Leveraging natural defenses to fight viruses

The Foxman Lab

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Yale SCHOOL OF MEDICINE

Why study respiratory viruses?

Annual impact, U.S.:

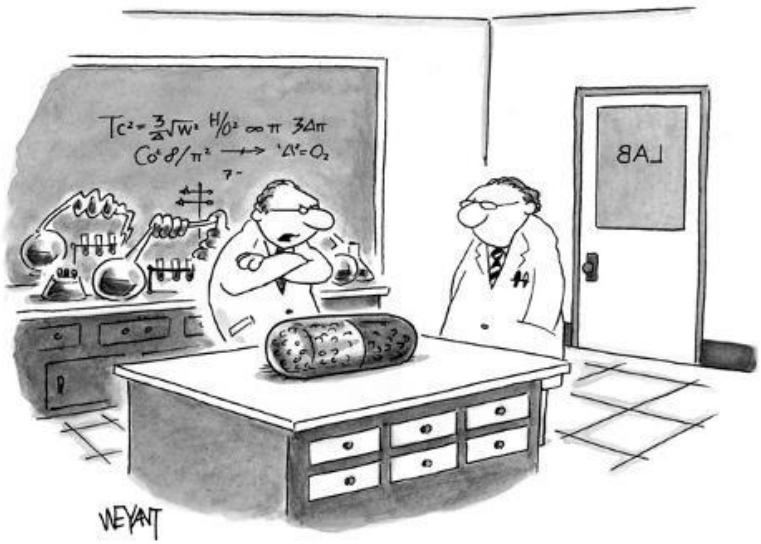
- **Acute respiratory illnesses: ~500 million**
- **Serious illness/hospitalization: ~2 million**
- **Exacerbations of asthma (25 million affected)**

Image:https://edc2.healthtap.com/

How can we reduce this burden?

Fendrick et al. *Arch Intern Med* **2003**; 163:487-94.
Fleming-Dutra KE et al, *JAMA*. 2016;315(17):1864-73.

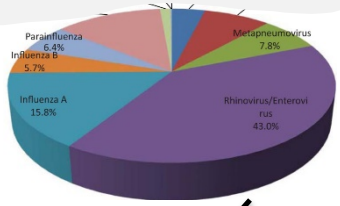
The challenge



"That's just great. I discover the cure for the common cold and all you can do is criticize."

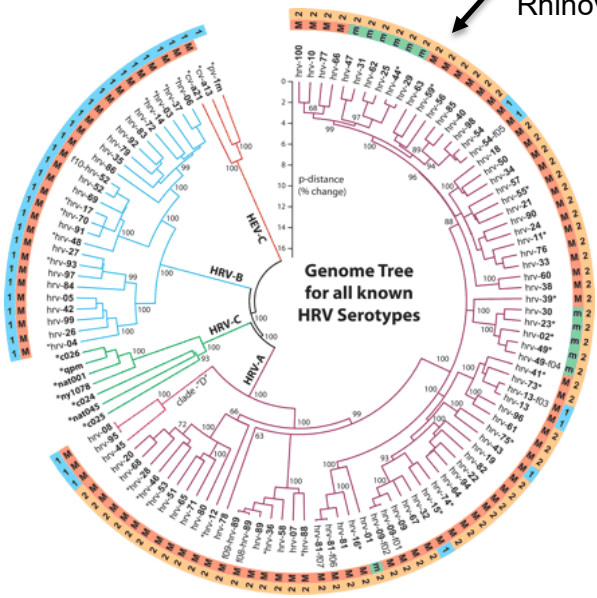
The New Yorker

Common respiratory viruses
Rhinovirus
Influenza A,B
RSV
Parainfluenza
MPV
Adenovirus



