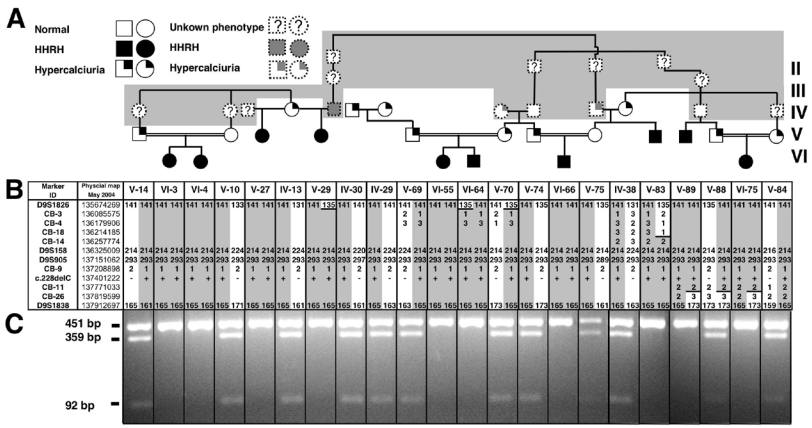


Metabolic Pi sensors in skeletal muscle



Endocrine Pi sensor?





Drosophila Pi-homeostasis

Genetic disorders of Pi-homeostasis

Summer projects 2020

Our research focuses on inborn errors of phosphate metabolism and the endocrine regulation of phosphate homeostasis with emphasis on the metabolic and homeo-static effects of phosphate.

<u>Students will independently conduct one the following projects (2-3 slots available):</u>

- Determine the function of mutant phosphate transporters (adenoviral transduction of cells and life mice followed by Western blot analysis to measure transporter protein expression)
- Determine ATP content and mitochondrial function in skeletal muscle lacking phosphate-transporters (cell culture, seahorse assays, luciferase-based ATP/ADP measurements in cells and muscle tissues)
- Determine mineral metabolism of mice lacking phosphate transporters in skeletal muscle or bone cells (ELISA and colorimetric assays to measure blood phosphate, FGF23, urine phosphate and creatinine)
- Translational research to improve care of patients affected by Hereditary Hypophosphatemic Rickets with Hypercalciuria (HHRH) (review patient records with referring physicians, genotyping PCR and GENEIOUS software analysis of Sanger sequencing reads)

Mentorship

Jan-Feb 2020: Help with applications for summer student scholarships

June-August 2020: Provide written protocols and one-on-one supervision by PI or postdoc during 12 week summer internship, which enables students to independently conduct a small project, which will - if successful - earn them a co-authorship in a line of research that is close to publication

Sept 2020: Opportunity to continue independent research on a 12-hr/week basis during the semester

Track record 2014-2018: 11/12 undergraduate students received scholarship funding, 12/12 students published (7 in peer-reviewed journals, 2 as lead authors, 11 abstracts in international conferences), 9/12 students continued in the semester or returned next summer (3 senior thesis, 2 postbachelaurate, 6 semester projects, see Lab website for names and contact info).

Bleichert Lab

Molecular Mechanisms of Chromosome Duplication

franziska.bleichert@yale.edu

www.bleichertlab.org

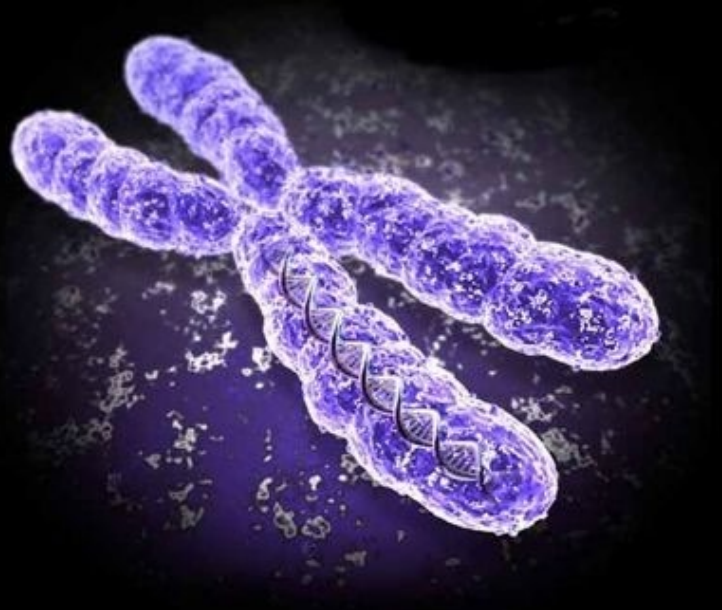


Image credit: Los Alamos National Laboratory

Every human synthesizes ~2 light years of DNA during their lifetime

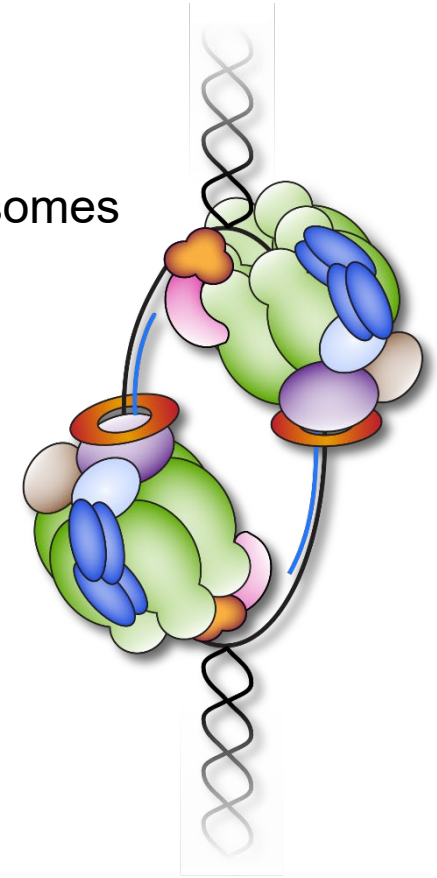
< 1 mistake per 100 million nucleotide incorporation events

Bleichert Lab – Our scientific questions

franziska.bleichert@yale.edu

www.bleichertlab.org

Replisomes



How are DNA replication machineries assembled?

How does chromatin structure influence DNA replication?

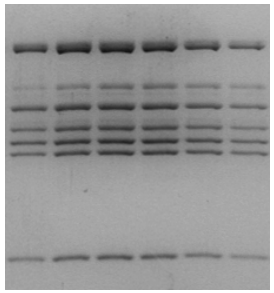
How is dysregulation of these events linked to human diseases?

Bleichert Lab – Our approaches

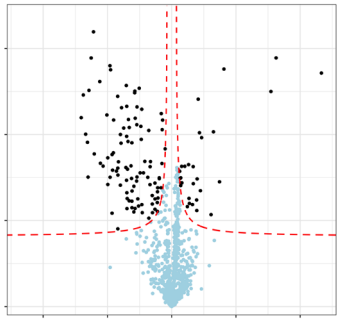
franziska.bleichert@yale.edu

www.bleichertlab.org

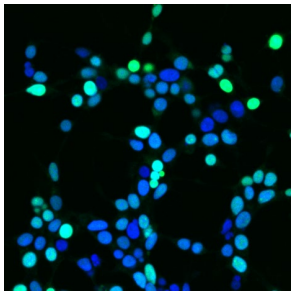
Reconstitution biochemistry



Proteomics

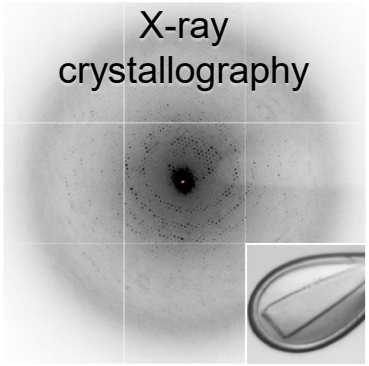


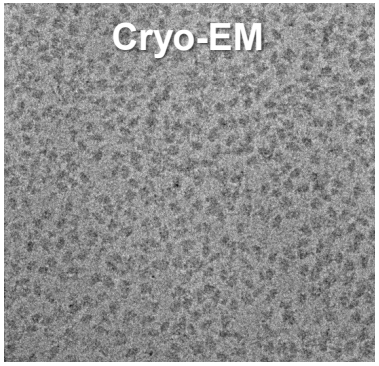
Cell-based



Structural biology

X-ray crystallography





Bleichert Lab – We hope you join us!

franziska.bleichert@yale.edu *www.bleichertlab.org*

We offer:

- Get close mentoring (from PI + student or postdoc)
- Participate in weekly lab meetings/journal club
- Work in an international group
- Study biomedically relevant research question
- Use interdisciplinary approaches

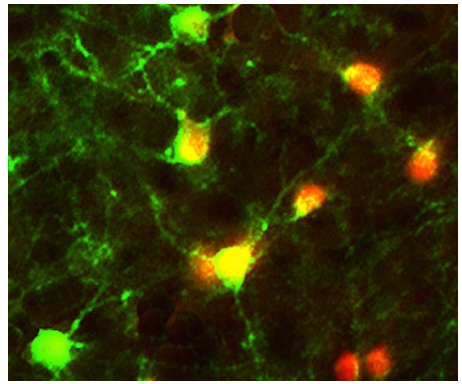
Crair Lab: Neural Circuit Development

Main Question:

How does the brain 'self-organize' (wire itself up) during development?

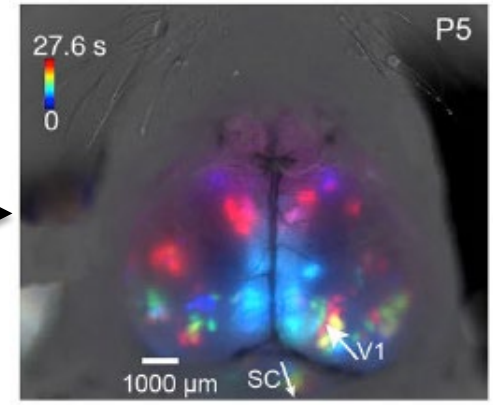
Michael C. Crair
Department of Neuroscience
SHM B301
Yale

Local circuits



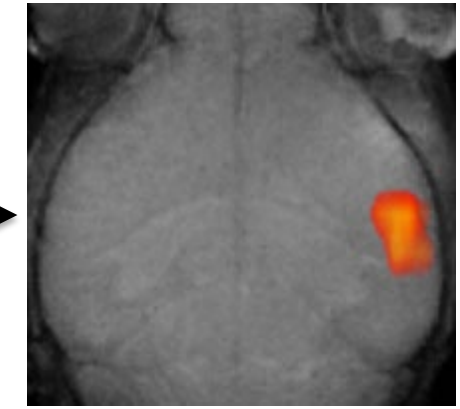
Microscopic (2p Ca^{2+}) activity in single cells

Cortex wide



Mesoscopic (1p Ca^{2+}) wide field imaging

Whole brain



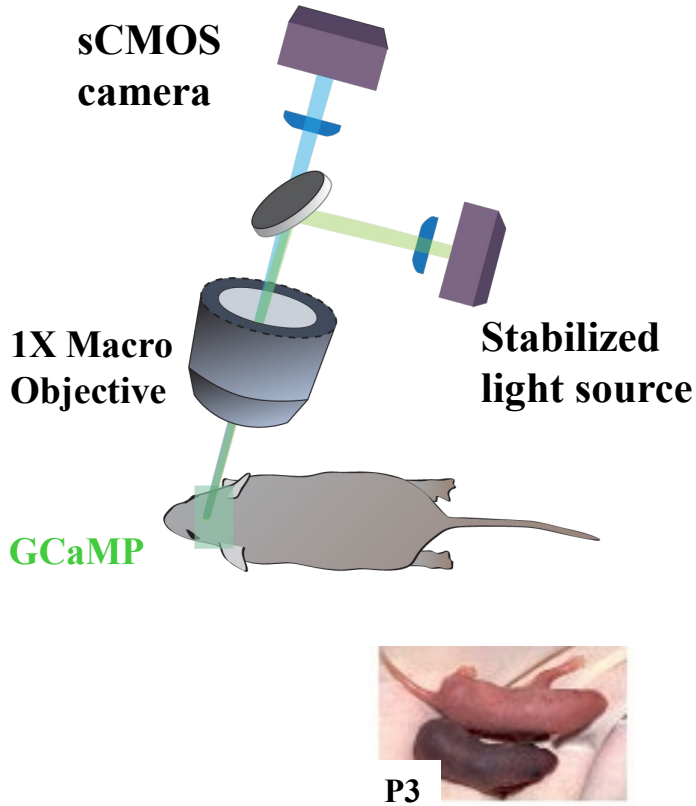
functional MRI

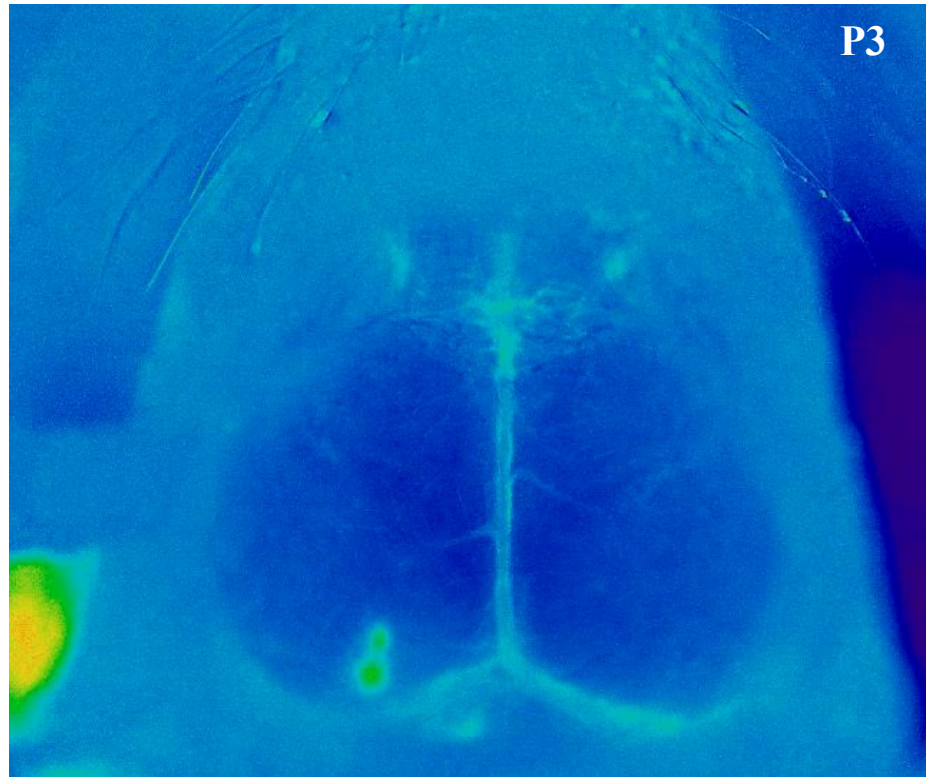
Crair Lab: Neural Circuit Development

Model System:

Mouse (rodent) cortex and sensory systems, particularly vision.

Michael C. Crair
Department of Neuroscience
SHM B301





Crair Lab: Neural Circuit Development

Experimental Approaches:

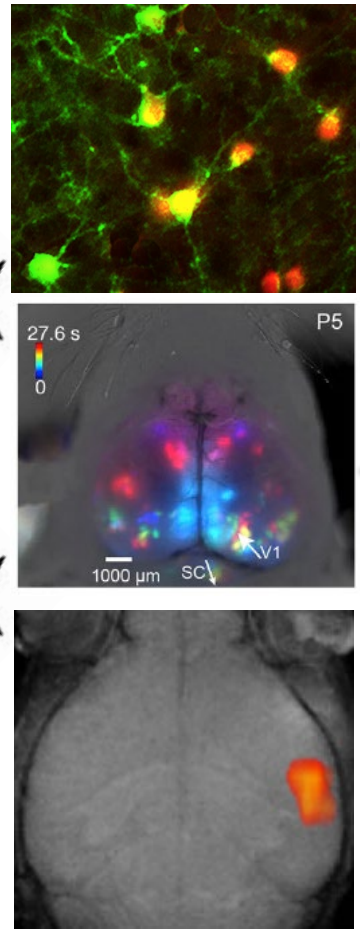
- ***In vivo* imaging of neural activity.**
- **Optogenetic and chemogenetic manipulation of neural activity.**

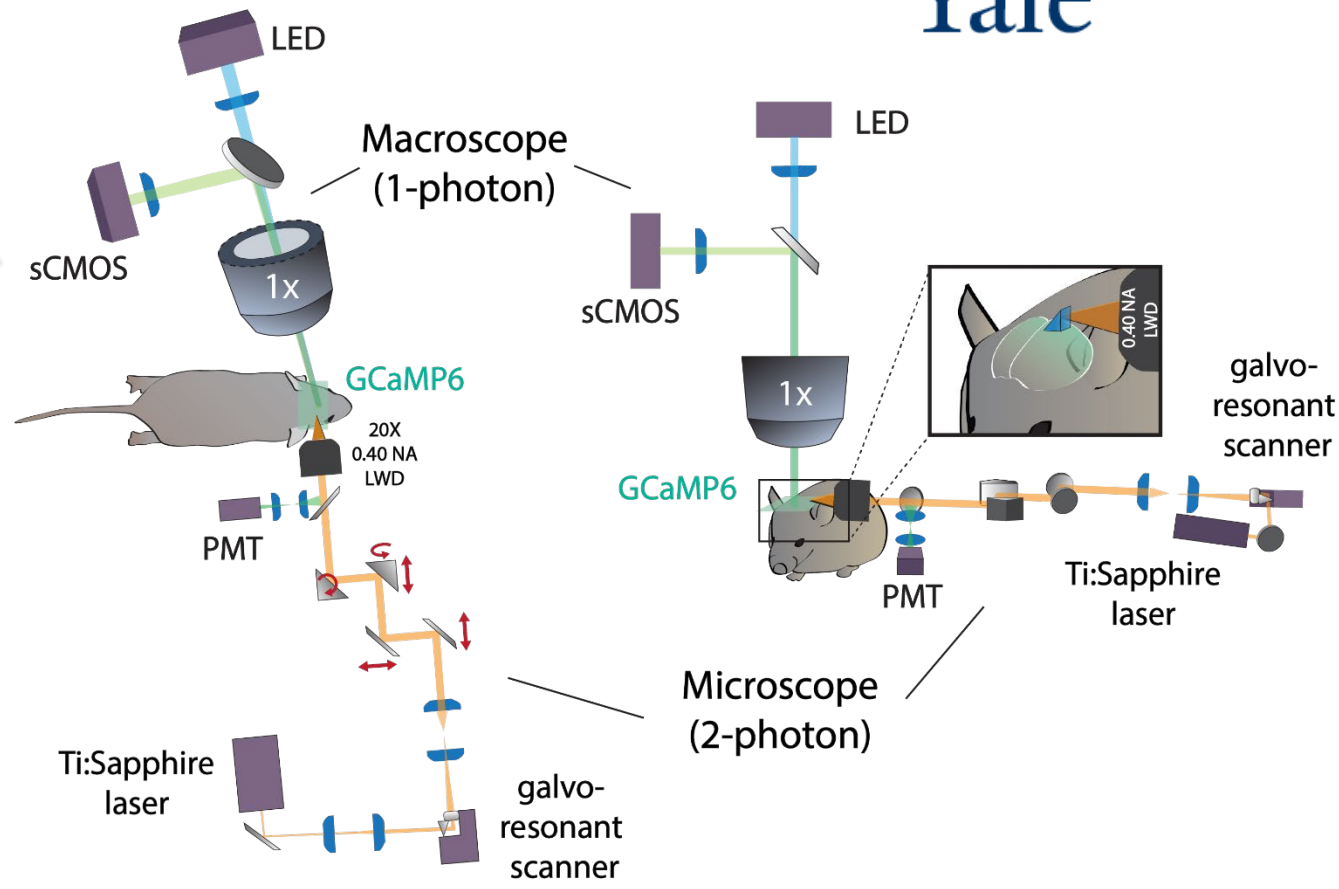
Michael C. Crair
Department of Neuroscience
SHM B301
Yale