J Clin Micro 2015 53:3110

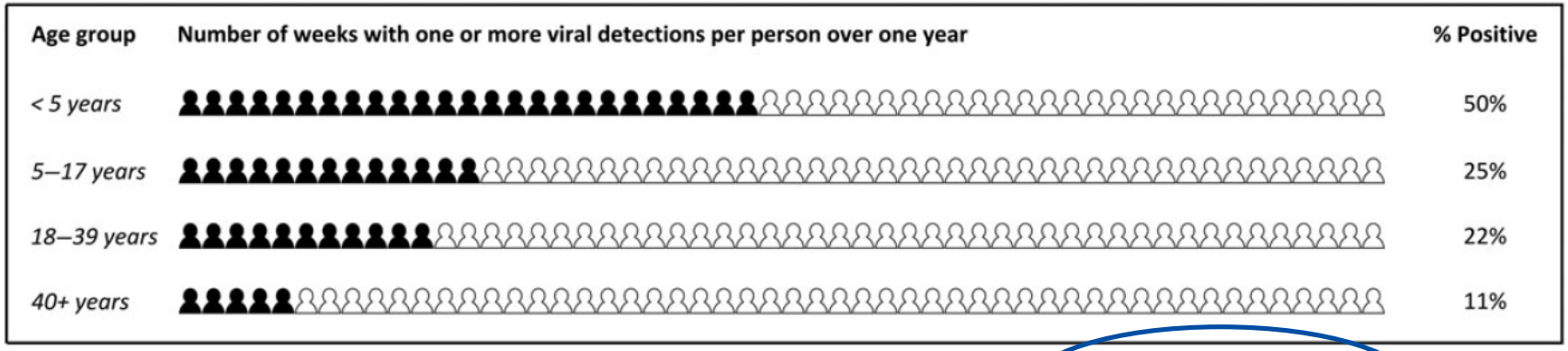
Rhinovirus



Palmenberg et al. (2009) *Science*

Too many different viruses to block with vaccines and drugs

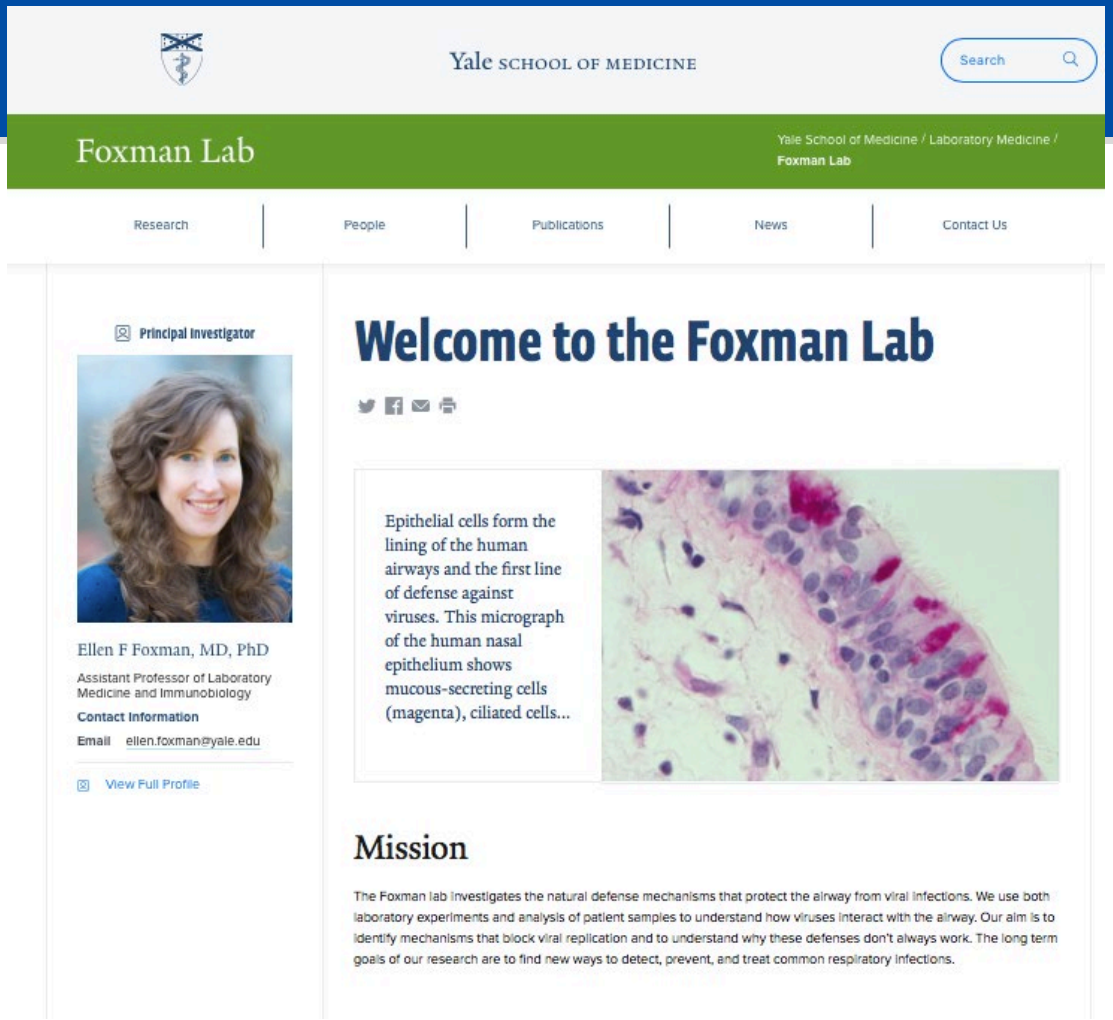
Better tests->new understanding of viral infection

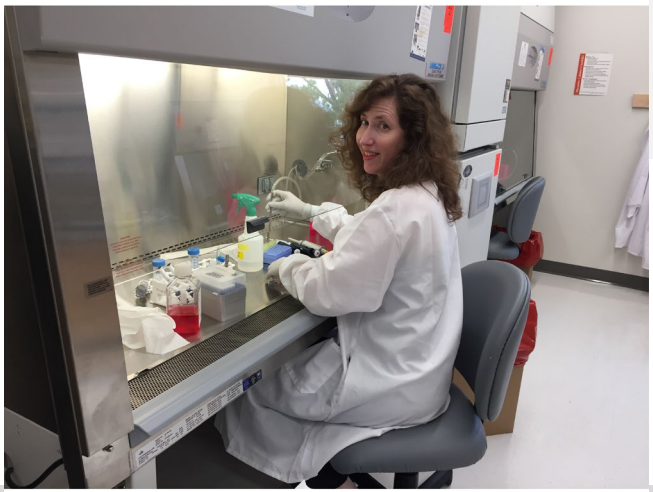


Utah Family study: Number of virus-positive weeks per year. ***Many asymptomatic***

Byington et al, 2015. *Clin Infect Disease*, 61(8):1217-1224

What is the body doing right?