Single cells

Cortex

Whole brain





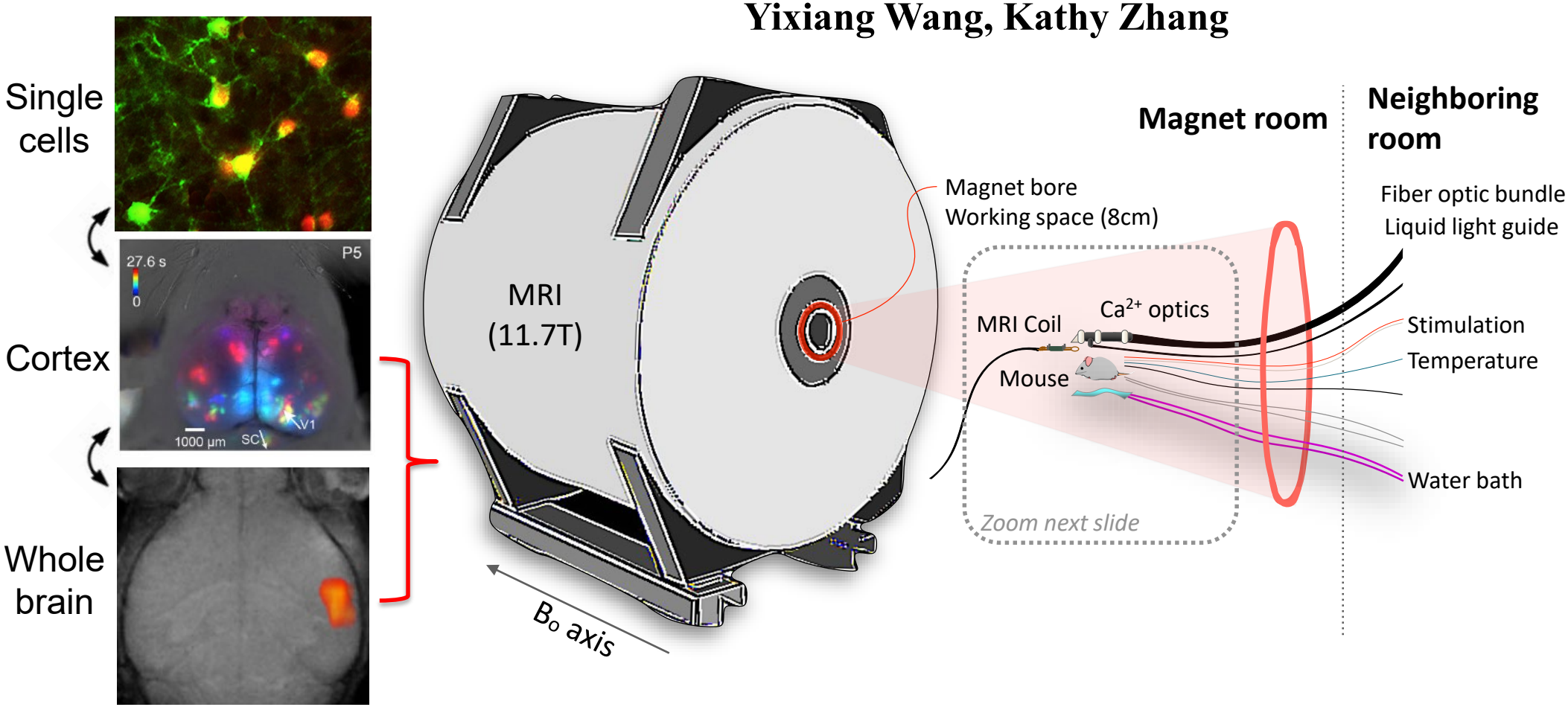
Crair Lab: Neural Circuit Development

Lab Style:

- **Student driven, collaborative, collegial.**

Current Yale Neuroscience Undergrads and Grads:

Jummie Akinwuni, Dan Barson, Sol Bernardez, Xinxin Ge, Jake Lister, Israel Robinson, Yixiang Wang, Kathy Zhang



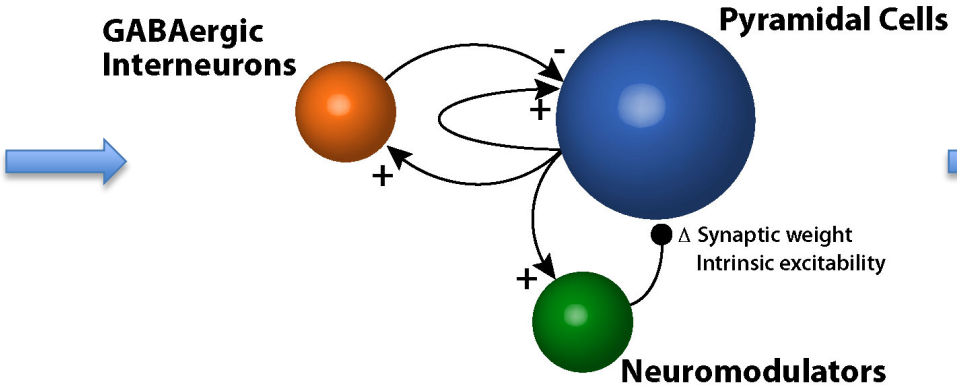
Investigating the functional architecture of cortical circuits

Higley Lab, Yale Neuroscience
m.higley@yale.edu
@mjhigley
http://higleylab.org

"Bridging the gaps between molecular, cellular, and systems neuroscience…"

Sensory Information

Internal States



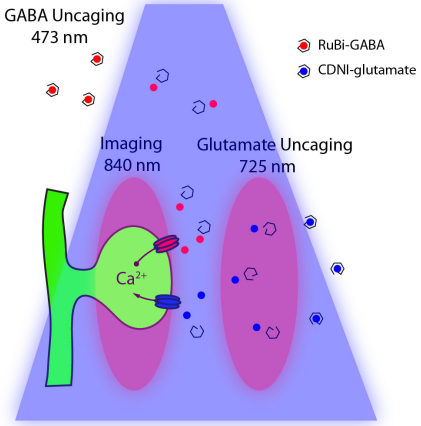
Behavior!

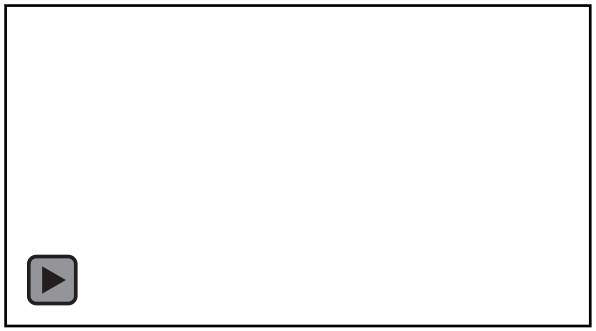
…electrophysiology, 2-photon imaging, photo-uncaging, optogenetics, viral tracing, CRISPR, behavior…

Function and plasticity of GABAergic synaptic inhibition

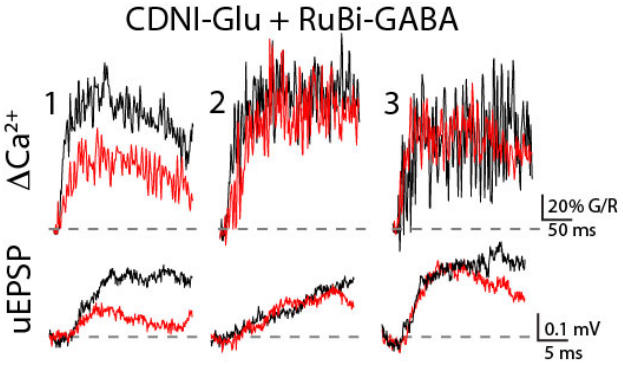
Chiu et al., *Science*, 2013
Lur and Higley, *Cell Reports*, 2015
Kannan et al., *J. Neurosci.*, 2016
Chiu et al., *Neuron*, 2018

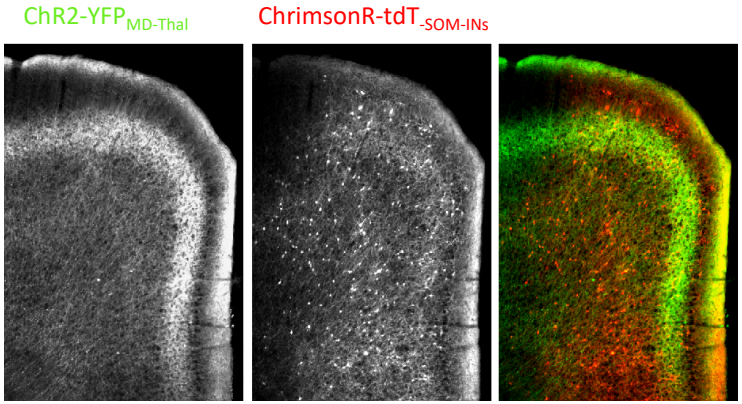
Dual glutamate & GABA uncaging

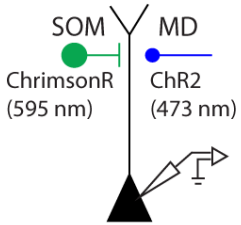


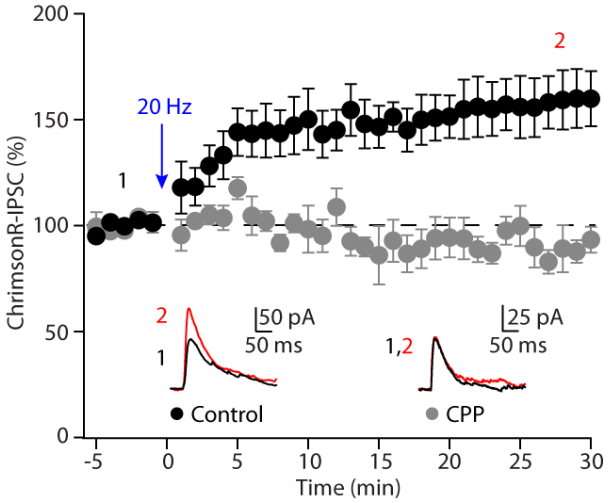


1 micron



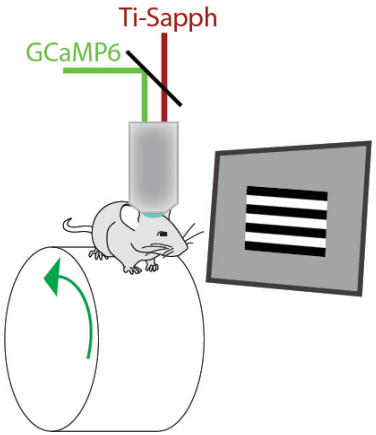


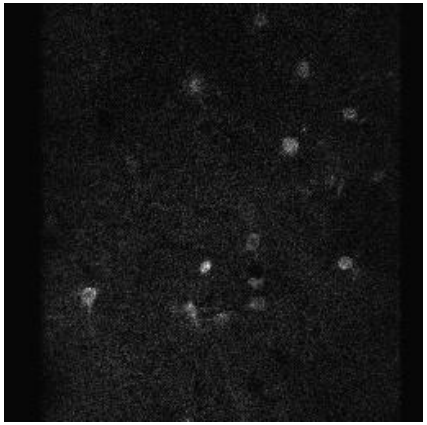


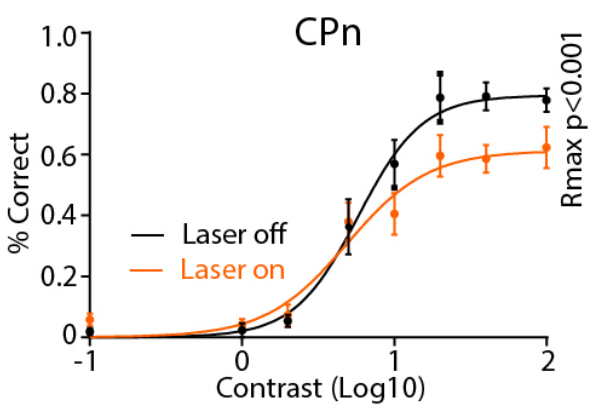


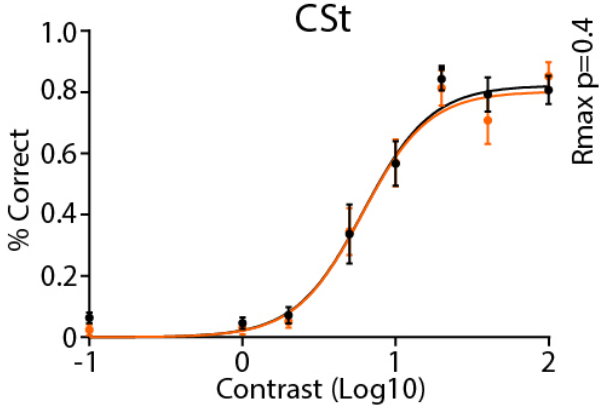
Circuits underlying visual perception and behavior

Lur et al., *Cell Reports*, 2016
Tang and Higley, *Neuron*, 2019
Puscian et al., *BioRXiv*, 2019









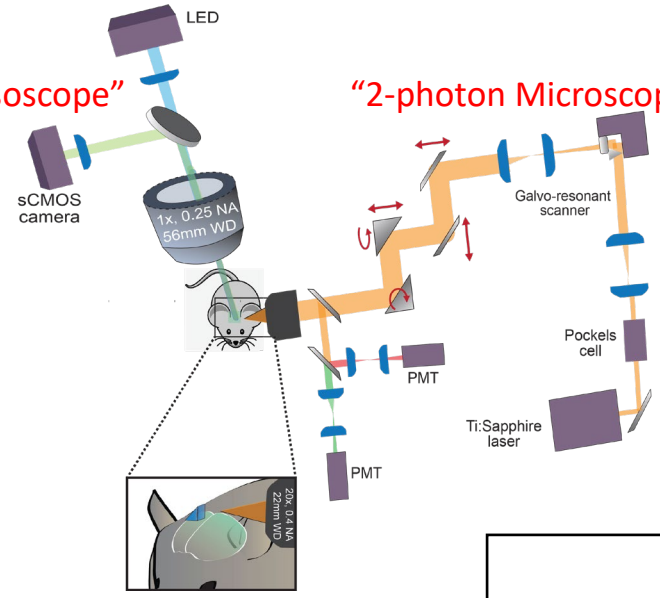
Simultaneous imaging of local and global cortical dynamics

Barson, Hamodi, et al., *Nature Methods*, 2019

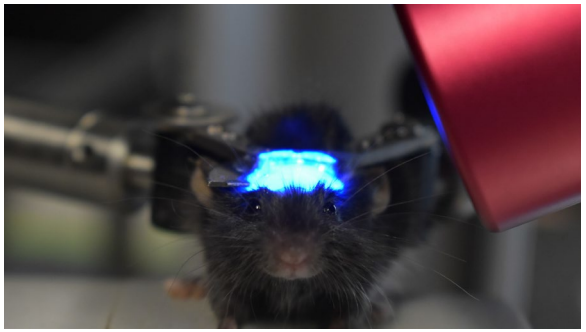
With labs of M. Crair, T. Constable, J. Cardin

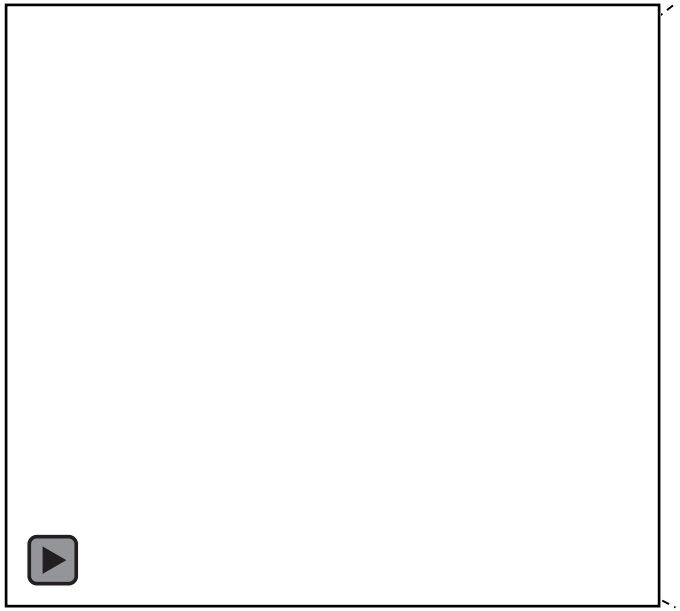
"Mesoscope"

"2-photon Microscope"

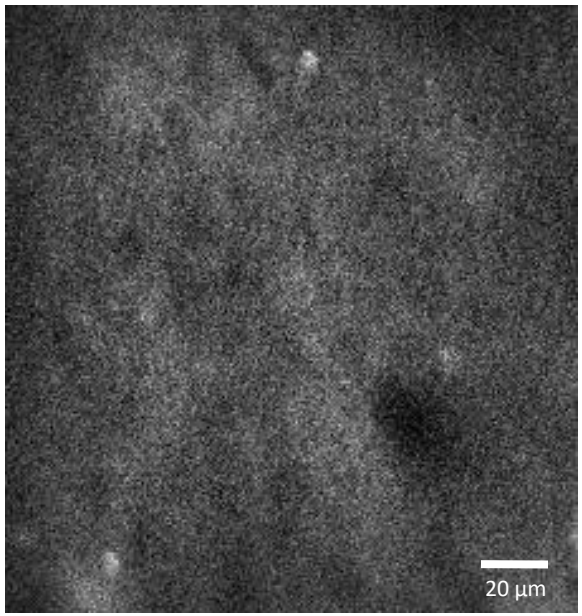


"GCaMP6-expressing mouse"





Mouse neocortex



Layer 2/3 Somatosensory Cortex

Higley Lab

Dan Barson
Hadas Benisty
Jyoti Gupta
Andrew Moberly
Tom Morse
Chika Ogbejesi
Alicja Puscian
Lan Tang
Antalique Tran

Collaborators

Jess Cardin (Yale)
Mike Crair (Yale)
Todd Constable (Yale)
Tony Koleske (Yale)

Funding Sources

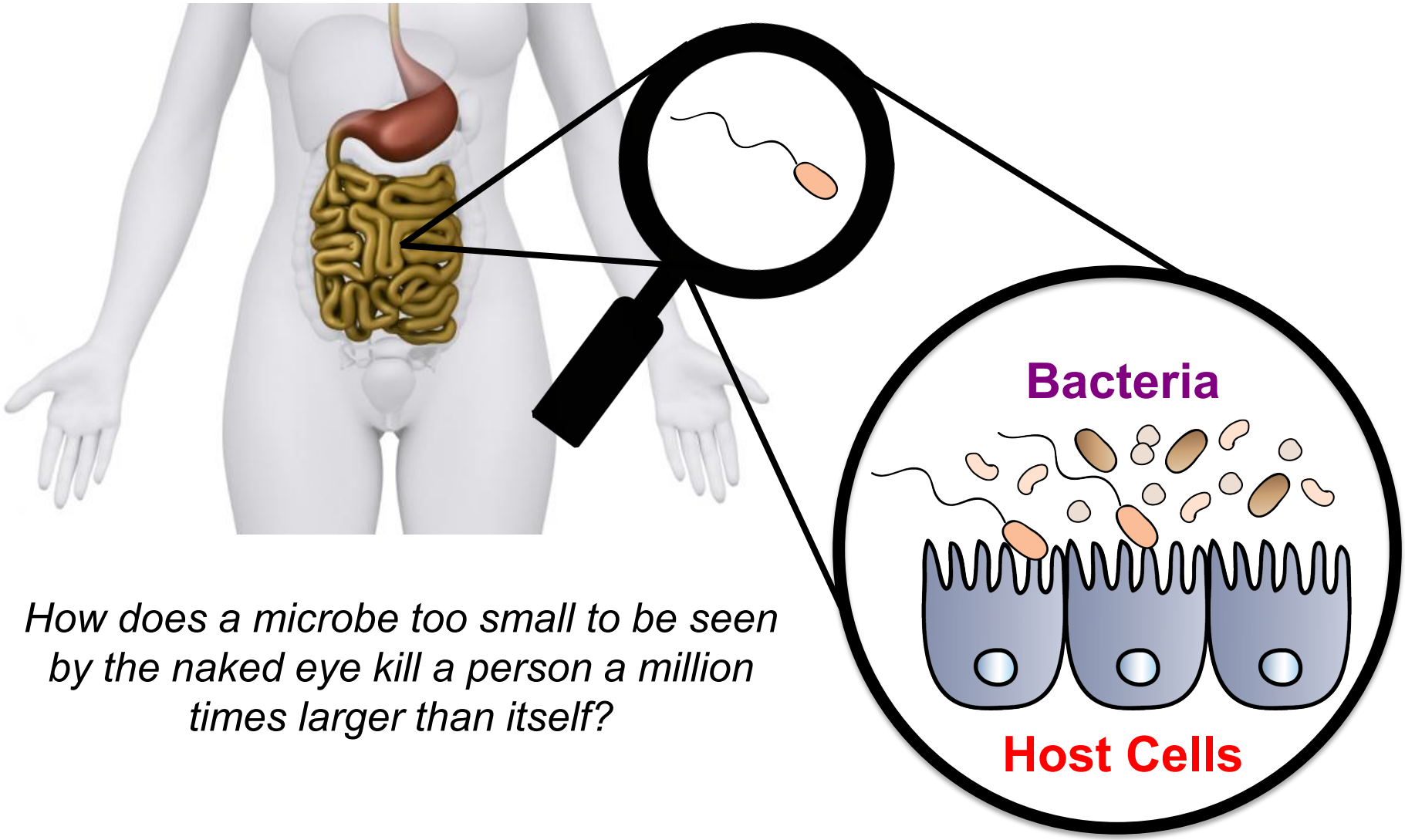
NIMH: R01 MH099045, R01 MH113852
NINDS: R01 NS105640, U01 NS094358
Simons Foundation, Kavli Foundation