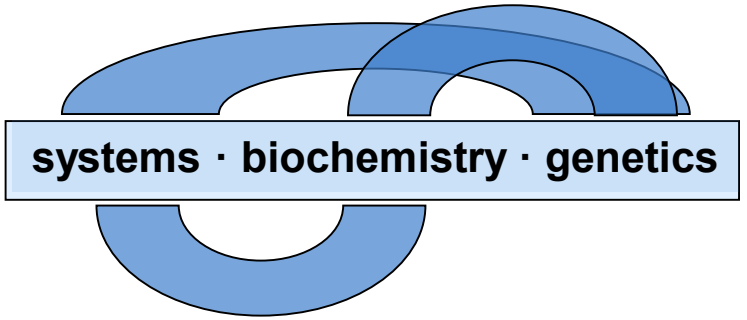


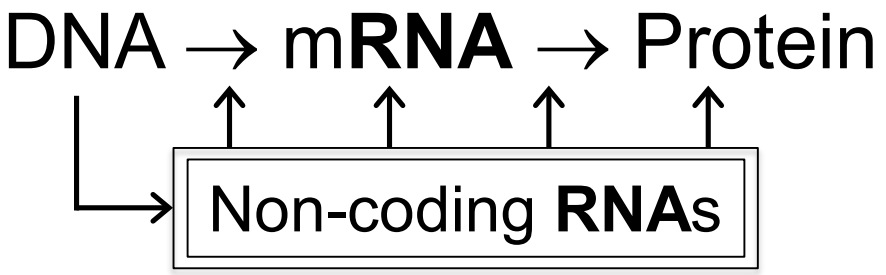


https://medicine.yale.edu/lab/foxman/

The Gilbert Lab @ Yale

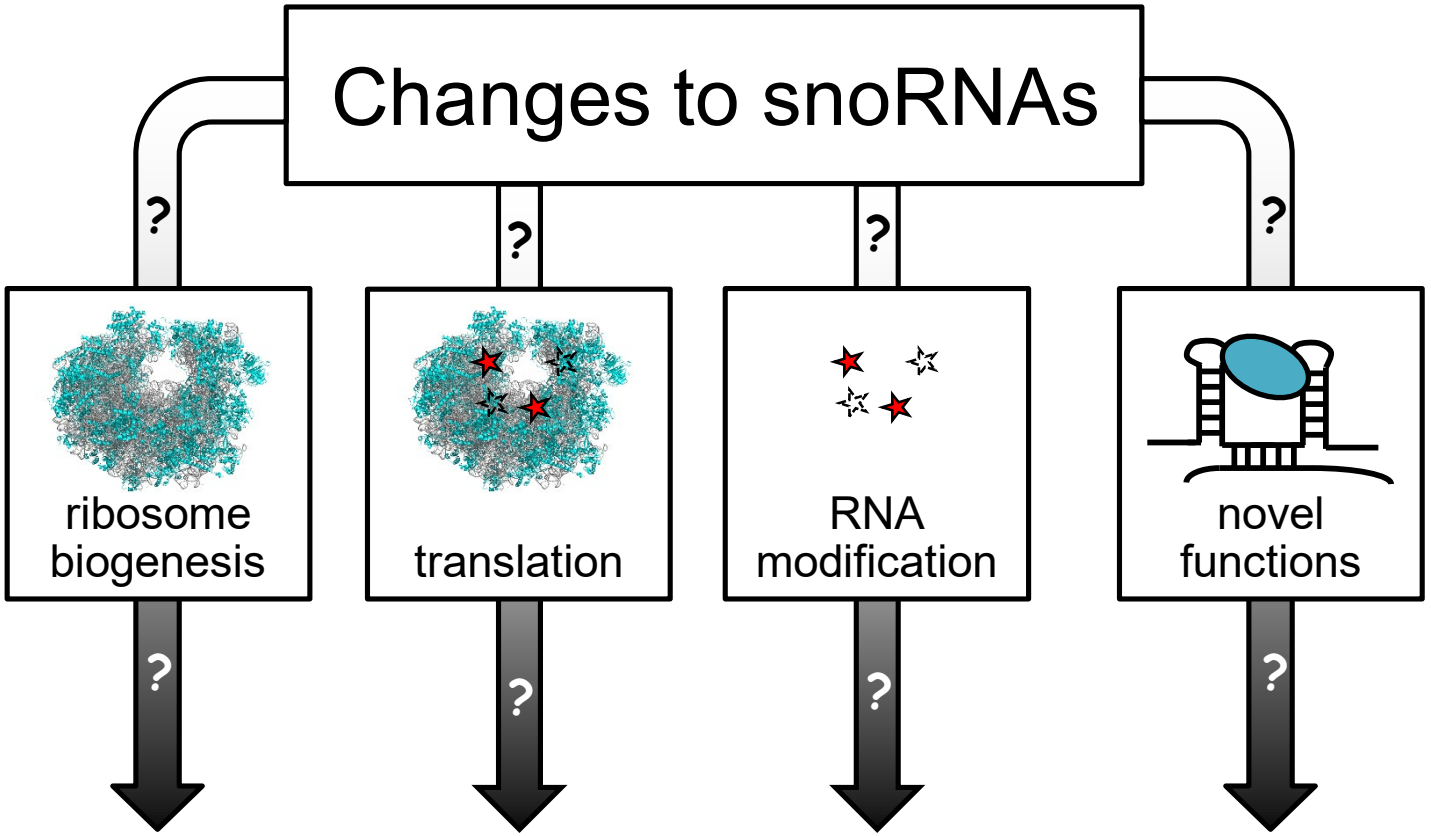
We invent new technology and investigate the ***how*** and ***why*** of post-transcriptional gene regulation





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!

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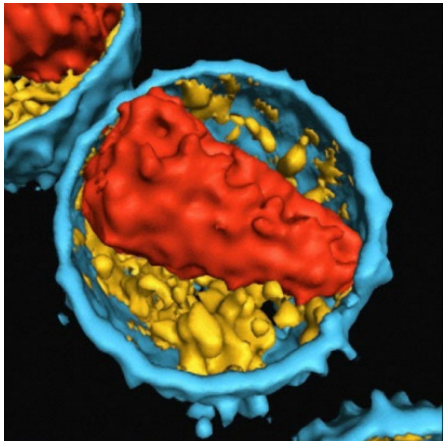
@GilbertLabRNA @WendyGScientist

Host Genetic Control of HIV/HIV Cure

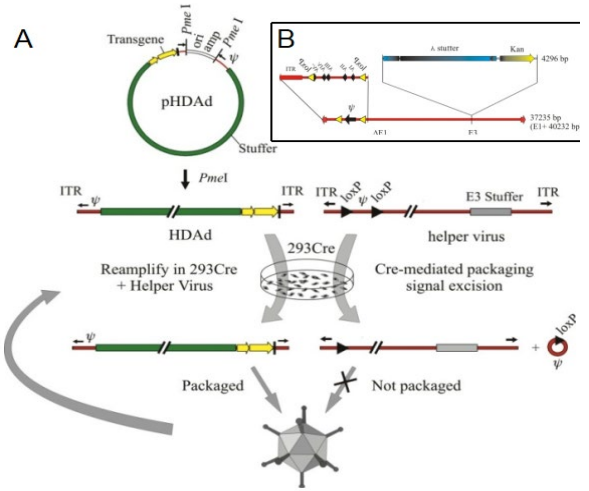


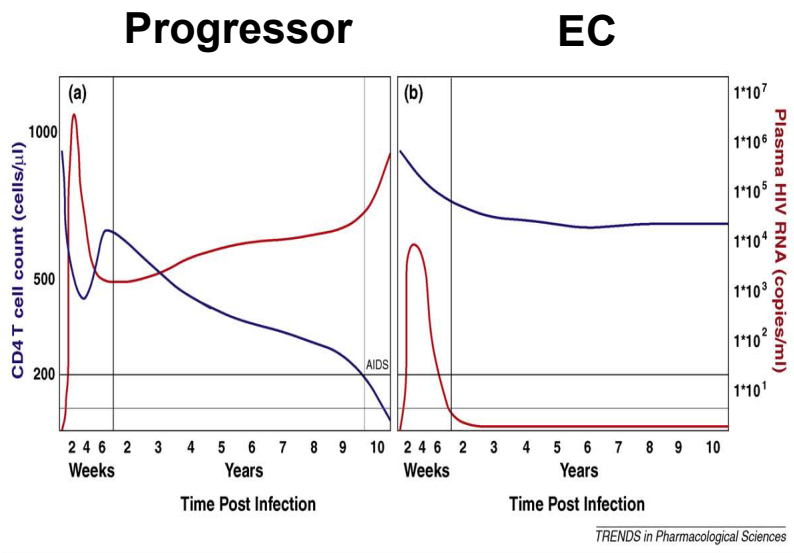
My office

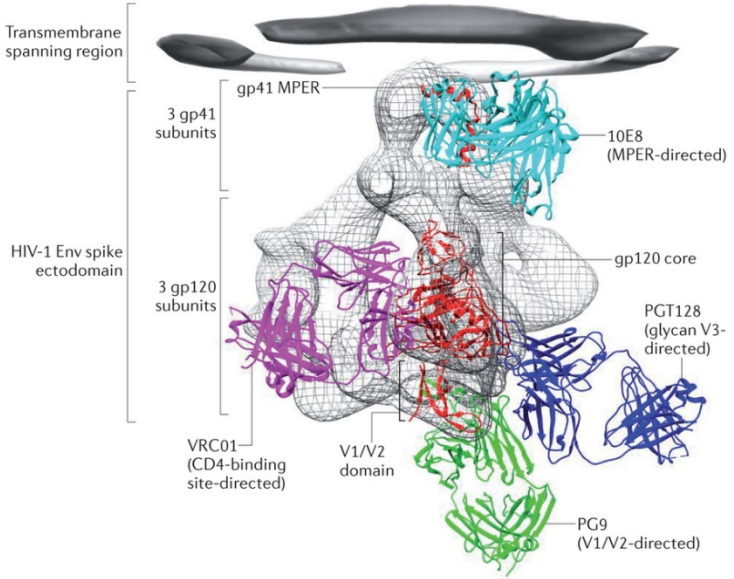
Richard Sutton, MD-PhD
Section of Infectious Diseases
& Department of Microbial Pathogenesis
Yale University School of Medicine
Richard.Sutton@yale.edu

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)

Protein Folding and Dynamics Revealed by Single-Molecule Force Spectroscopy

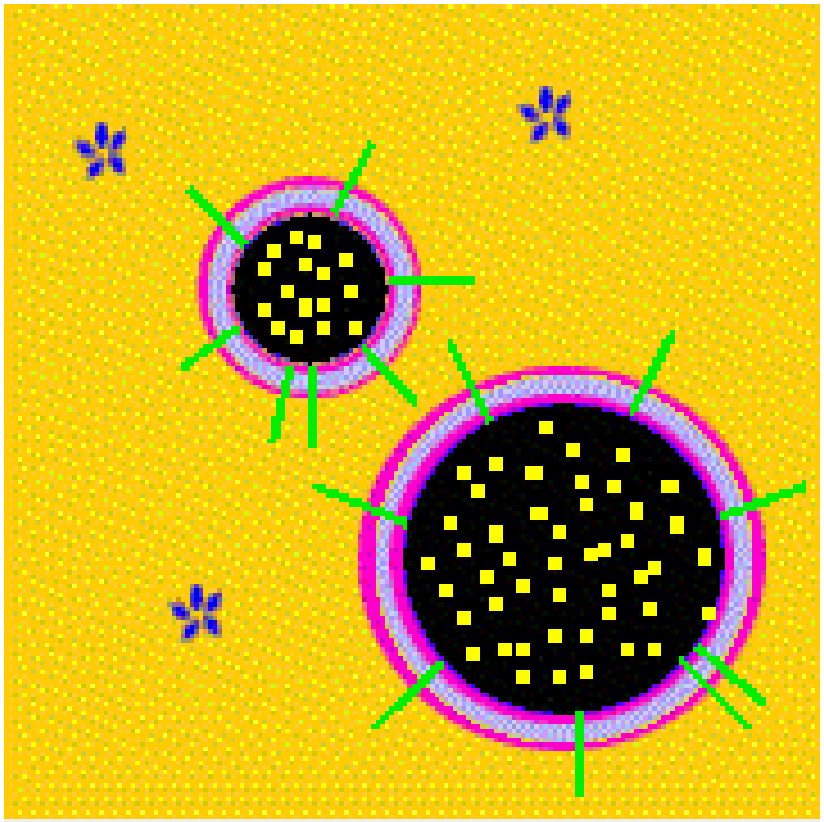
Yongli Zhang

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

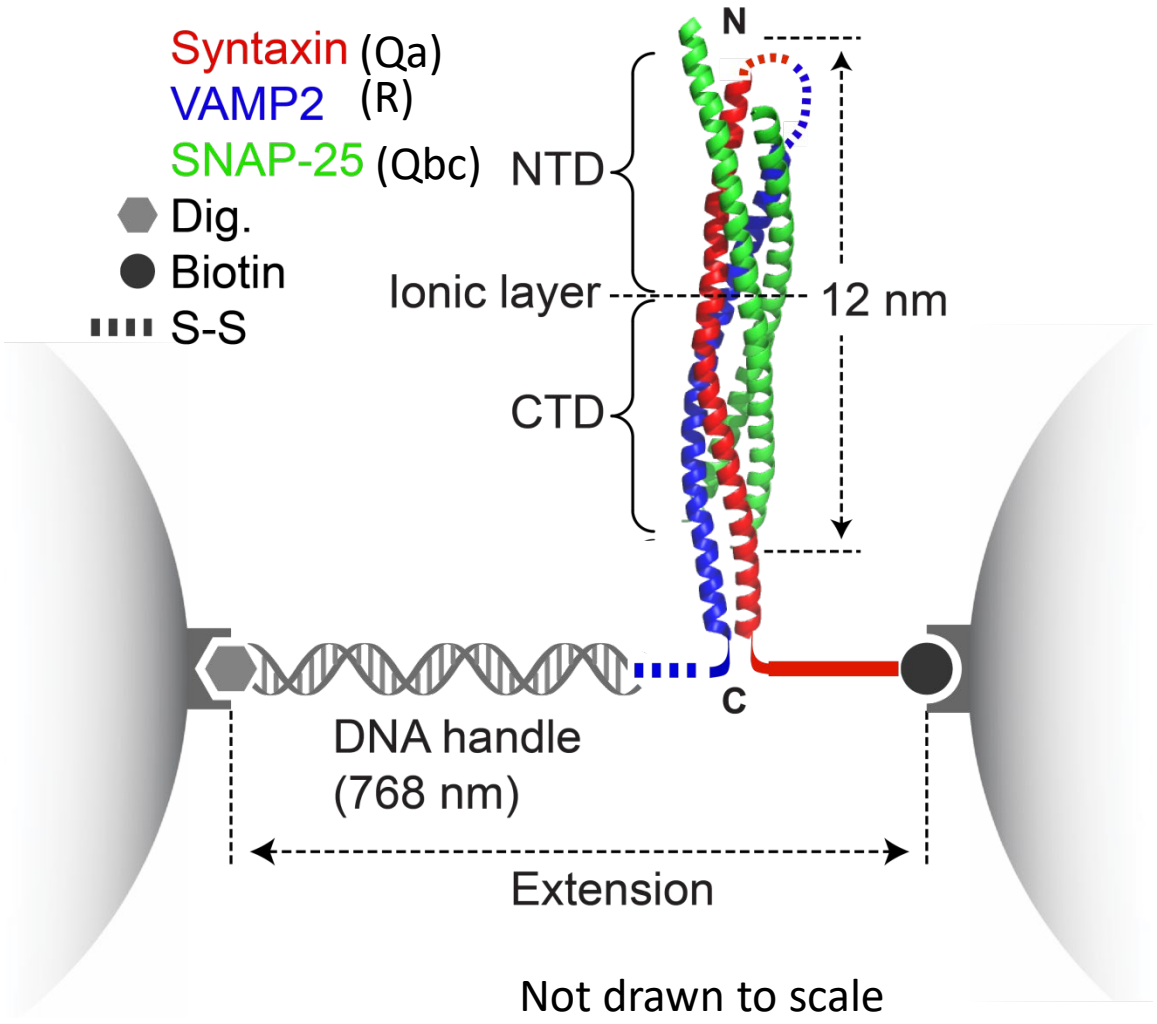
SNAREs couple their folding/assembly to membrane fusion