"Bridging the gaps between molecular, cellular, and systems neuroscience…"

m.higley@yale.edu @mjhigley http://higleylab.org

Hatzios Lab

Department of Molecular, Cellular, and Developmental Biology
Microbial Sciences Institute - **Yale West Campus**

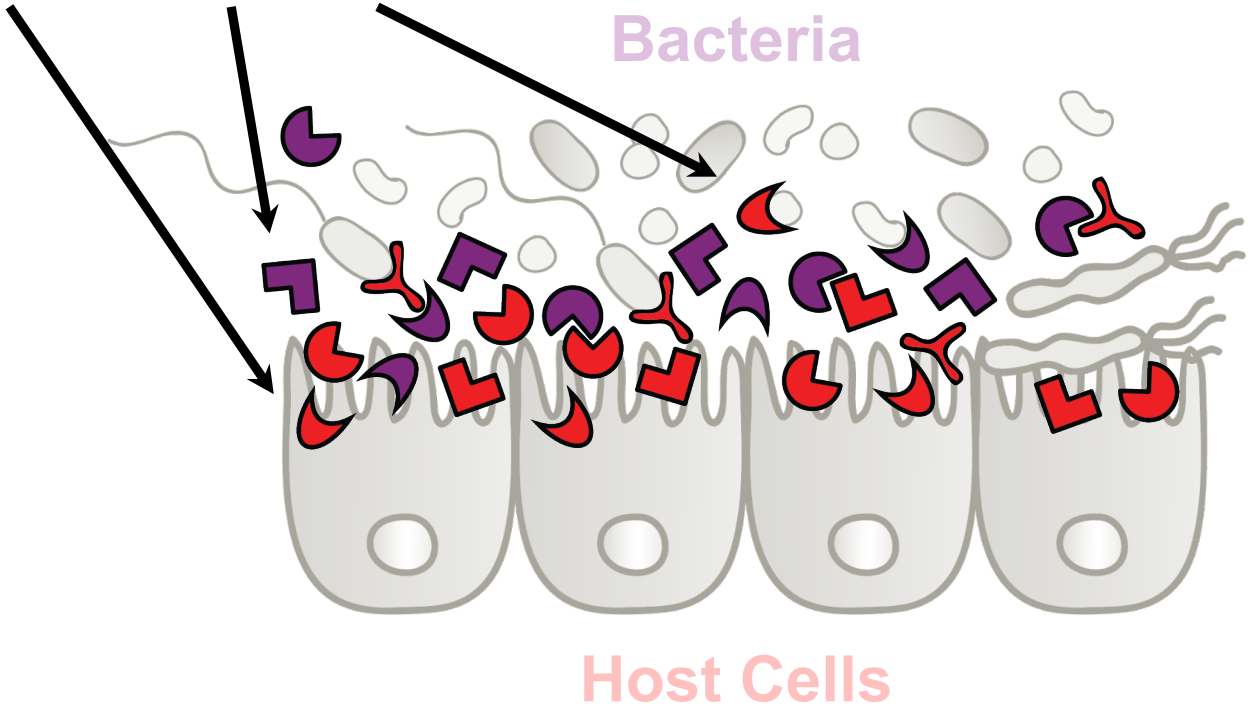


How does a microbe too small to be seen by the naked eye kill a person a million times larger than itself?

Central questions

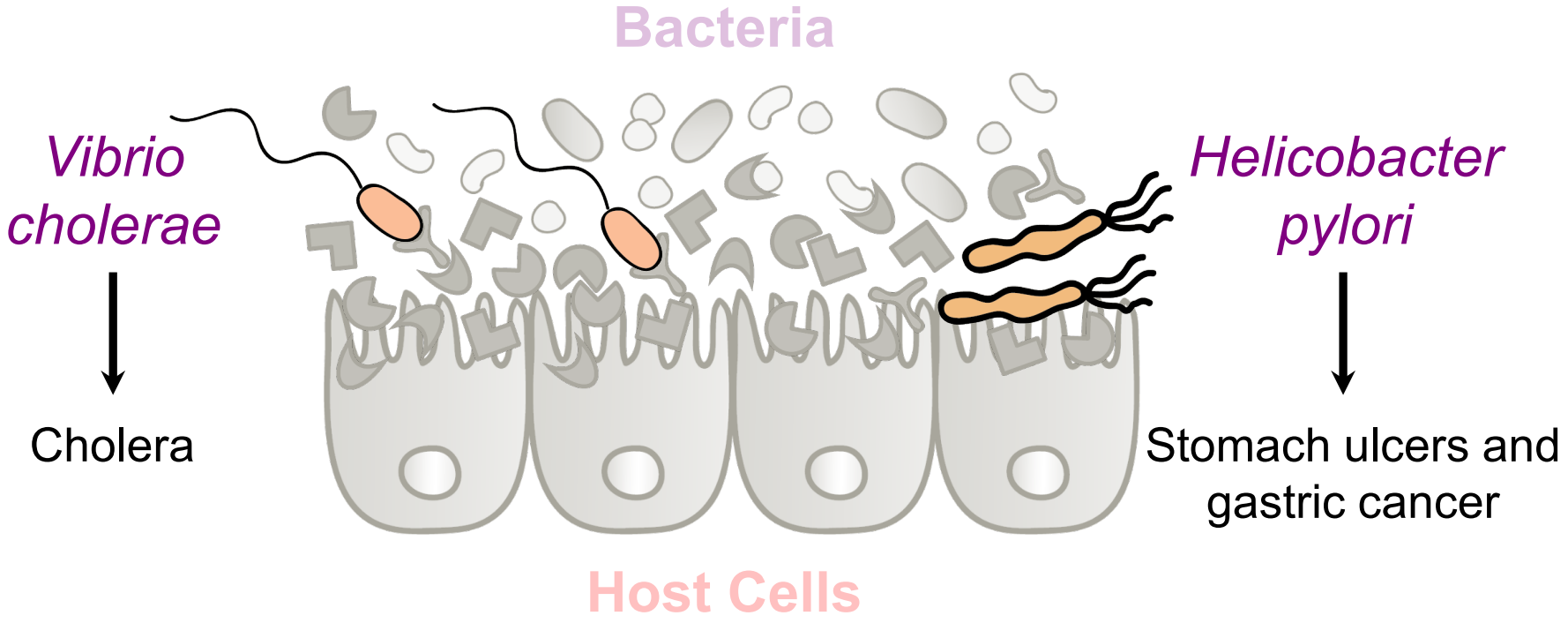
What proteins are functional at the host-microbe interface?

How do they influence microbial interactions with the host?



Can we use these proteins to better predict or improve infection outcomes?

Our work focuses on two globally important gastrointestinal pathogens



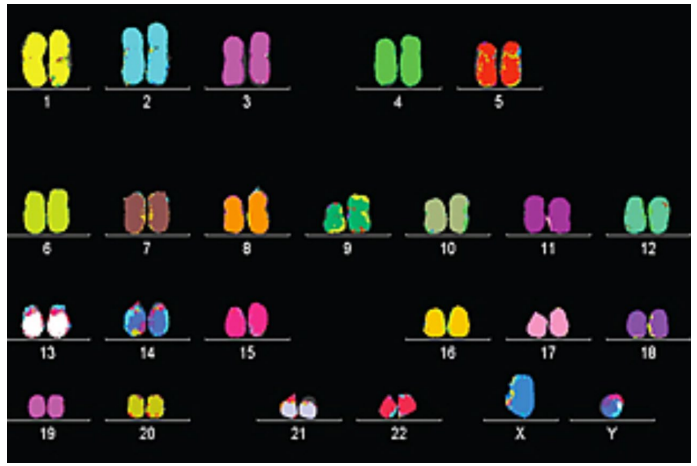
We use chemical biology, genetics, and microbiology to study bacterial and host proteins that contribute to infection

To learn more: Visit hatzioslab.yale.edu
Contact Postdoc Alicia DeColli (alicia.decolli@yale.edu) or
Prof. Stavroula Hatzios (stavroula.hatzios@yale.edu)

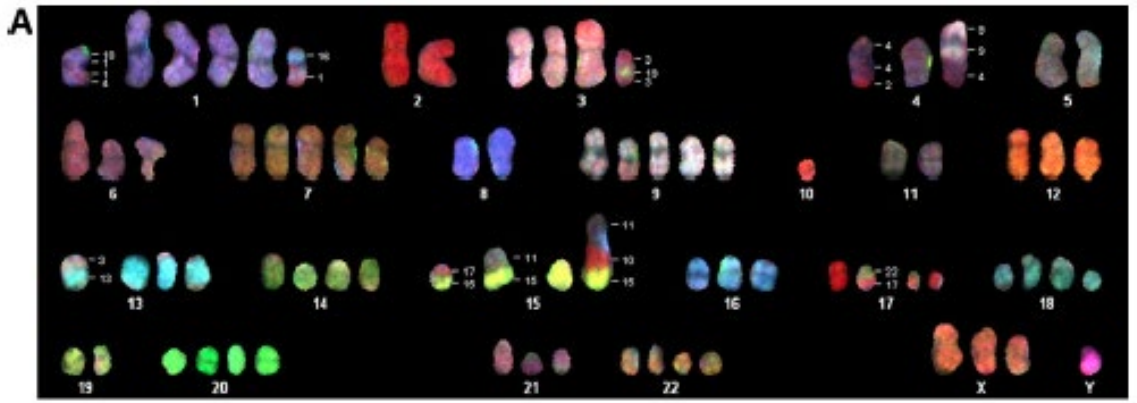
The Kabeche lab works on investigating the mechanisms that prevent aneuploidy and chromosomal instability

Adapted from the Broad Institute
Thompson and Compton, 2011

Diploid 46, XY



Aneuploid 70, XXXX



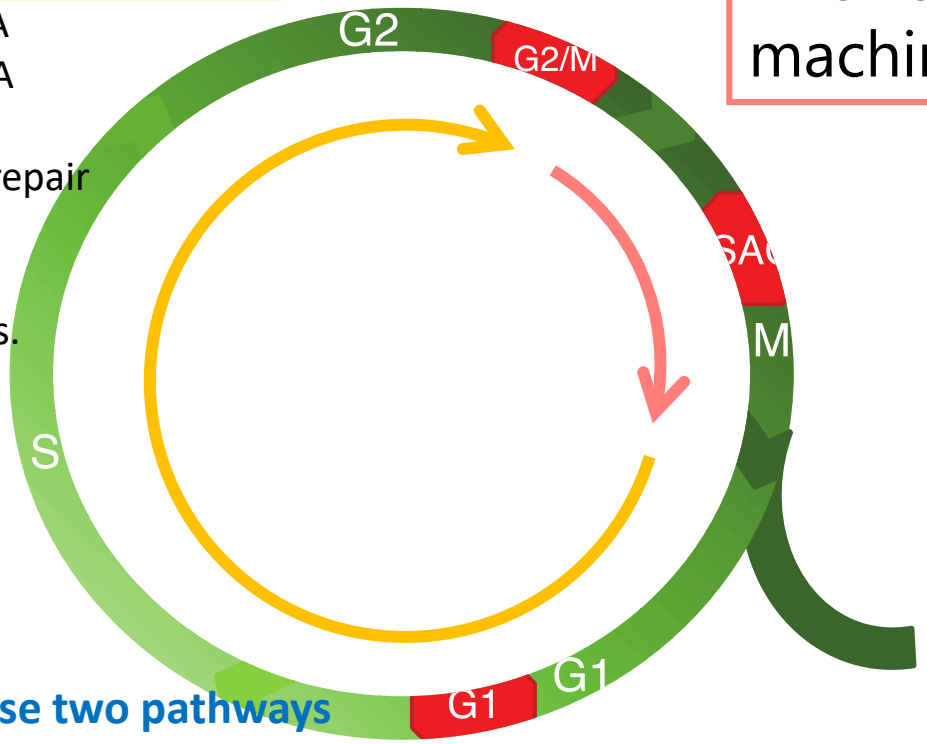
Aneuploidy is the deviation from the diploid karyotype and is a hallmark of cancer. Many times cancer cells will not only be aneuploid, but will continuously missegregate their chromosomes (a state we call chromosomal instability). This leads to heterogenous karyotypes within a tumor.
It is estimated that 95% of solid tumors are aneuploid
Chromosomal instability is correlated with increased metastasis, decreased immune response to the tumor, increased drug resistance and overallpoor patient prognosis

Cell cycle checkpoints that prevent proliferation errors are often perturbed in cancer cells

DNA damage repair pathway

Error correction machinery

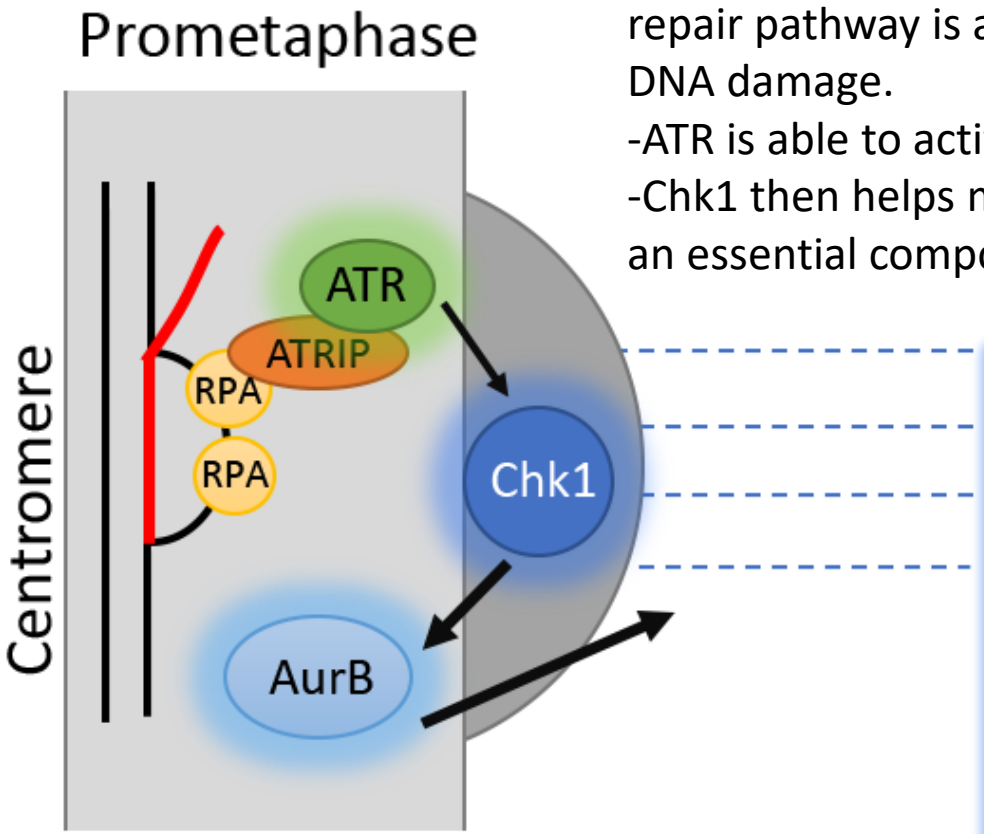
- In conjunction to these checkpoints, the DNA damage repair pathway, promotes proper DNA replication and repairs damaged DNA before entering mitosis, where proper DNA damage repair cannot occur.
The Error correction machinery promotes the proper segregation of chromosomes in mitosis.



There are several checkpoints throughout the cell cycle that ensure that proper DNA replication and segregation occur before continuing through.

-For a long time, it was thought that these two pathways worked separately throughout the cell cycle.
-Our lab has demonstrated that these two pathways work in concert throughout the cell cycle to promote chromosome stability

Our work has demonstrated that the DNA damage repair pathway components are important in mitosis, in a DNA damage independent manner.



-We showed that ATR, a major regulator of the DNA damage repair pathway is active in mitosis at centromeres indepdent of DNA damage.
-ATR is able to activate Chk1, its downstream effector kinase.
-Chk1 then helps maintain proper Aurora B activity. Aurora B is an essential component of the Error correction machinery.

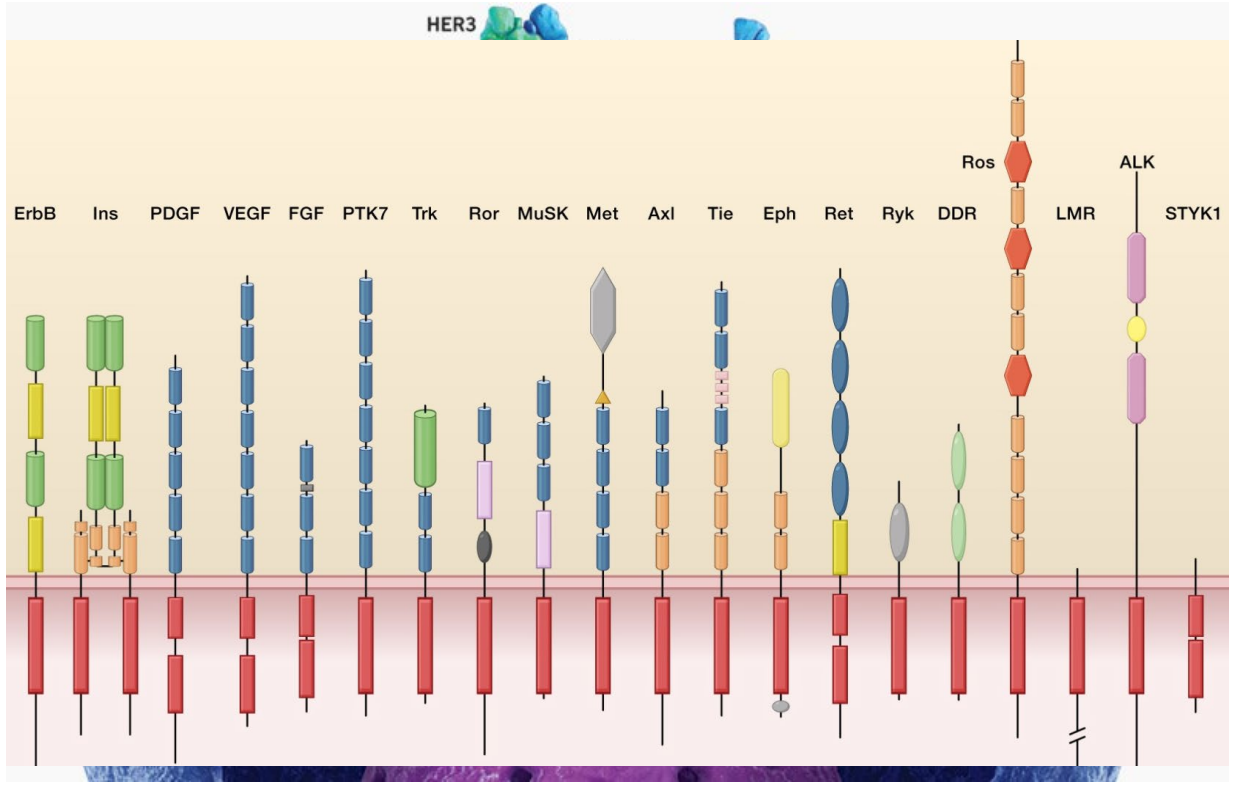
-Our lab is focusing on:

1. **Understanding the mechanisms by which ATR is activated in mitosis**
2. **Identify other components of the DNA damage repair pathway present in mitosis and define their roles**
3. **Investigate the downstream targets of ATR in mitosis.**

A little more about us and contact information:

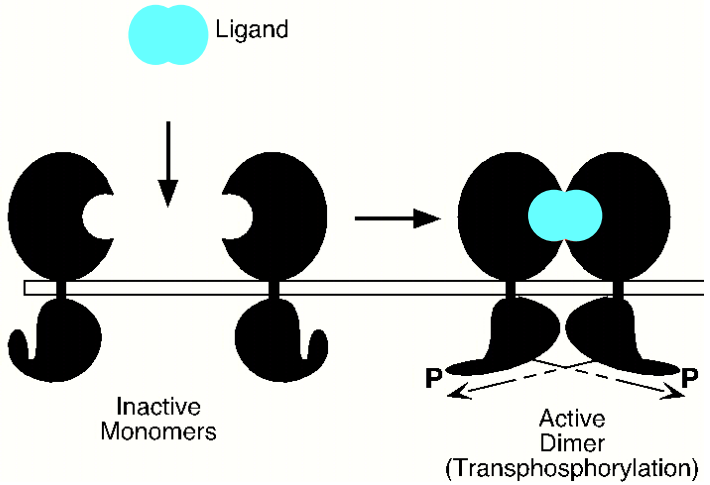
- We are a small but mighty lab comprised of one professor **(Lilian Kabeche)** and several graduate students. This means that we are a very hands-on group and work really closely as a lab, helping each other learn new techniques and work through scientific problems.
- We are located on the West Campus in the Advanced Biosciences Complex on the 3rd floor in the Cancer Biology Institute (840 West Campus Drive).
- If you are interested in learning more about the research and projects available in the lab please contact me at: **lilian.kabeche@yale.edu**