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)

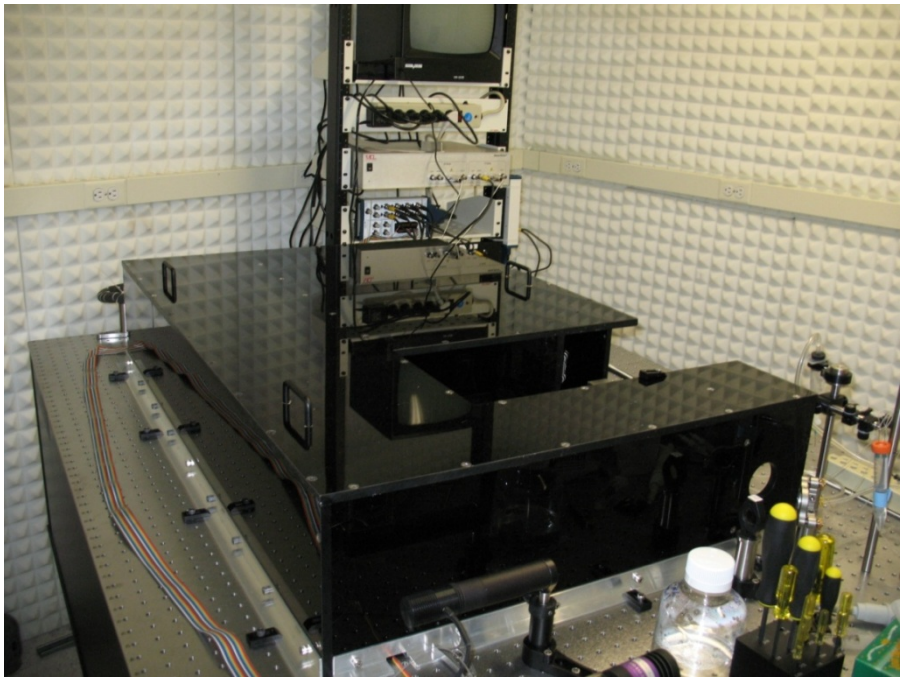
Single-molecule manipulation of SNARE complexes



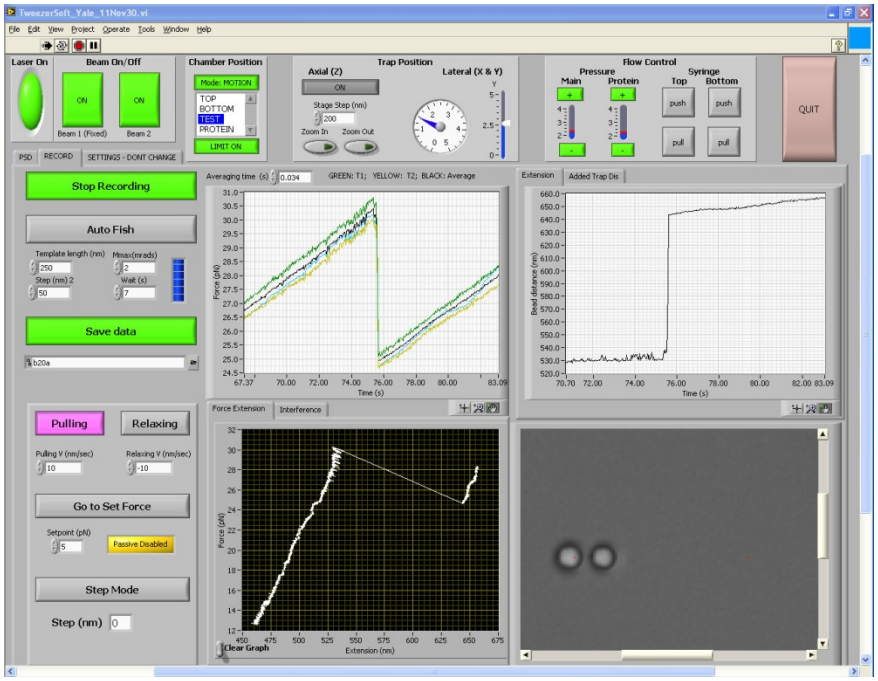
Y. Gao, …, J. E. Rothman, Y. L. Zhang, *Science* **337**, 1340 (2012).
Jiao, J., He, M., …, Hughson, F. and Zhang, Y., ***Elife***, 2018

High-resolution optical tweezers

Hardware



Software



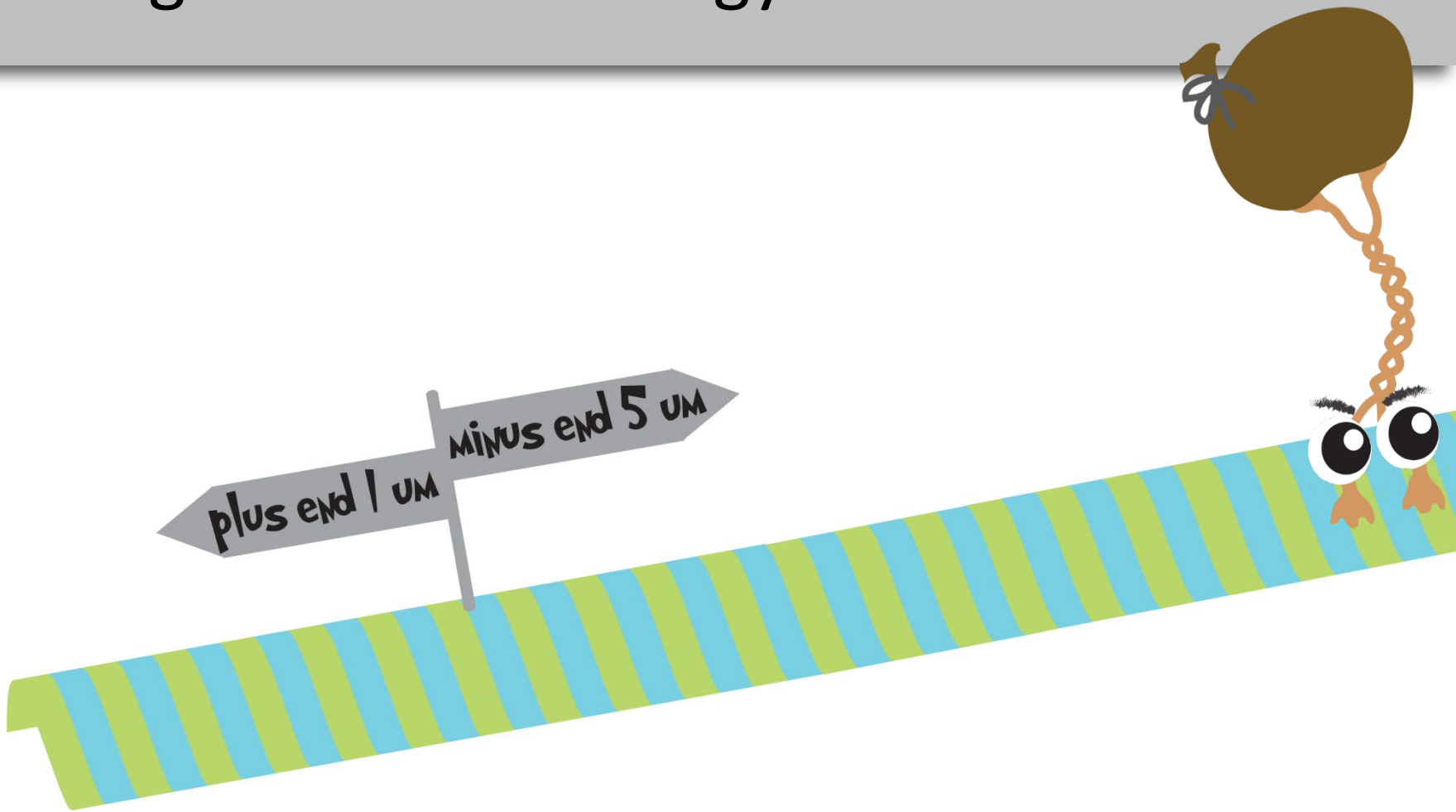
Measurement range

- 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

Yogev lab: Cell biology of the neuron



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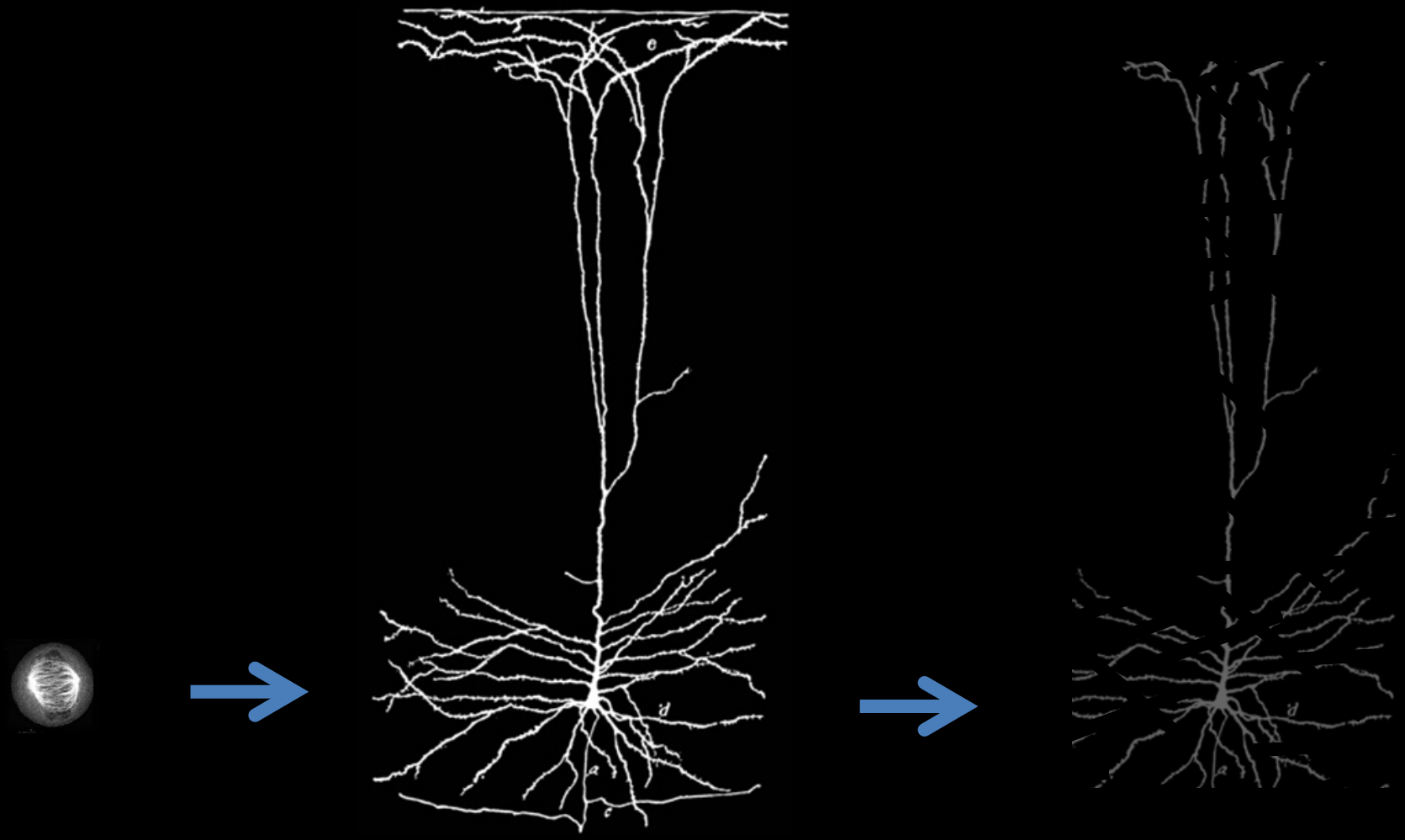
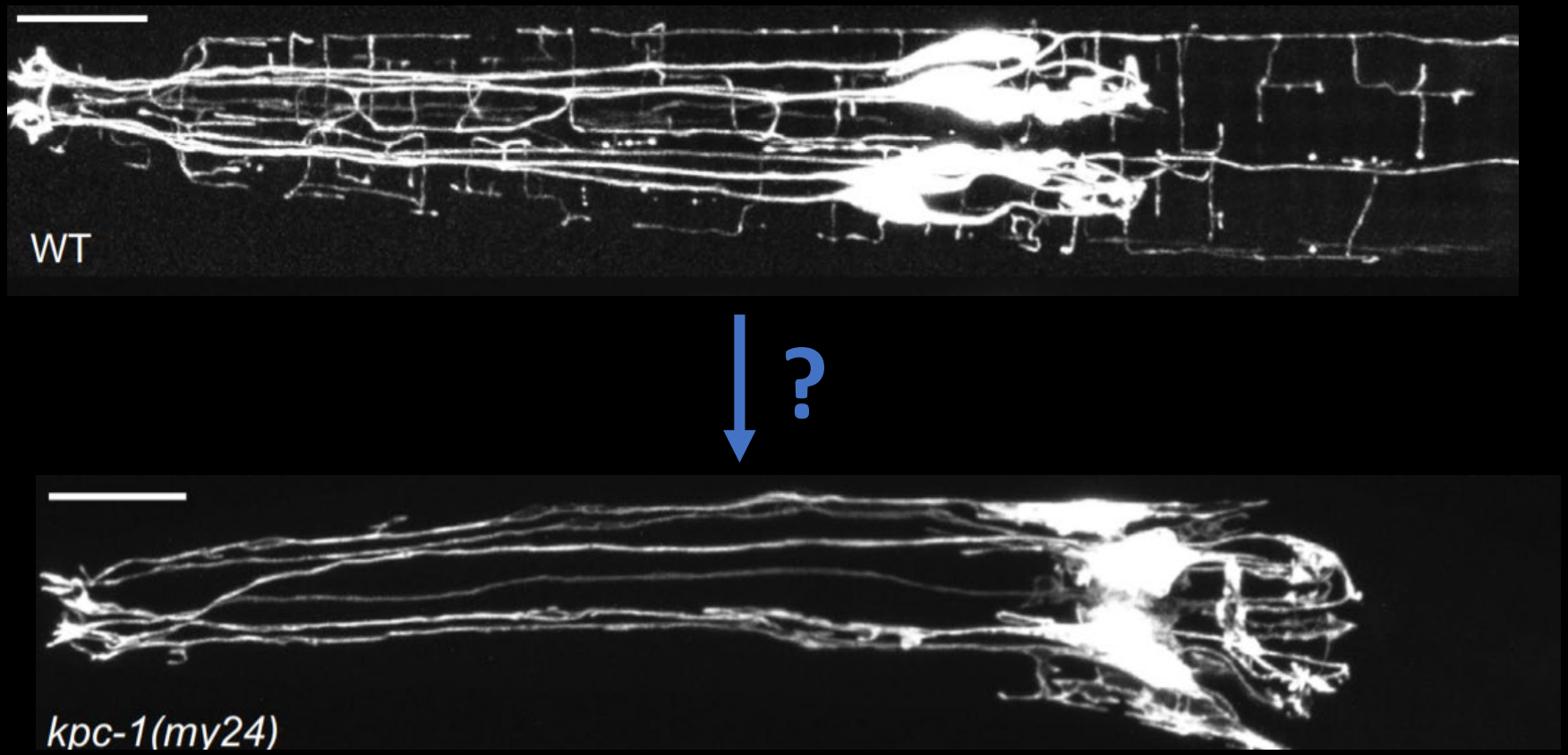
www.yogevlab.org