Regulation of Receptor Tyrosine Kinases (RTKs)



Regulate key cellular processes (proliferation, differentiation)
Dysregulation can cause cancer and other diseases

"Textbook" view of receptor activation by
ligand induced receptor dimerization



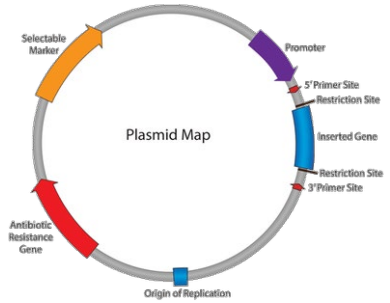
Elegant, but **it's more complex** for many of the 20 families of RTKs –
larger oligomers, lifetimes, co-receptors

Kate Ferguson

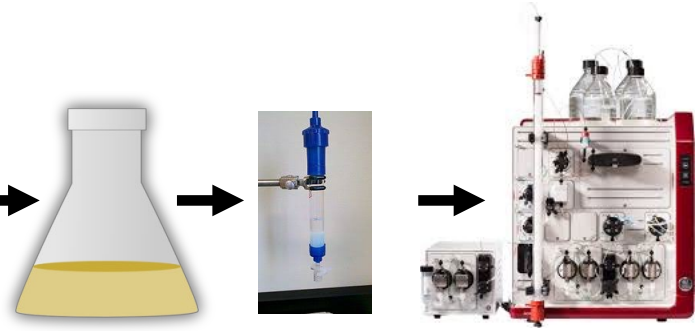
Yale Cancer Biology Institute & Department of Pharmacology,
Advanced Biosciences Building, Yale West Campus
kathryn.ferguson@yale.edu

Yale University
School of Medicine

Research Projects

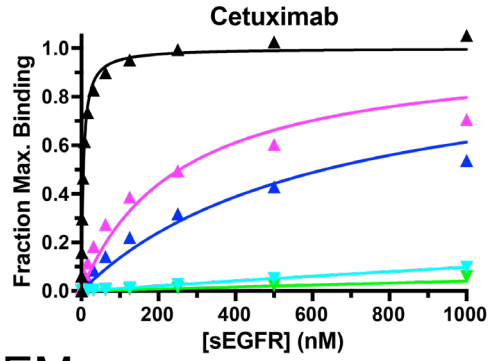


Generate/alter plasmids for protein expression



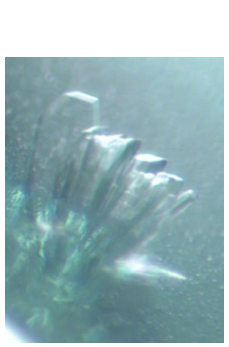
Recombinant protein purification

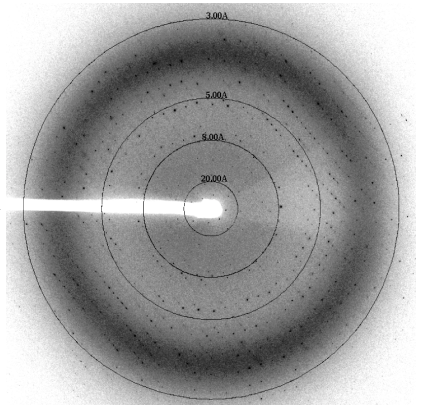
Quantitative Biophysical Experiments – oligomerization, ligand binding analysis

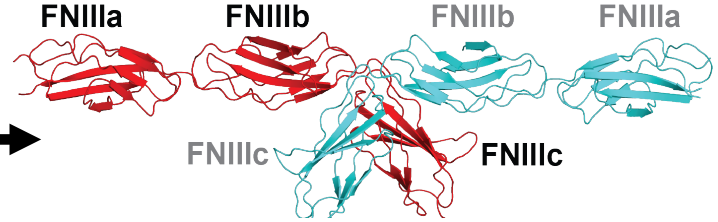


Low resolution shape information – SAXS, EM

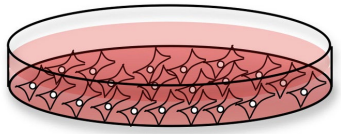
Atomic resolution structure determination: X-ray crystallography, EM





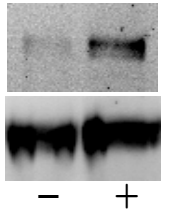


Predict mechanism and test hypothesis in cellular assays



Expression in mammalian cell

Functional assay



Yale Cancer Biology Institute

What to expect in the Ferguson Lab




- Small lab (two postdocs, one postgrad)
- Share space and collaborate with Lemmon Lab
- You would
  - work directly with one of my postdocs on daily basis
  - meet with me at least weekly to discuss progress and plans
  - participate in our weekly group meetings (with Lemmon lab)
  - quickly become proficient with simpler procedures
  - shadow to learn more advanced techniques
- Please email if you are interested!

THANKS!

Kate Ferguson

Yale Cancer Biology Institute & Department of Pharmacology,
Advanced Biosciences Building, Yale West Campus
kathryn.ferguson@yale.edu

Yale University
School of Medicine

Want to get involved in **cutting edge clinical neuroscience research**?

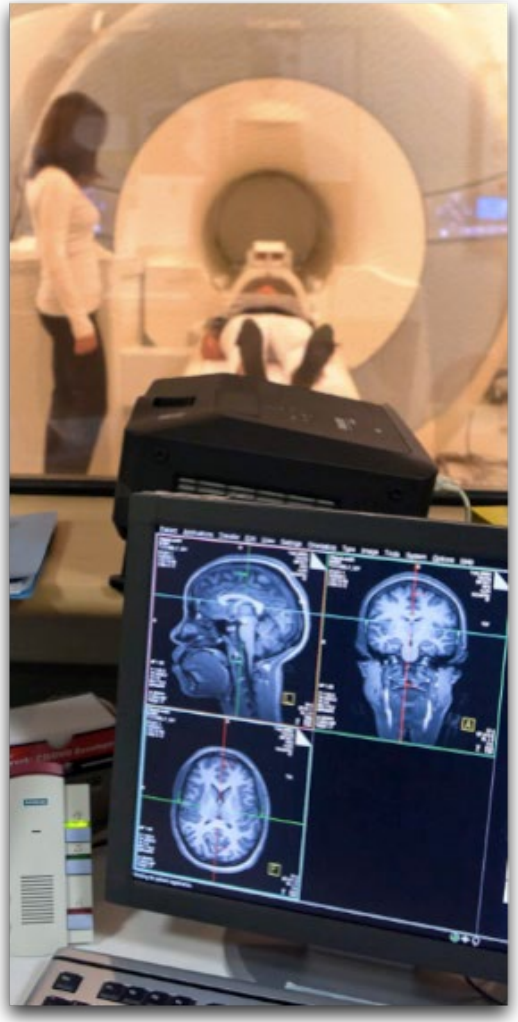
Interested in **Mindfulness**? **Substance Use Disorders**? **Eating Disorders? Emotion Regulation**?

Want to learn about neuroimaging methods such as **functional MRI**?

(PI: Prof. Hedy Kober)

Join us this summer at **CAN Lab!**

Yale Clinical and Affective Neuroscience Laboratory



Did you know you can train your brain to choose to...

...eat this...

...instead of this...

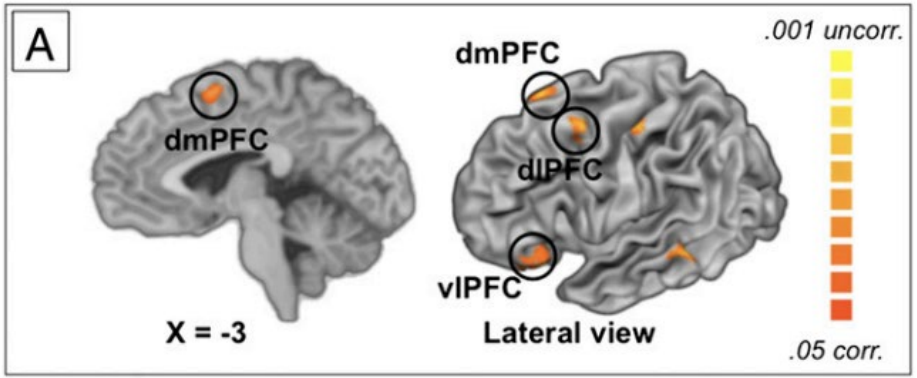
...in just a **short training period** on **regulating your cravings**?

Boswell, Sun, Suzuki & Kober, 2018; Kober & Boswell 2018; Boswell & Kober 2016

Current projects to get involved in:

-Online studies of food choice training
-Brief training for weight loss
-Food diary studies
-Imaging studies of eating disorders

Did you know that these regions in your brain are activated when regulating cravings for drugs and food?



Knowing the underlying mechanisms of addiction and emotion regulation can help people struggling with substance use...

...and at CAN Lab, we develop treatments for addiction through empirical methods!

Kober et al., 2010; Kober et al. 2014; Naqvi et al 2015; Suzuki et al. In press, and many more!

Current projects to get involved in:

-Regulation of craving for young adults who drink
-The effect of shock-induced stress on regulation of craving in smokers
-Risky decision making in cocaine users

Did you know that just 10-minutes of **mindfulness practice…**

…can improve your **attention**?

Even if you have **never meditated**!

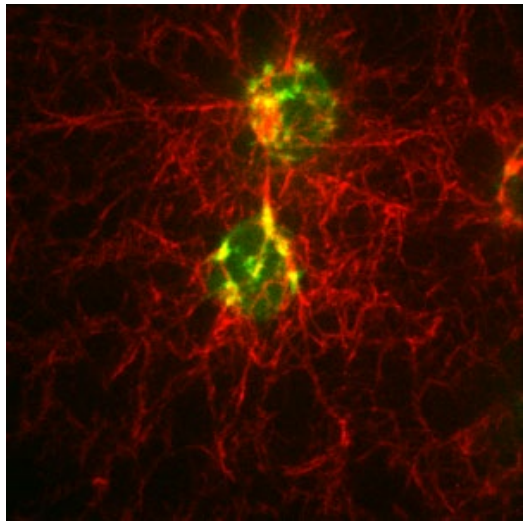
Norris, Creem, Hendler & Kober, 2018; Wesbrock et al. 2013; Kober et al. 2017; Kober et al. In Press

Current projects to get involved in:

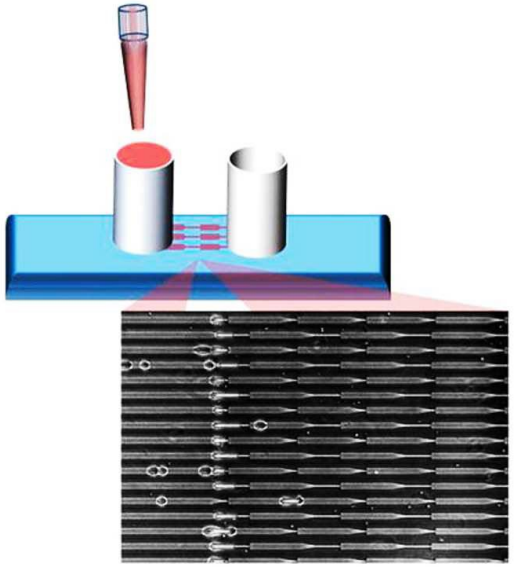
-Brief mindfulness training and cognitive performance
-Mindfulness training in children with ADHD
-Neuroimaging and mindfulness

Multiscale Mechanobiology Lab

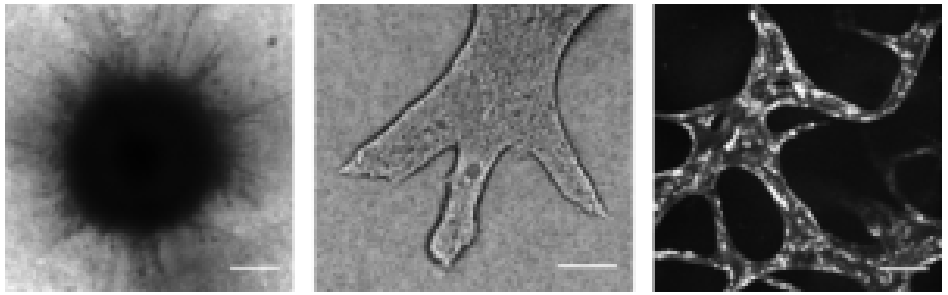
Cell-Matrix Interactions



Microfluidic Assays



Collective Cellular Systems



- Prof. Michael Mak
- Michael.Mak@Yale.edu
- MakResearchLab.com

- **Mechanobiology:** intersection of mechanics and biology
- **Topics:** cell biophysics, tumor microenvironment, extracellular matrix, microscopy, image analysis, microfluidics, cancer immunotherapy, collective systems
- Computational and experimental approaches

Projects

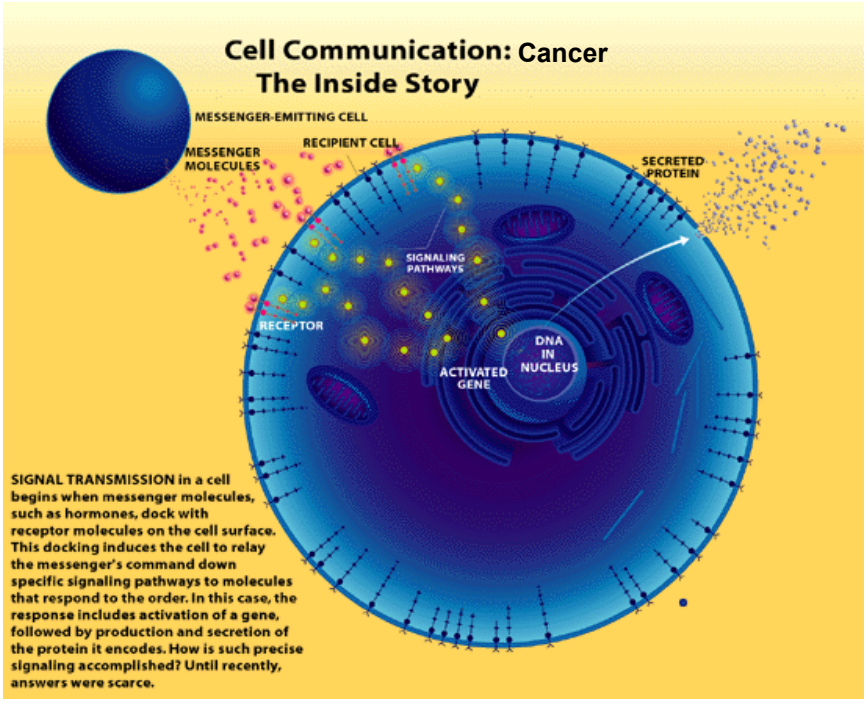
1) Studying cell-matrix and cell-cell interactions in cancer and other diseases.
2) Microfluidic assays for measuring biophysical properties of cells.
3) Computational modeling of cell migration and tumor invasion, intracellular signaling, and cytoskeletal dynamics.
4) Additional topics can be discussed.

Activities

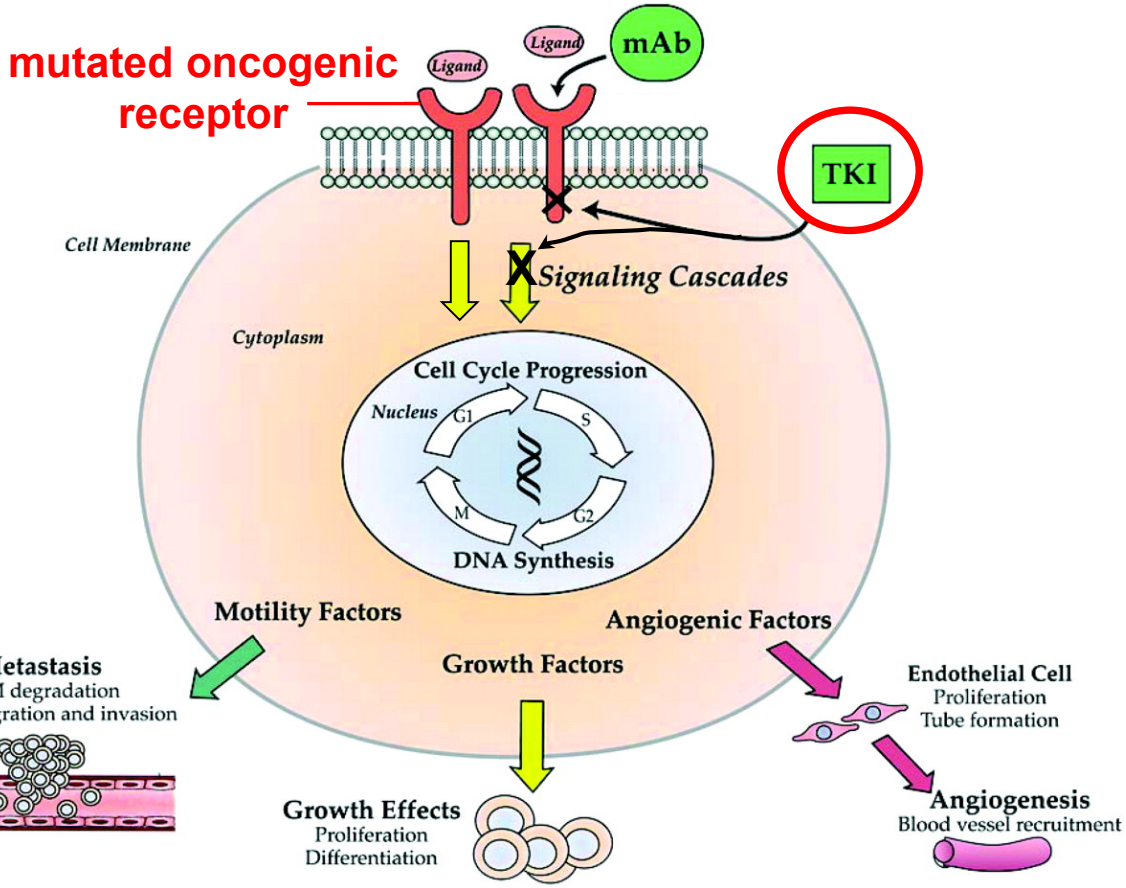
- Weekly individual meetings.
- Weekly group meetings.
- Regular guidance from graduate students and postdocs.
- Interactive, multifaceted, and integrative environment with opportunities for both individual and group projects.