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



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

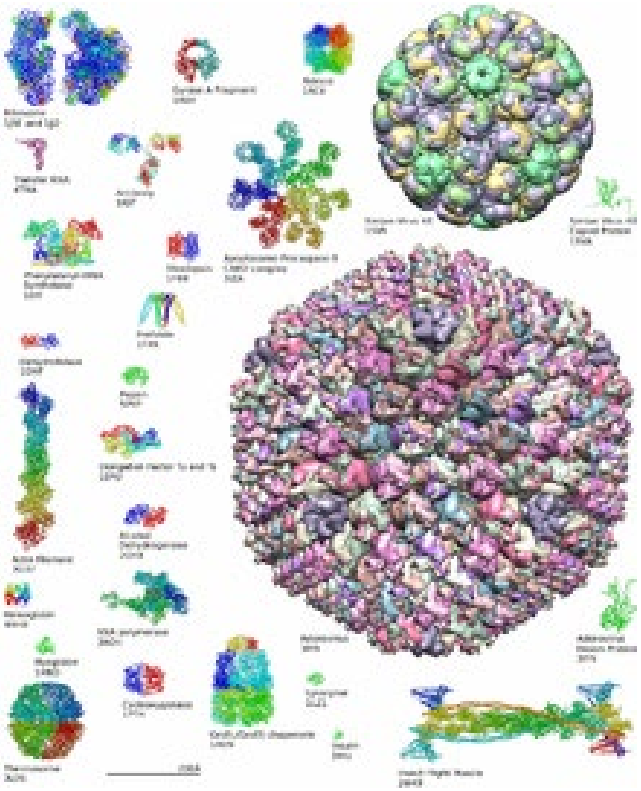


Methods: genetics and imaging
Mentoring by PhD student (daily) and PI (weekly)

Cryo-EM Studies of Membrane Proteins in Bacterial Pathogens

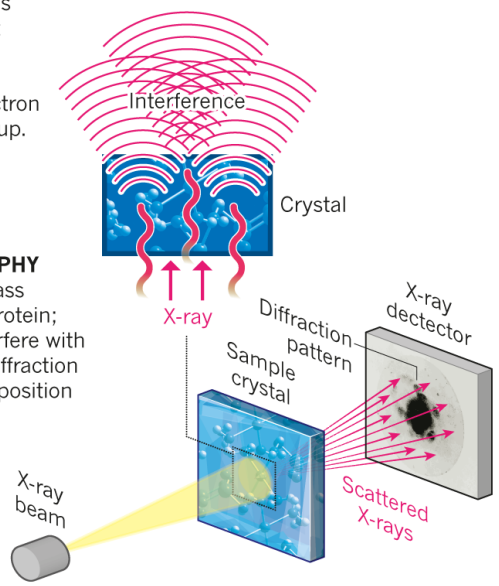
Wei Mi
Department of Pharmacology
SHM B 251
wei.mi@yale.edu

Structural Biology

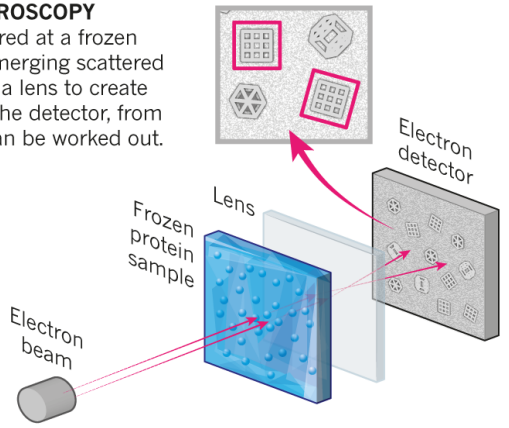


X-ray crystallography has long been the dominant method for deducing high-resolution protein structures, but cryo-electron microscopy is catching up.