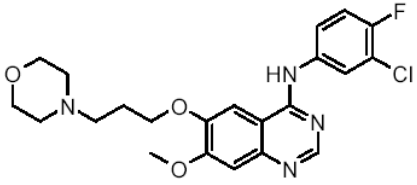
Yale *Cancer Biology Institute*

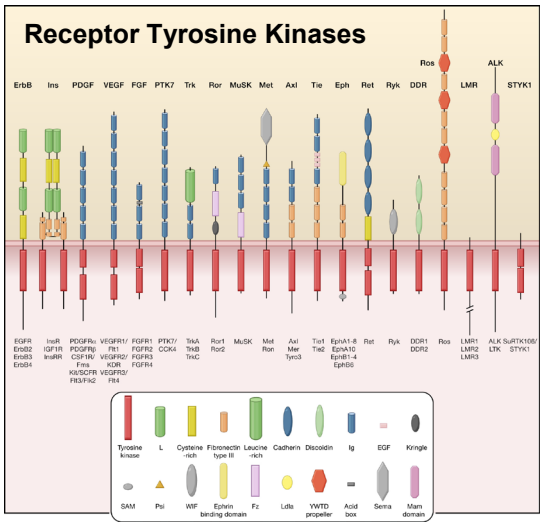
Signaling by cell-surface growth factor receptors: in biology and disease (cancer)

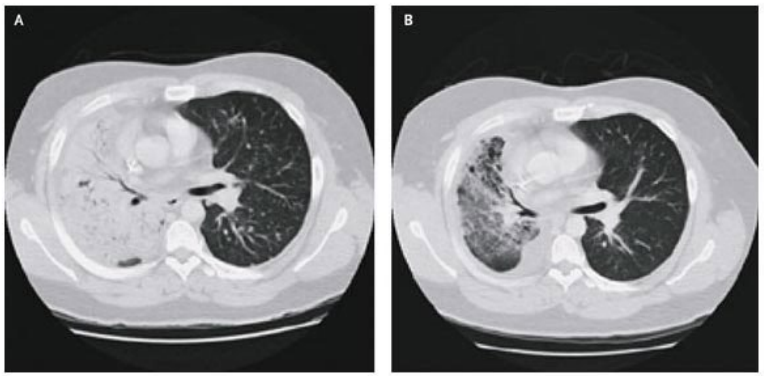


Mark A. Lemmon: Yale Cancer Biology Institute
Department of Pharmacology, YSM
mark.lemmon@yale.edu

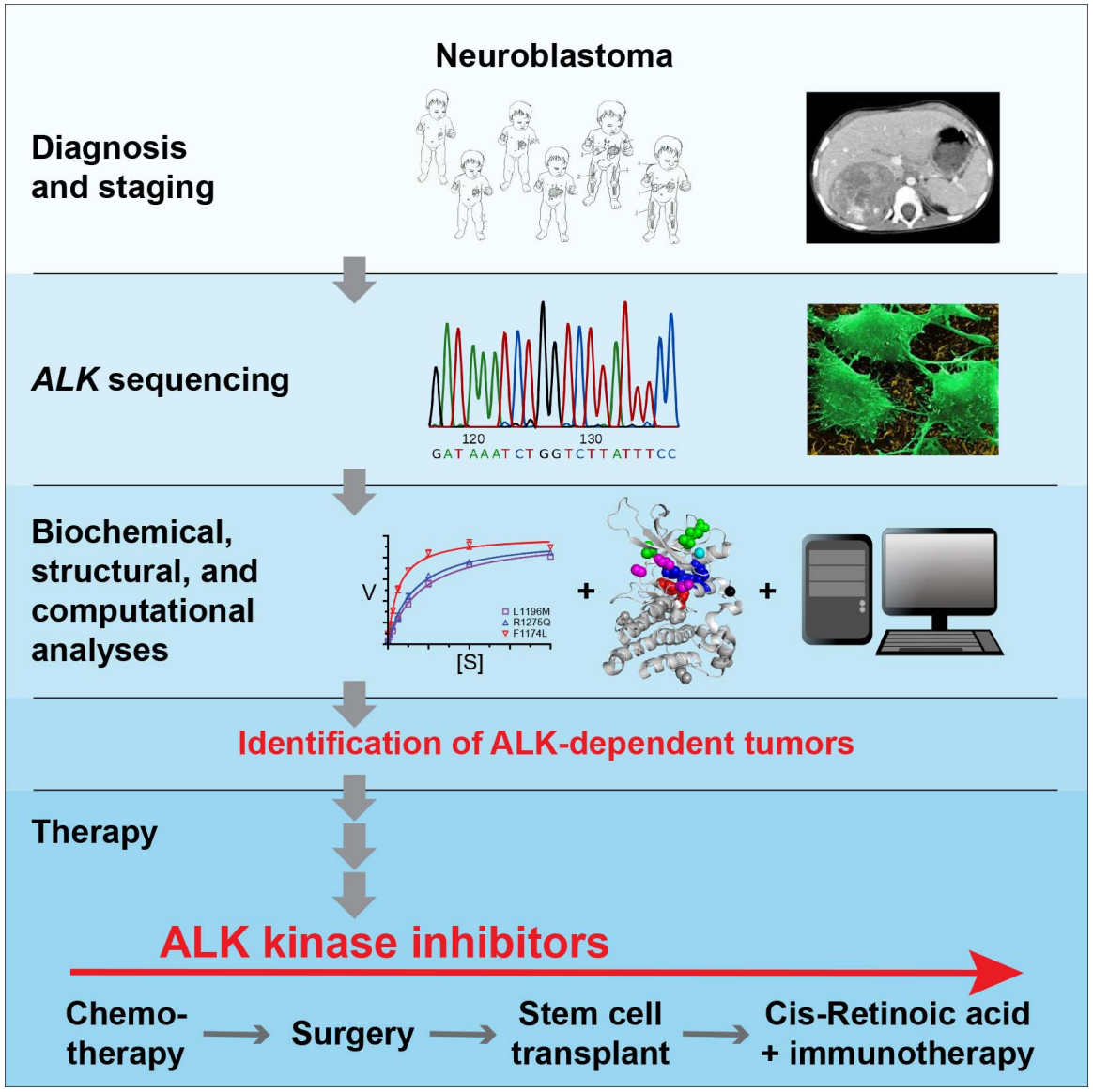








Lynch *et al., N.E.J.M.* **350,** 2129 (2004)

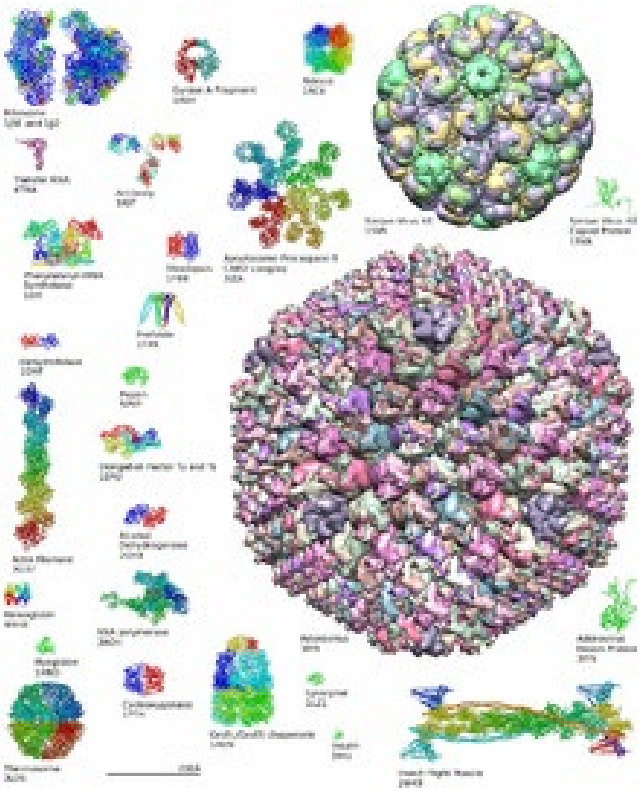


- Lab of 6 grad students, 4 post-docs, 3-4 undergrads, plus lab manager
- Direct Supervision by 1-2 grad students or postdoc
- Lab meetings Thurs afternoons
- Learn to make mutated recombinant protein and assess activity – for mutations found in lung cancer rebiopsy program at YNHH
- Help identify ‘rules’ for inhibitor application/choice that also give us mechanistic lessons

Cryo-EM Studies of Membrane Proteins in Bacterial Pathogens

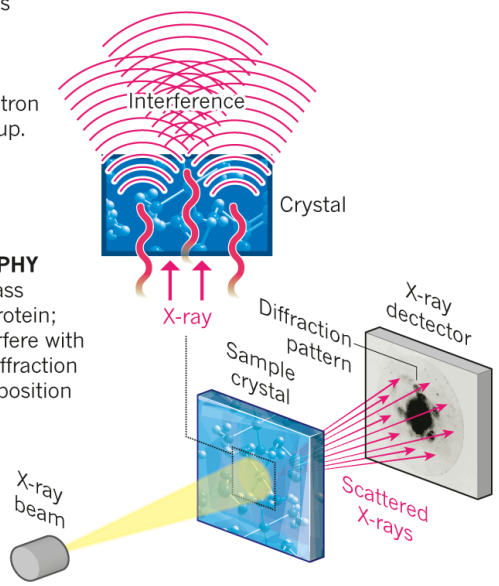
Wei Mi
Department of Pharmacology
SHM B 251
wei.mi@yale.edu

Structural Biology

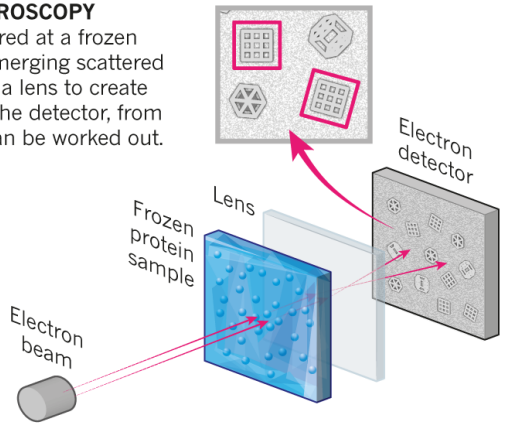


X-ray crystallography has long been the dominant method for deducing high-resolution protein structures, but cryo-electron microscopy is catching up.

X-RAY CRYSTALLOGRAPHY
X-rays scatter as they pass through a crystallized protein; the resulting waves interfere with each other, creating a diffraction pattern from which the position of atoms is deduced.



CRYO-ELECTRON MICROSCOPY
A beam of electron is fired at a frozen protein solution. The emerging scattered electrons pass through a lens to create a magnified image on the detector, from which their structure can be worked out.

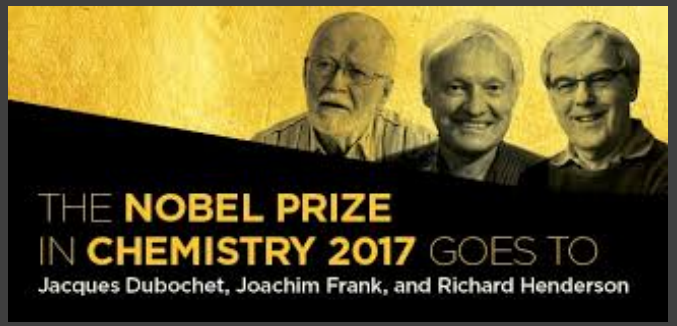


Resolution Revolution

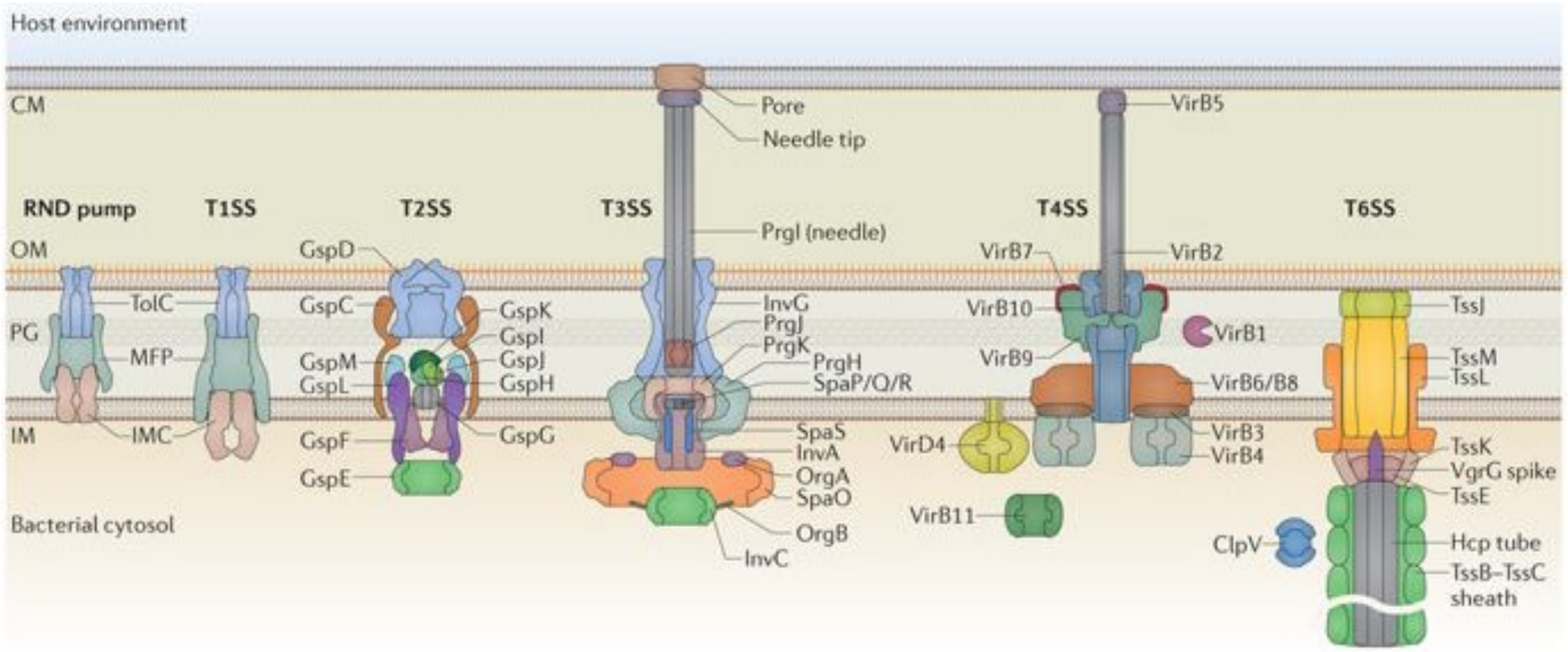
Breakthroughs in detector and algorithm

Method of the year 2015

The Nobel prize in chemistry 2017



Protein Secretion in Gram-negative Bacteria



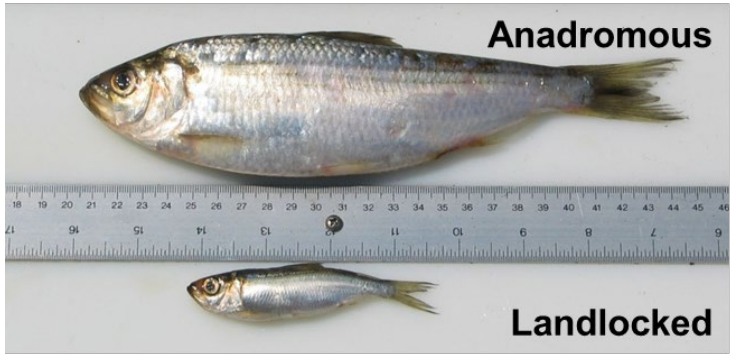
Costa TR, et al
Nat Rev Microbiol. 2015

Post Lab

- Kenya and Connecticut

Connecticut: eco-evolutionary interactions in lakes

- Interactions between ecology and contemporary evolution in lake food webs

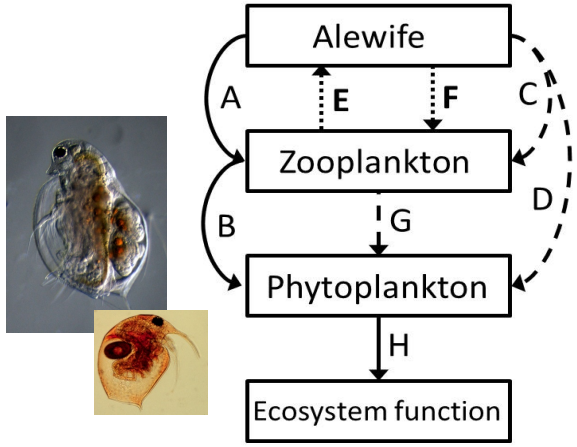


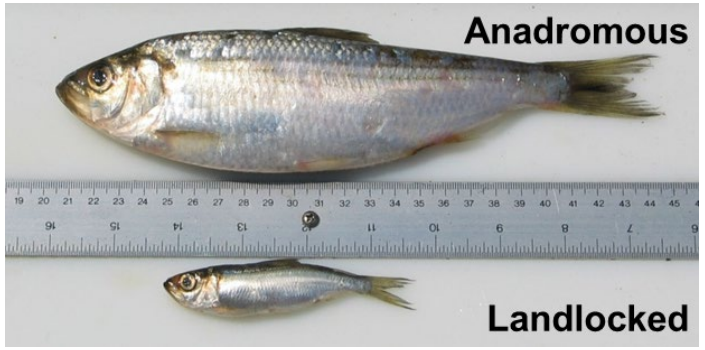
- Alewife (Alosa pseudoharengus)
  - Two life history forms

- Dams isolated populations in the late 1600s
  - Evolution of foraging morphology, habitat use, prey selectivity and a number of other traits in landlocked populations

Connecticut: eco-evolutionary interactions in lakes

- Alewife evolution initiated a cascade of evolutionary and ecological changes that propagated through the food web
  - Community structure, water quality, evolution in other species
- Fish passage to restore access to historical spawning habitat
  - Ecological and evolutionary dynamics of secondary contact between anadromous and landlocked alewife





Kenya - role of animal migrations

- Influence of hippos and wildebeest on the ecology of the Mara River, Kenya

- Hippos
  - Daily foraging migration
  - Each hippo eats about 3 tons of grass each year and deposits much of that into the Mara River

- Wildebeest
  - Annual wildebeest migration
  - Mass drowning events when crossing the Mara

- Scavengers, biogeochemistry, food webs, microbiome

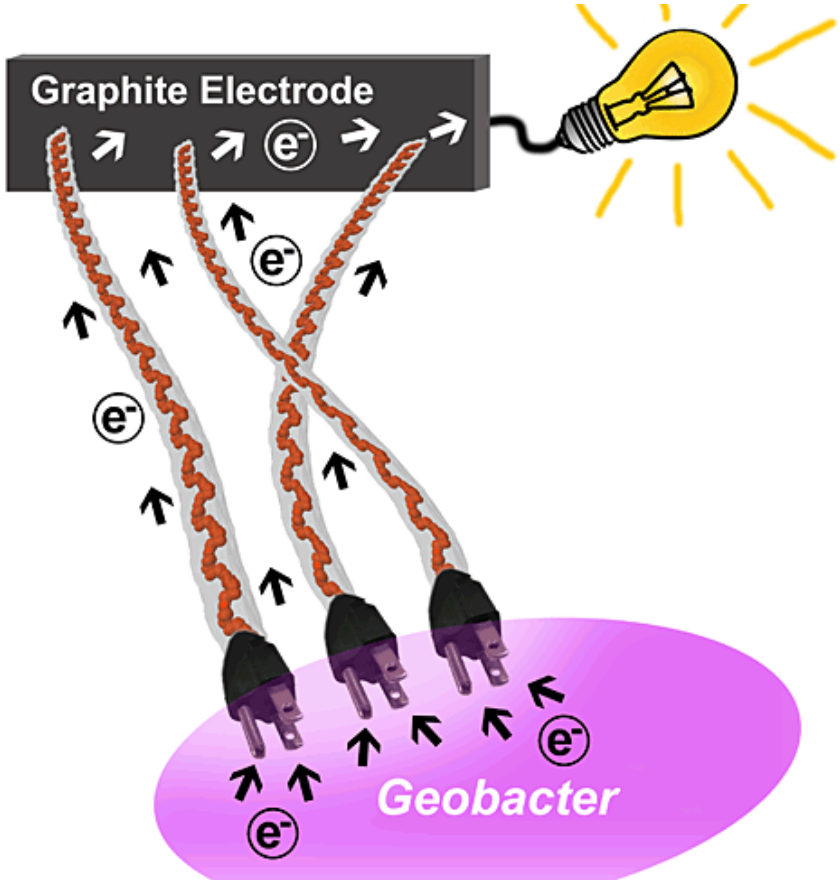
Outreach and Education

- Short Courses for US and East African Students

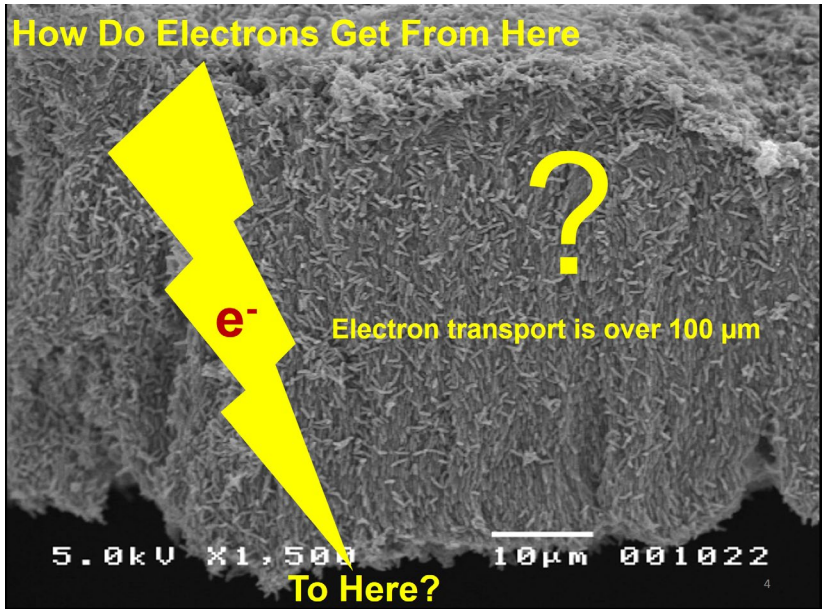
Nikhil Malvankar Lab

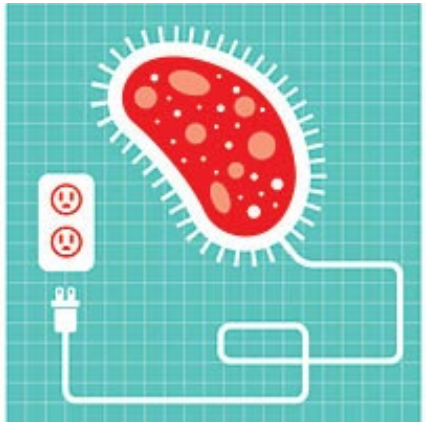
New imaging and measurement technologies to define the mechanisms by which microbes interact with and manipulate their environment. The ultimate goal is to engineer these interactions to control microbial pathophysiology and ecology.

Electric Bacterial Nanowires

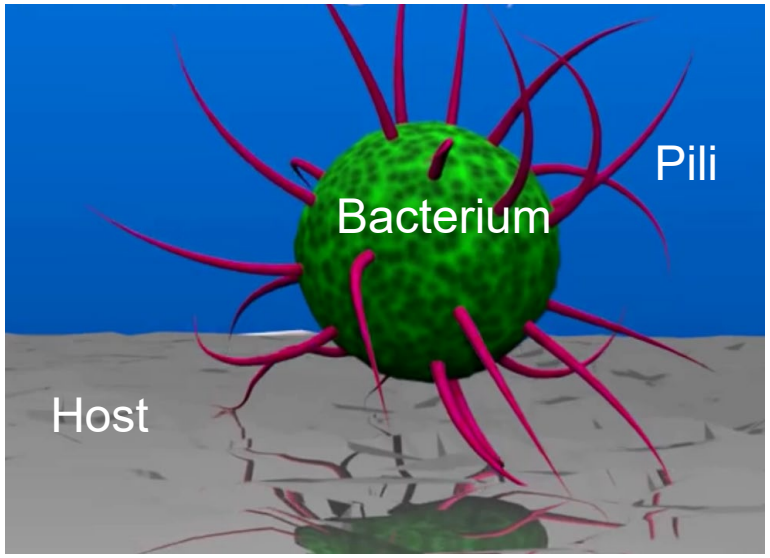


Bacterial communities in biofilms



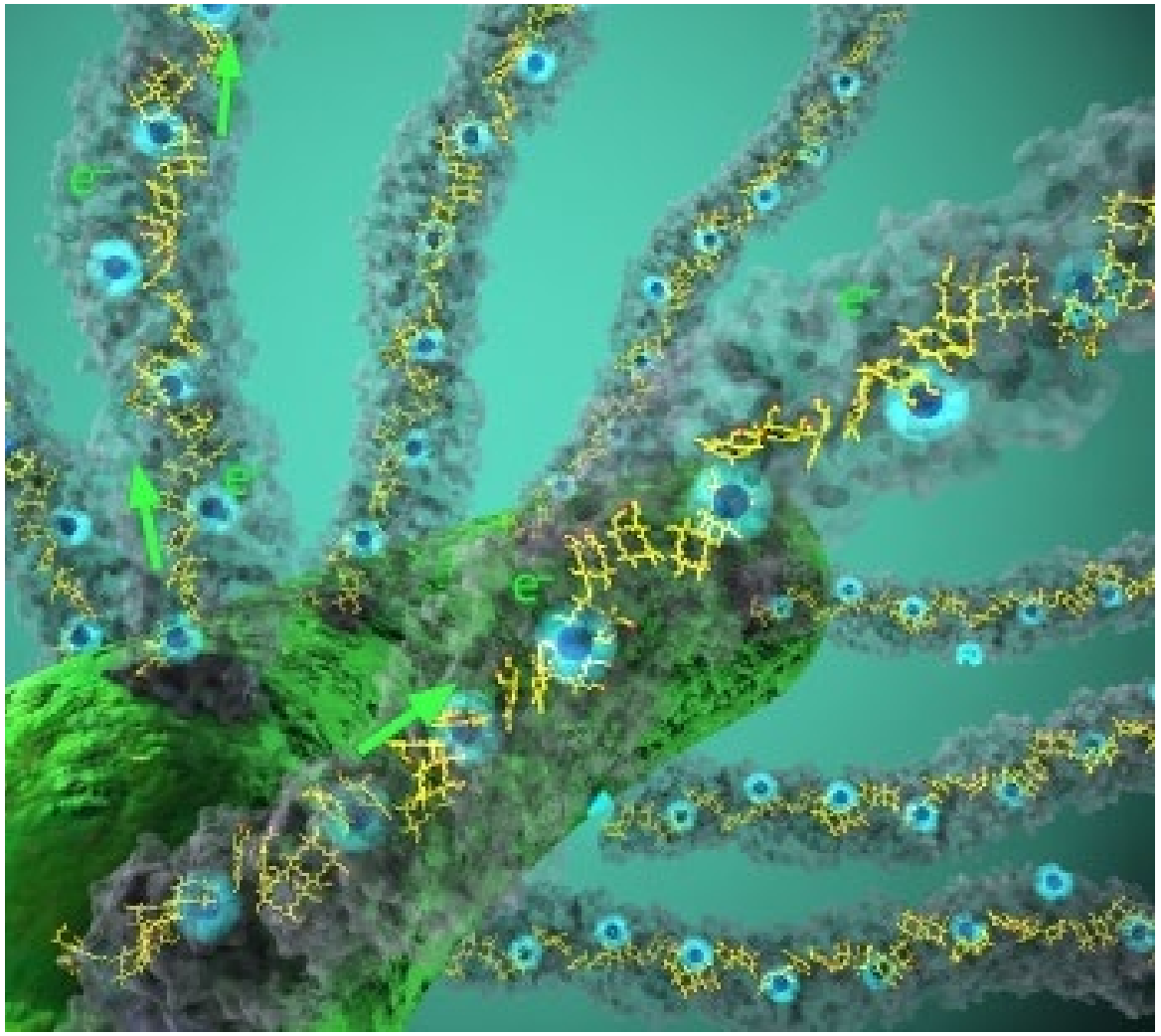


Host-pathogen Interactions in single cells and biofilms



Nikhil Malvankar
Mol. Biophysics & Biochem.
Microbial Sciences Institute
nikhil.malvankar@yale.edu

Cryo-EM structure of bacterial nanowires show stacked hemes



Cell, 2019

The New York Times

"To me, it's a strong reminder of how ready we are to ignore things we cannot imagine."

Wired Bacteria Form Nature's Power Grid: 'We Have an Electric Planet'

Electroactive bacteria were running current through "wires" long before humans learned the trick.

"There never had been a material like this before."

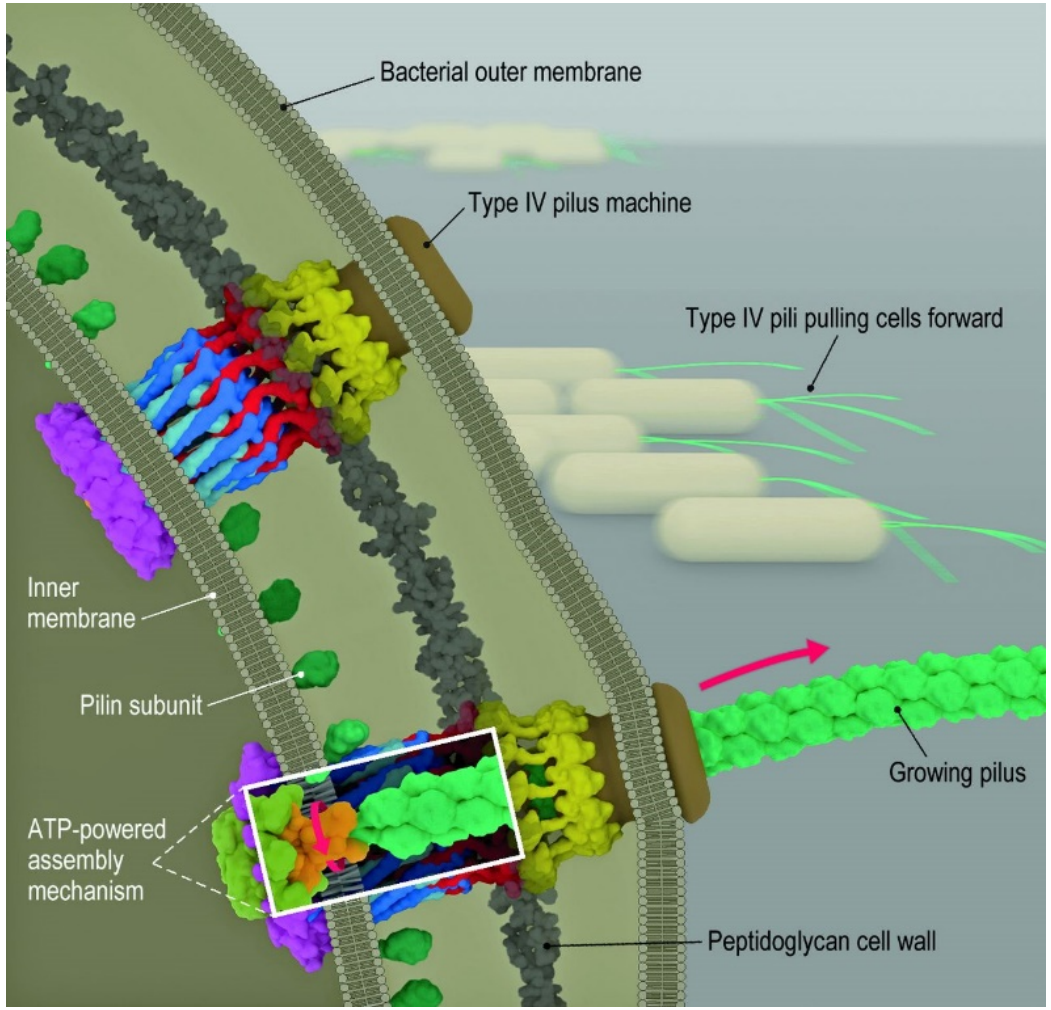
Among Highest Impact Structures of the Century

21st Century

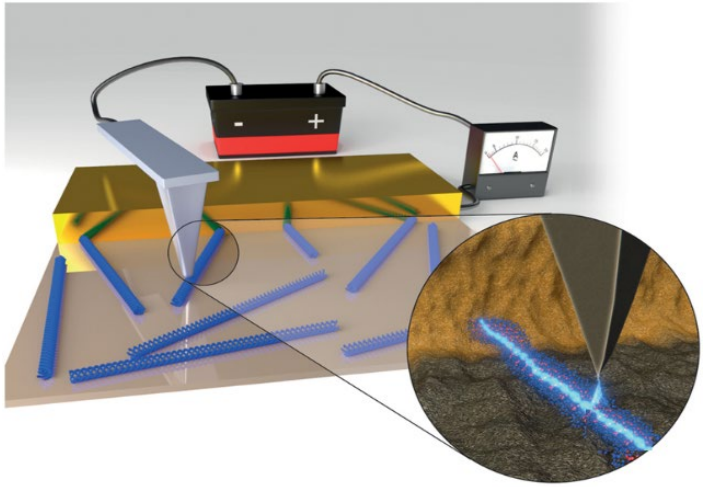
- **2000 - Ribosome**: This structure surprised almost everyone by showing that peptidyl transferase is a ribozyme, rather than a protein enzyme. It won the 2009 Nobel Prize in Chemistry.
- **2007 and 2011 - G protein-coupled receptor**: In 2007 the structure of the first ligand-activated G protein-coupled receptor and in 2011 the first activated G protein-coupled receptor bound to its G protein. This is a large class of proteins that have great importance as targets for drug development; it is estimated that 4% of the human genome devoted to protein coding encodes this class of proteins. The determination of the structures lead to Brian Kobilika sharing the 2012 Nobel Prize in Chemistry
- **2019 - Cytochrome nanowires**: 6ef8 was the first structure of an electrically-conductive bacterial protein nanowire, confirmed by 6nef. Such nanowires appear to be important in global carbon and metal redox phenomena in anoxic soils and sediments, and have many possible applications[6][7][8]. Prior to these cryo-EM structures, it had been believed for over a decade that nanowires were type IV pili assembled from pilA[9]. These structures surprisingly revealed nanowires as polymers of 6-heme C-type cytochromes, which called this belief into question. The unexpected protein making up these nanowires was determined from the cryo-EM density map. This is an unusual case in which the protein making up an extensively-studied structure was not known prior to solving the structure.

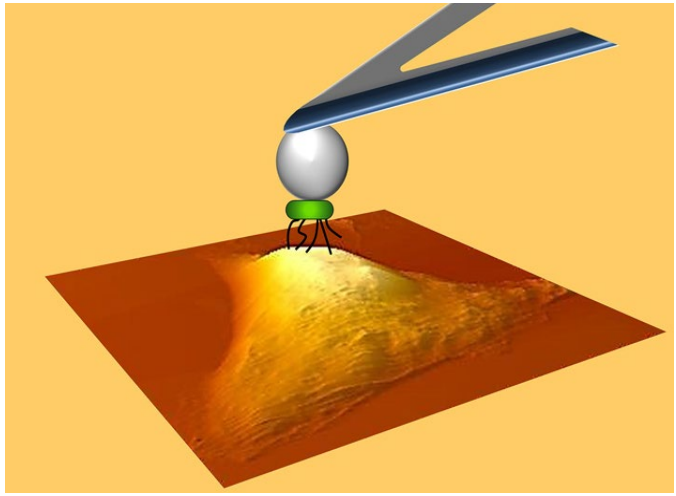
Student Projects – Physics, Chemistry, Biology & Engineering

Cryo Electron Microscopy & Tomography of bacterial nanowires and assembly

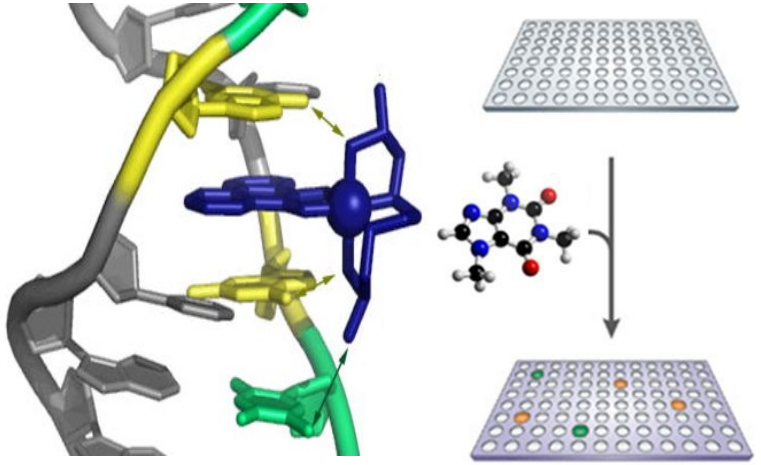


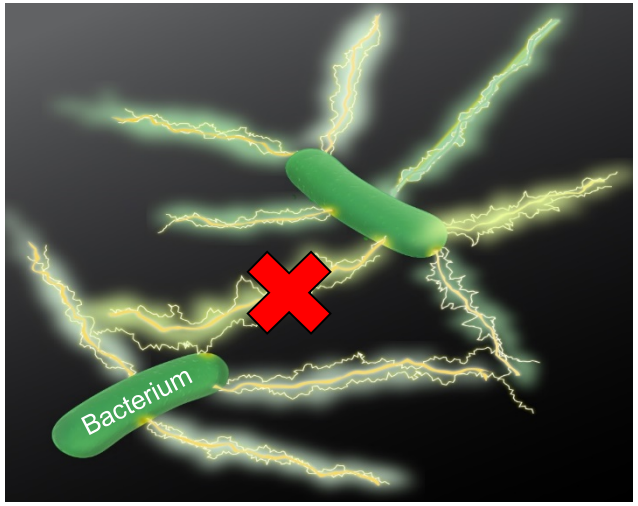
Targeting bacterial survival mechanisms





Novel drugs to neutralize host-pathogen interactions





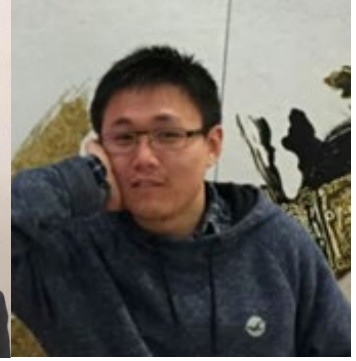

Sibel Yalcin


Catharine Shipps


Sophia Yi

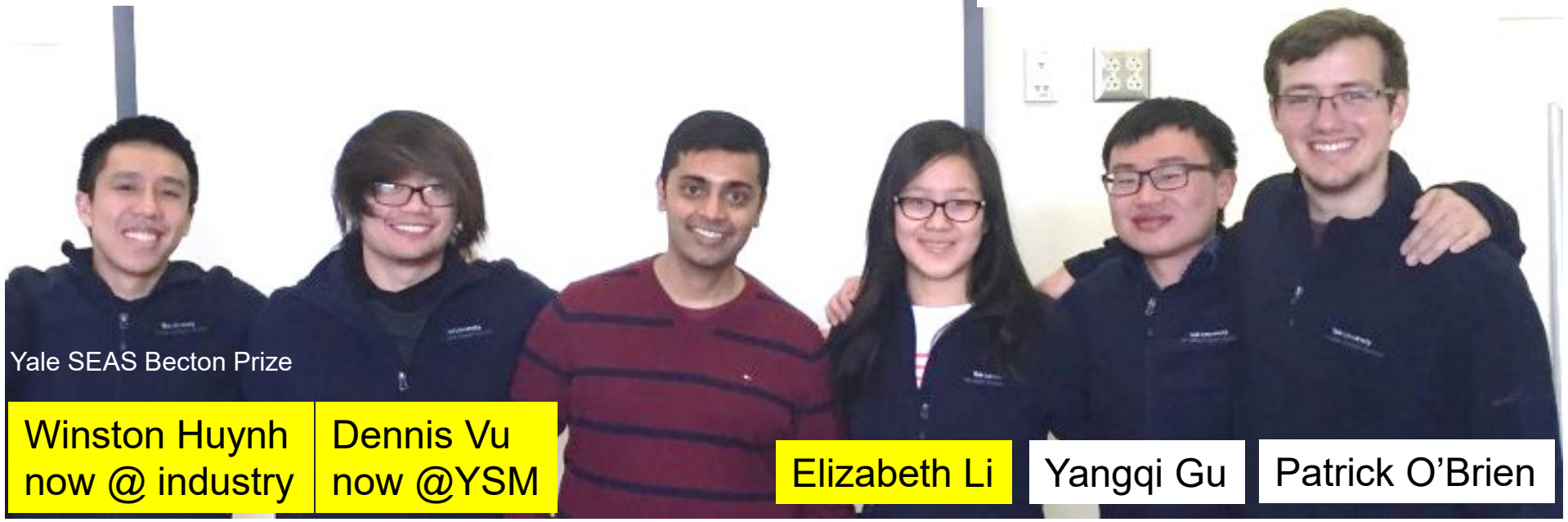

Peter Dahl


Vishok Srikanth


Cong Shen


Jens Neu


Dan Shapiro (now @ Duke)



Winston Huynh now @ industry

Dennis Vu now @YSM

Elizabeth Li

Yangqi Gu

Patrick O'Brien


Claire Sheen

Mitchell Lee

Current Ugrad Students
Guna Mandava
Ronald Hood
Lauren Delgado

Yale Ugrad students

BURROUGHS WELLCOME FUND
Career Awards at the Scientific Interface

NIH DIRECTOR'S NEW INNOVATOR AWARD

DARPA DEFENSE ADVANCED RESEARCH PROJECTS AGENCY

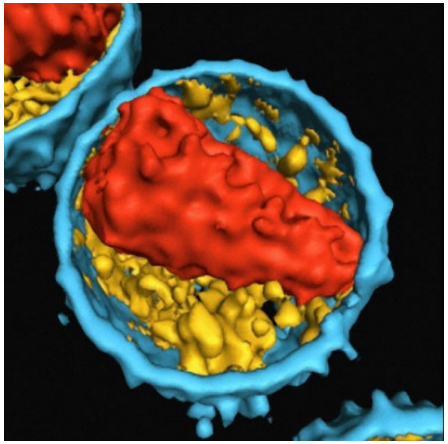
NSF CAREER Award

THE HARTWELL FOUNDATION

Charles H. Hood FOUNDATION

NSF GRFP

Host Genetic Control of HIV/HIV Cure

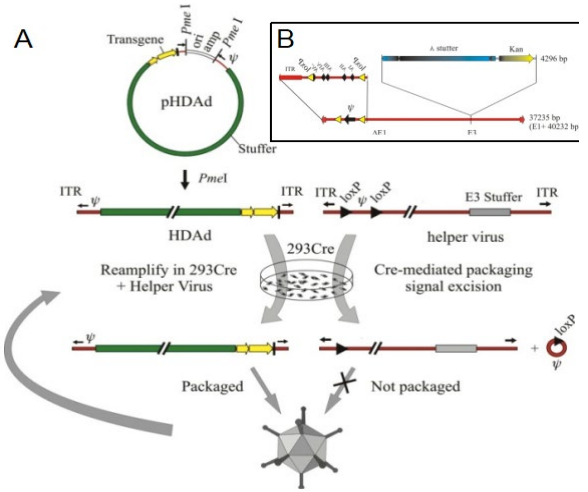


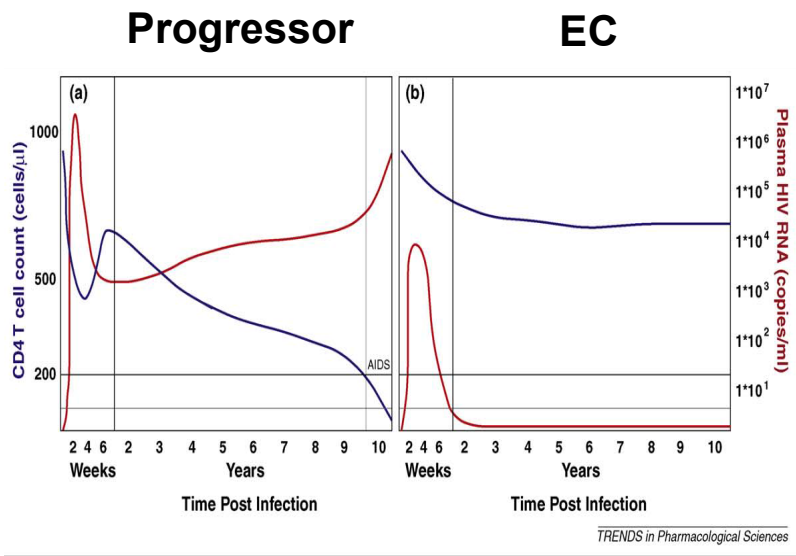
My office

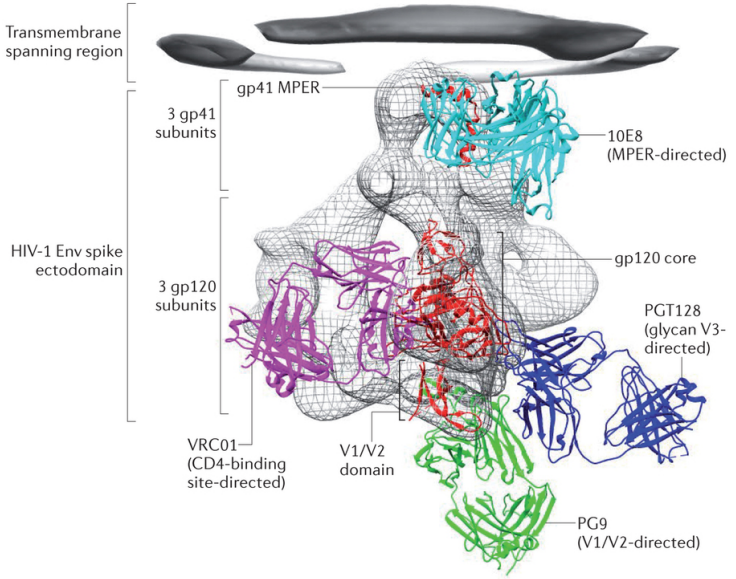
Richard Sutton, MD-PhD
Section of Infectious Diseases
& Department of Microbial Pathogenesis
Yale University School of Medicine
Richard.Sutton@yale.edu

Possible Projects:

- Post-transcriptional regulation of *ccr5*
- Vectored delivery of anti-HIV bnAbs
- Study of cnpy4 in HIV elite control
- KO of *ccr5* in hematopoietic cells





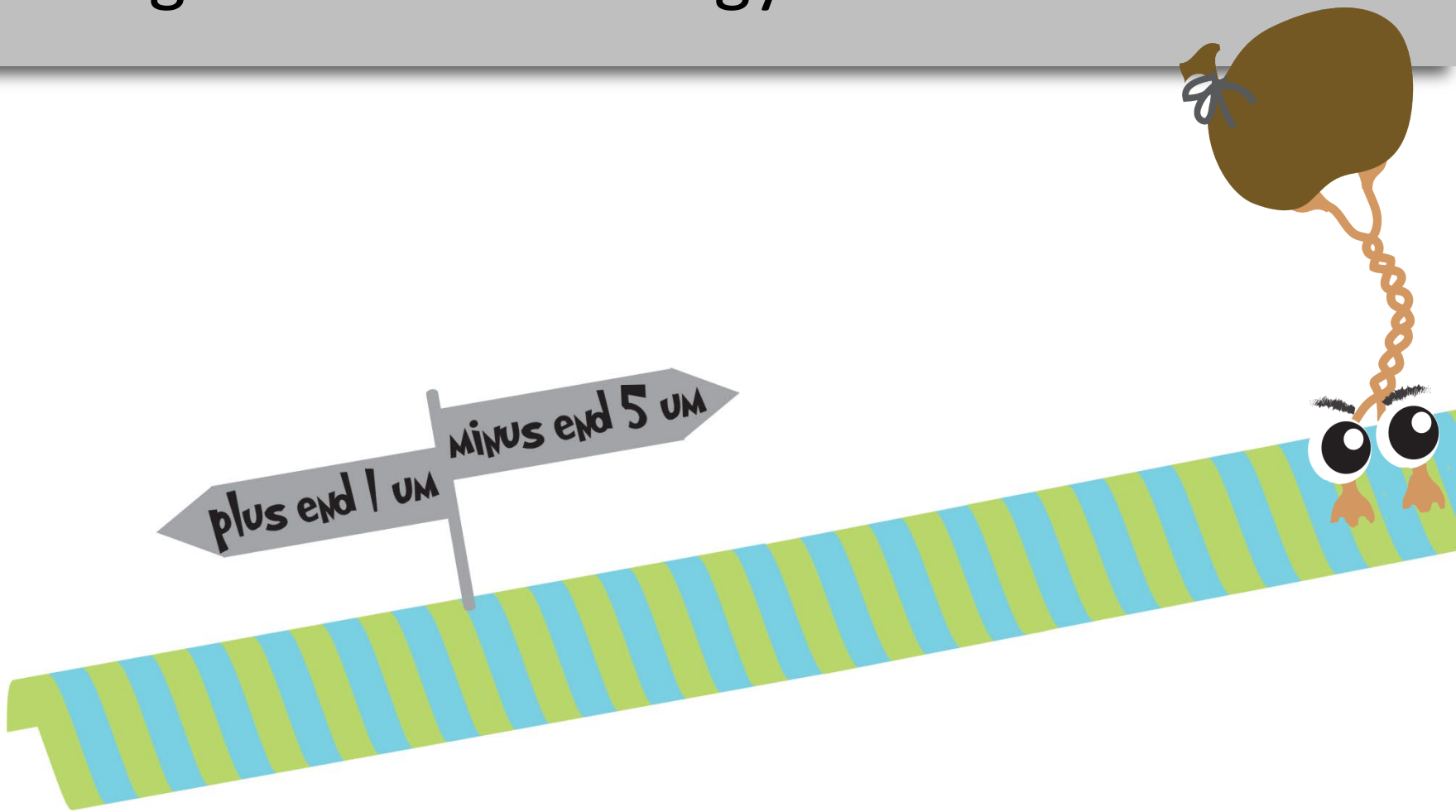


The student experience:

- Will work directly with post-doc or me (I am usu around)
- Typically we have 2-3 undergrads in the lab (Tucker H. and Ryan R. now)
- BSL1 or BSL2, focus is molecular biology
- Get to give lab meeting and co-author on papers!
- Recent former undergrads: med school, applying to med school, working in translational or clinical research (NYU & Pitt), grad school in chemistry (here) or applying to grad school (materials engineering)

Questions?

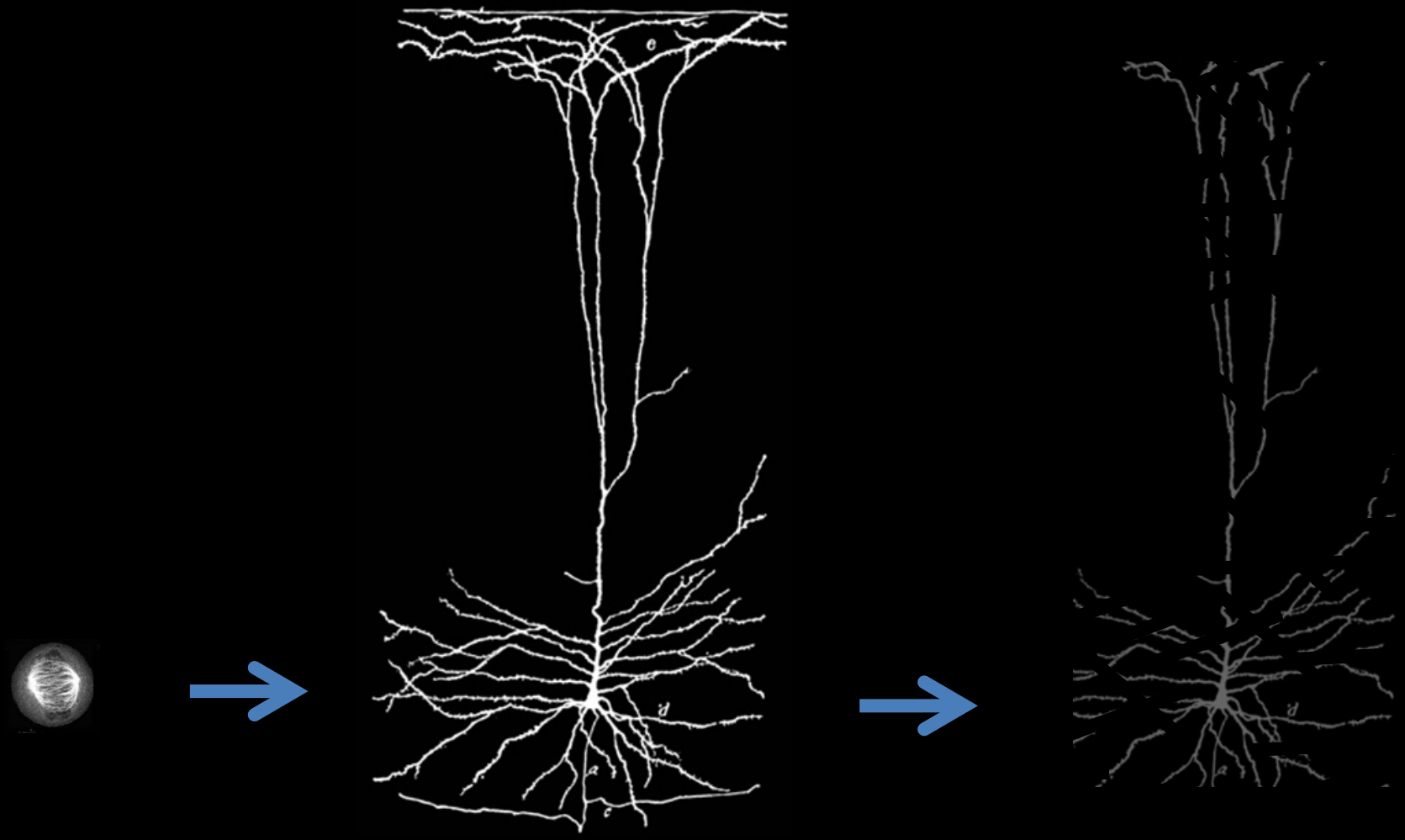
Yogev lab: Cell biology of the neuron



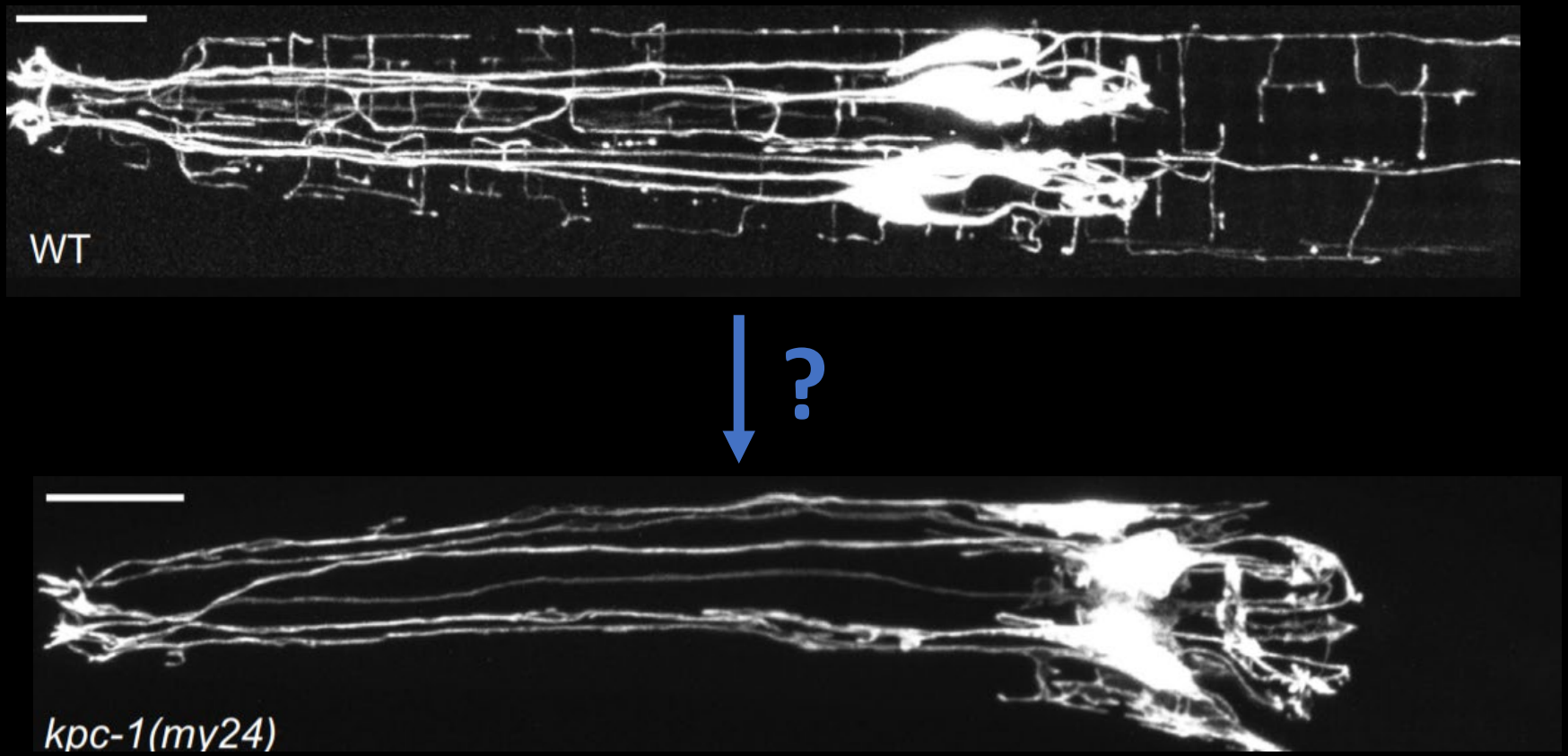
shaul.yogev@yale.edu
Depts of Neuroscience & Cell Biology

www.yogevlab.org

We are interested in neuronal cell biology – how neurons polarize, grow and remodel



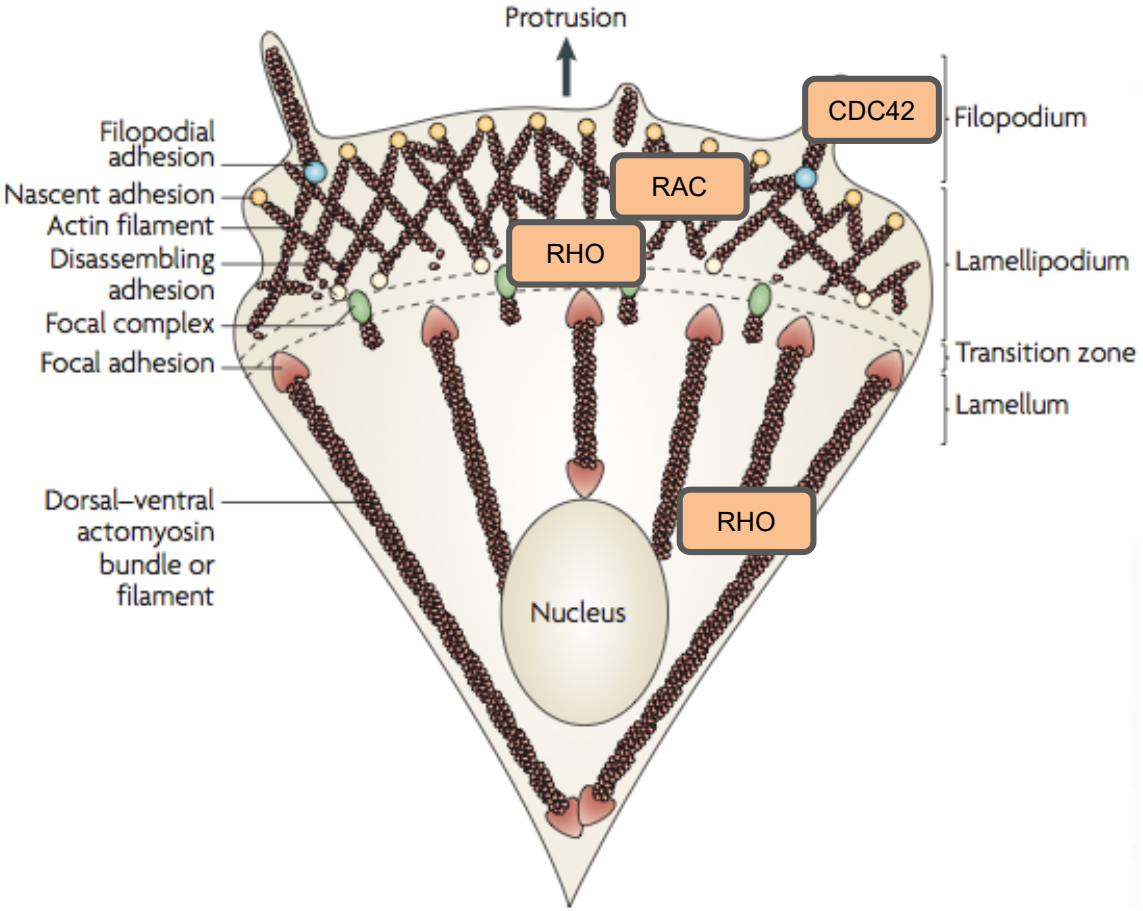
Summer project: study the mechanisms of neuronal remodeling in *C. elegans*



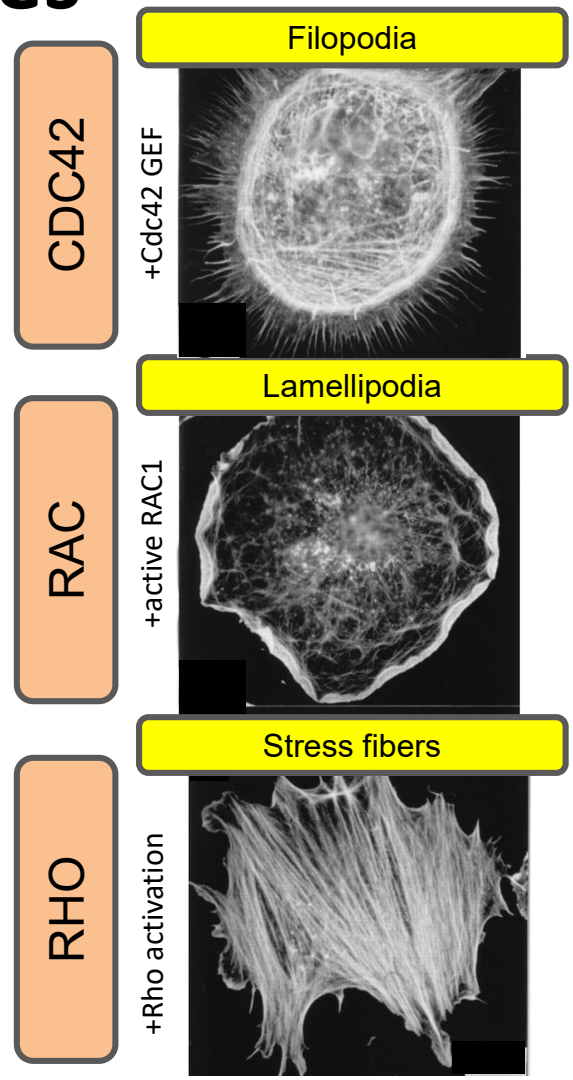
Methods: genetics and imaging
Mentoring by PhD student (daily) and PI (weekly)

Boggon Lab

Structural biology of Rho Signaling cascades

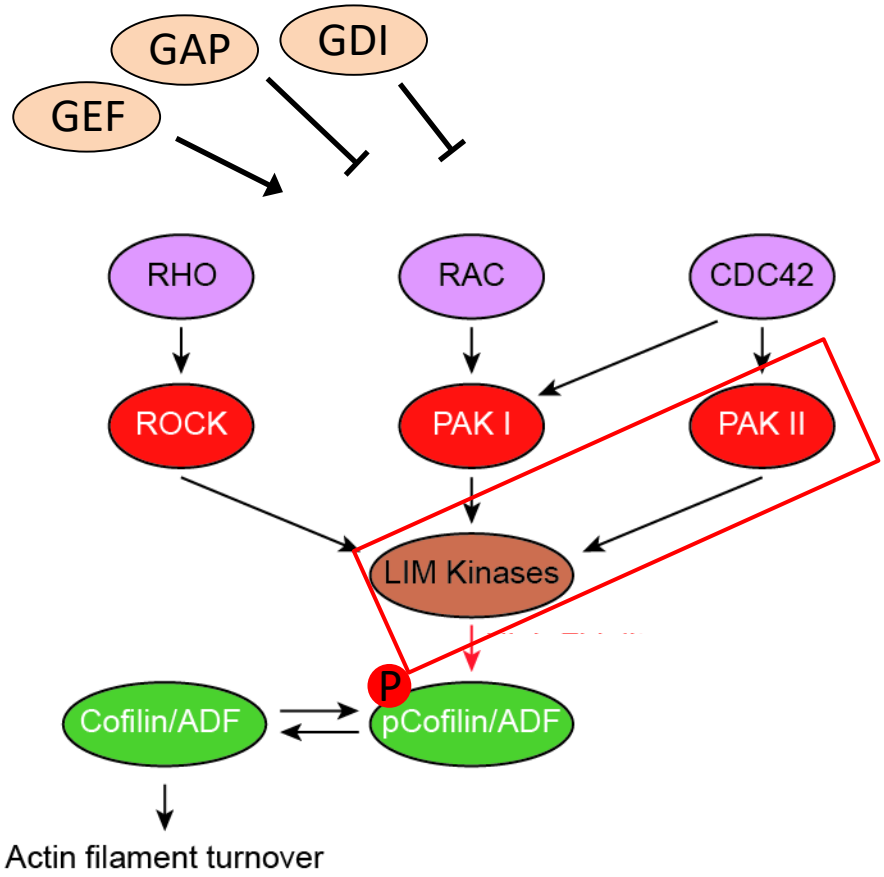


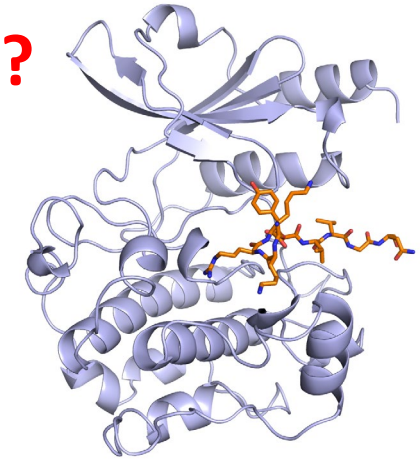
Parsons *et al.*, *Nature Reviews MCB*, 2010



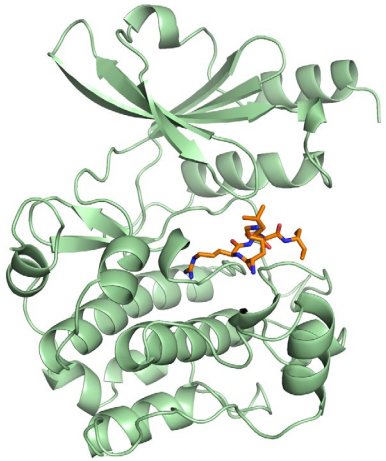
Hall, *Science*, 1998

What are the molecular mechanisms that regulate these cascades?





PAK4:LIMK substrate



PAK4:β-catenin substrate

Ashwin Chetty
MB&B Junior

Contents lists available at ScienceDirect

BBA - Proteins and Proteomics

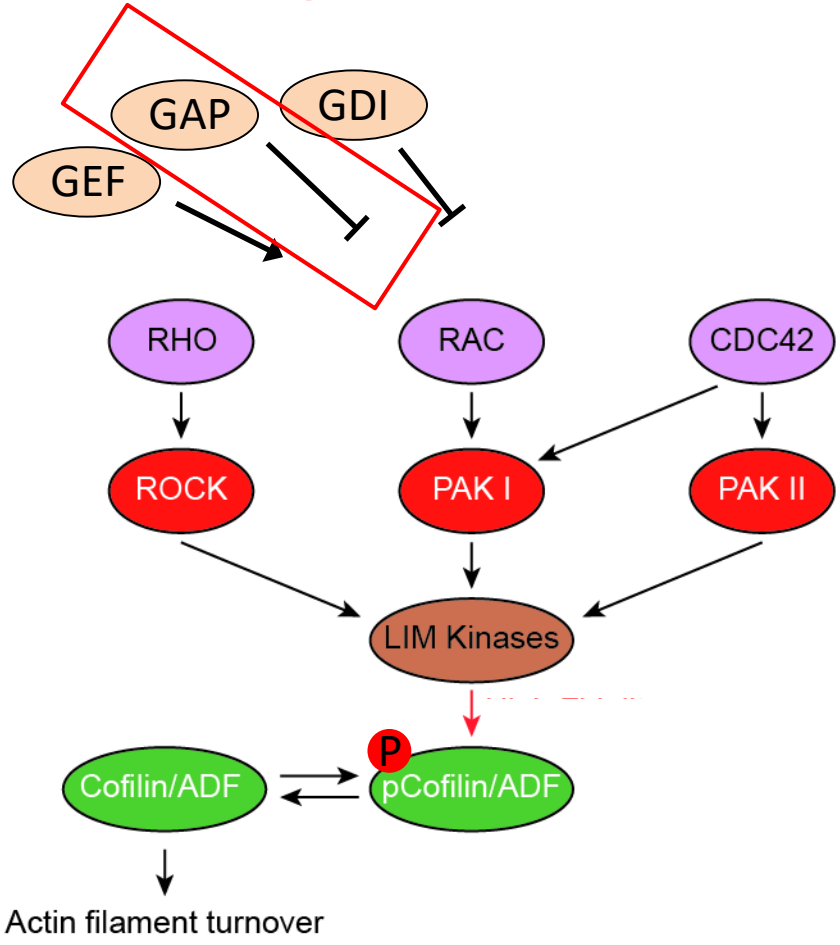
journal homepage: www.elsevier.com/locate/bbapap

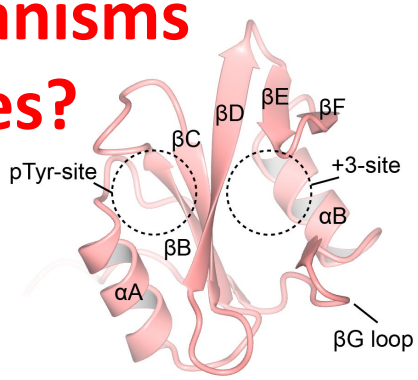
PAK4 crystal structures suggest unusual kinase conformational movements

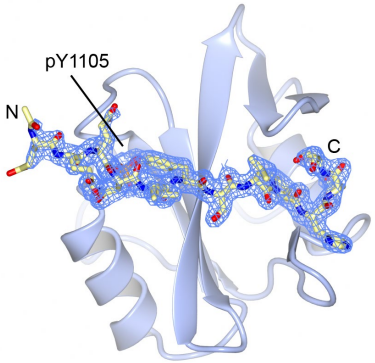
Eric Y. Zhang[a], Byung Hak Ha[a], Titus J. Boggon[a,b,*]

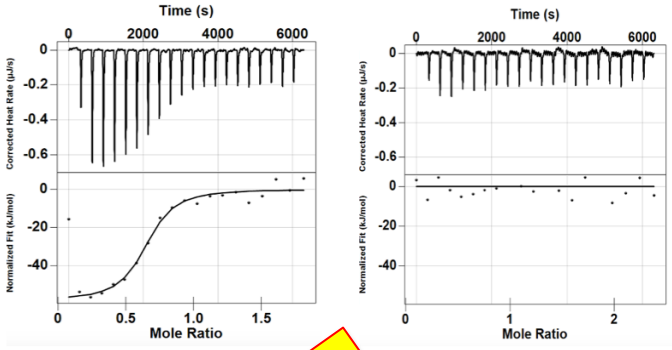
Eric Zhang
MB&B 2017

What are the molecular mechanisms that regulate these cascades?









Rachel Jaber Chehayeb MB&B Senior

Jessica Wang
MB&B 2019

PLOS ONE

Crystal structures of p120RasGAP N-terminal SH2 domain in its apo form and in complex with a p190RhoGAP phosphotyrosine peptide

Rachel Jaber Chehayeb[1,2], Amy L. Stiegler[3], Titus J. Boggon[2,3,4]*

Protein Folding and Dynamics Revealed by Single-Molecule Force Spectroscopy

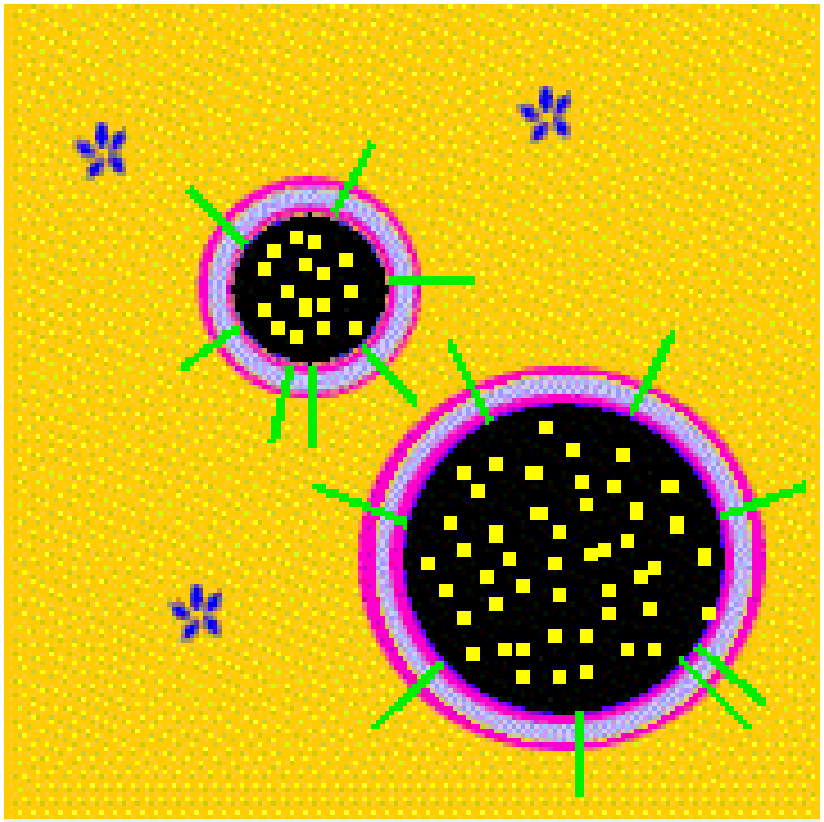
Yongli Zhang

Associate Professor
Department of Cell Biology
Yale University
Email: yongli.zhang@yale.edu

Some former Yale undergraduate students worked in the Zhang lab:

- Christina de Fontnouvelle, now medical student at Yale School of Medicine
- James Ting, now medical student at Johns Hopkins University
- Blessing Aghaulor, now medical student at North Carolina at Chapel Hill
- Gregory Gundersen, now graduate student at Princeton University

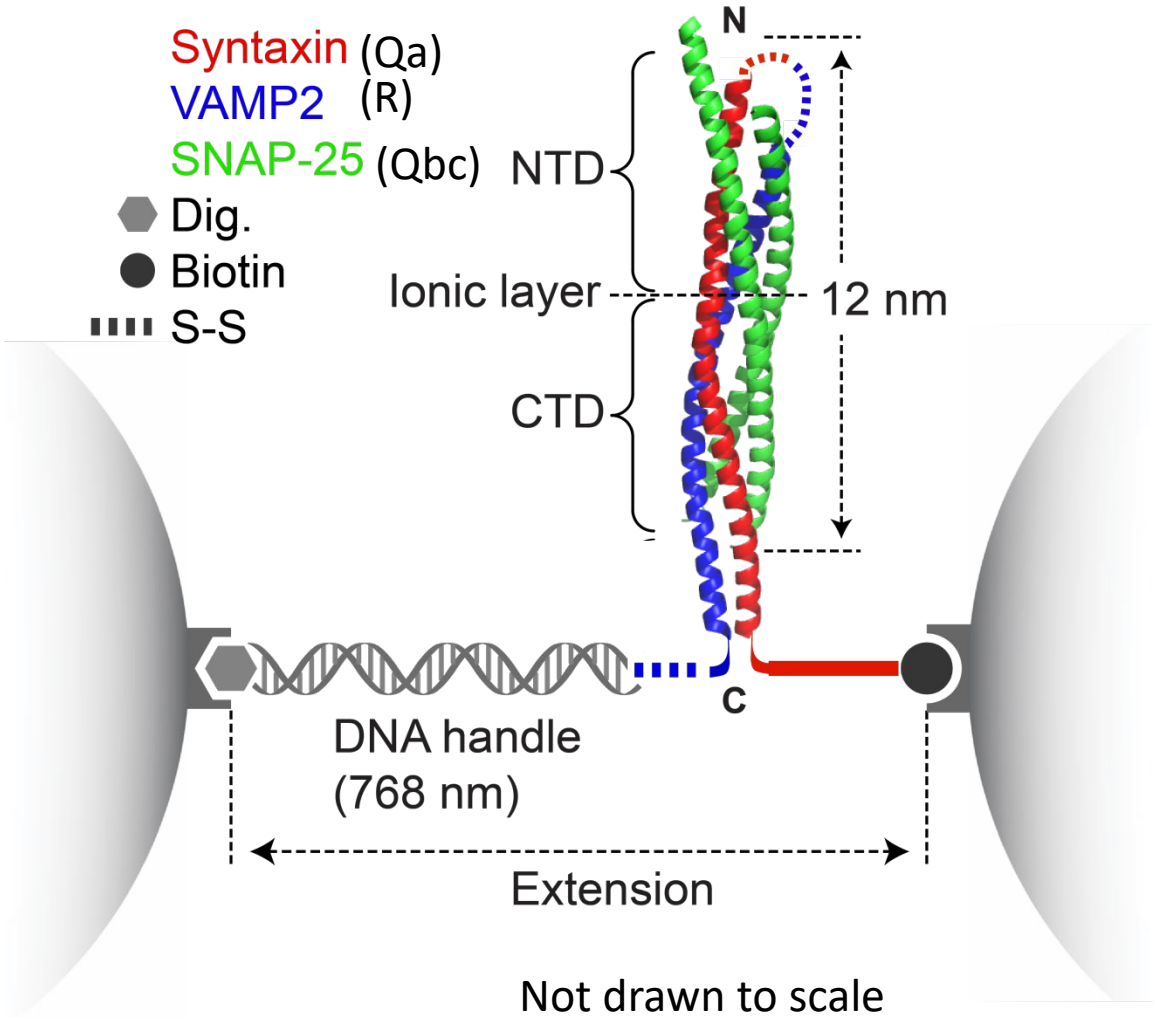
SNAREs couple their folding/assembly to membrane fusion



1. Energy barrier for fusion > 30 kT
2. Synaptic Vesicle fusion
   - Fast (<0.1 ms)
   - Frequent (>100 Hz)
   - Highly regulated
   - Related to many diseases
3. Complex kinetics of exocytosis (hemifusion, fusion pore flickering, itc.)

SNARE hypothesis: Sollner, T., …, Rothman, J.E. (1993). Nature *362*, 318-324.
SNARE zippering hypothesis: P. Hanson,,…, R. Jahn, J. Heuser, Cell, 90, 523 (1997)

Single-molecule manipulation of SNARE complexes



Y. Gao, …, J. E. Rothman, Y. L. Zhang, *Science* **337**, 1340 (2012).
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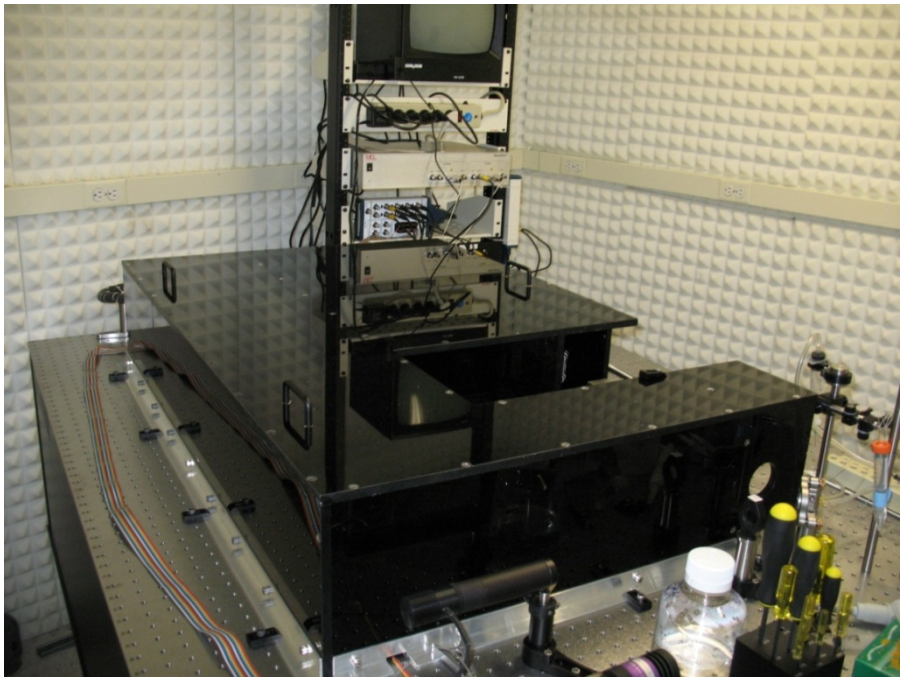
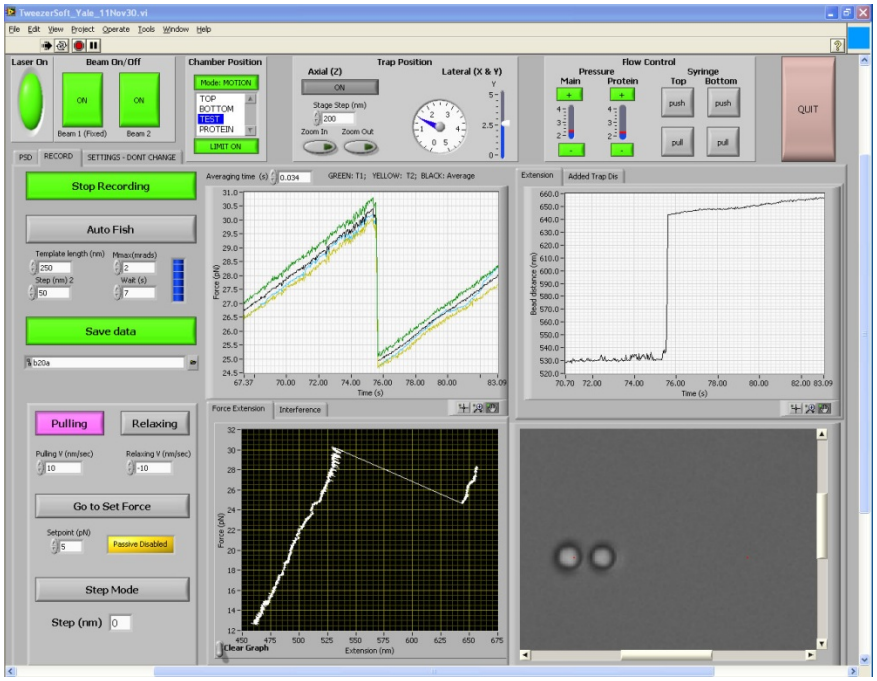
High-resolution optical tweezers

Hardware



Software



Measurement range

- Displacement: **0.2 nm** – 50 µm
- Force: **0.05 pN**– 200 pN (water); 10^{-21} N in vacuum
- Time: **20 µs** – 2 hours

Force to unfold macromolecules or generated by molecular motors: 1-40 pN

Force to break covalent bond: > 1000 pN