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.

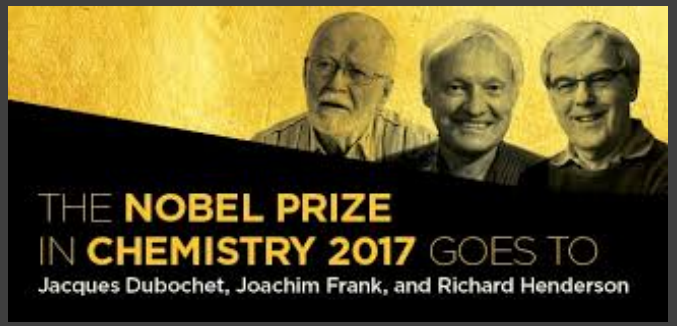


Resolution Revolution

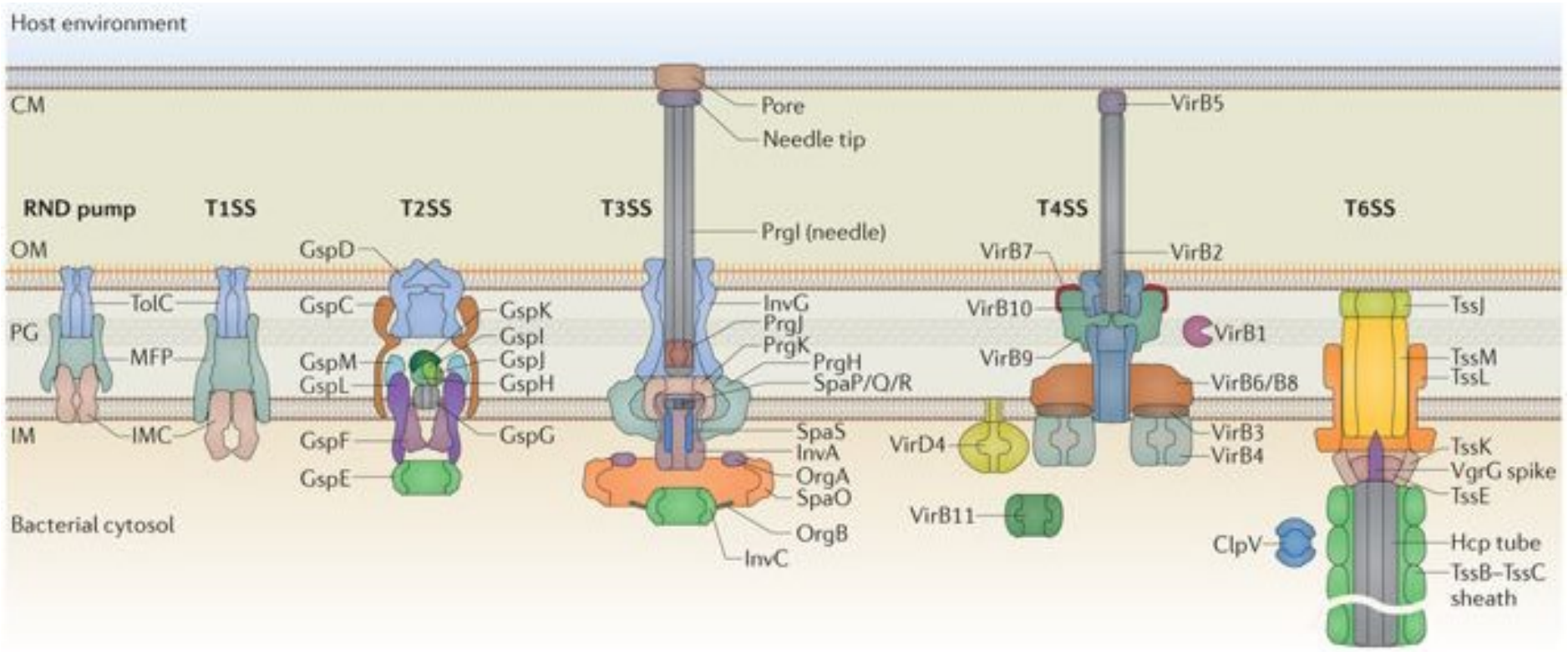
Breakthroughs in detector and algorithm

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

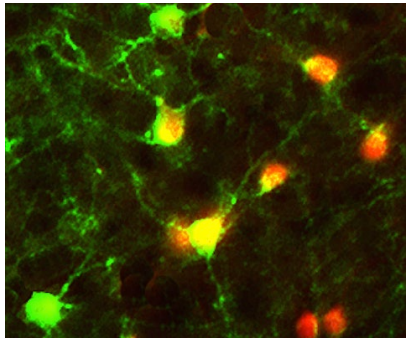
Crair Lab: Neural Circuit Development

Main Question:

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

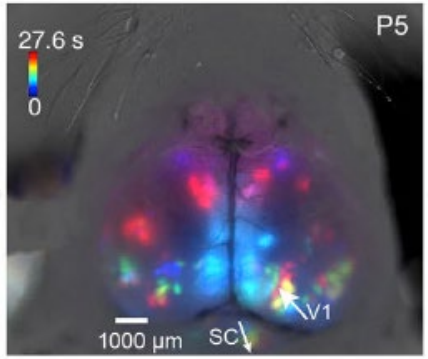
Michael C. Crair
Department of Neuroscience
SHM B301
Yale

Local circuits



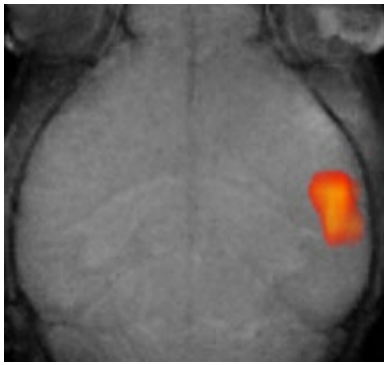
Microscopic (2p Ca^{2+}) activity in single cells

Cortex wide



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

Whole brain



functional MRI

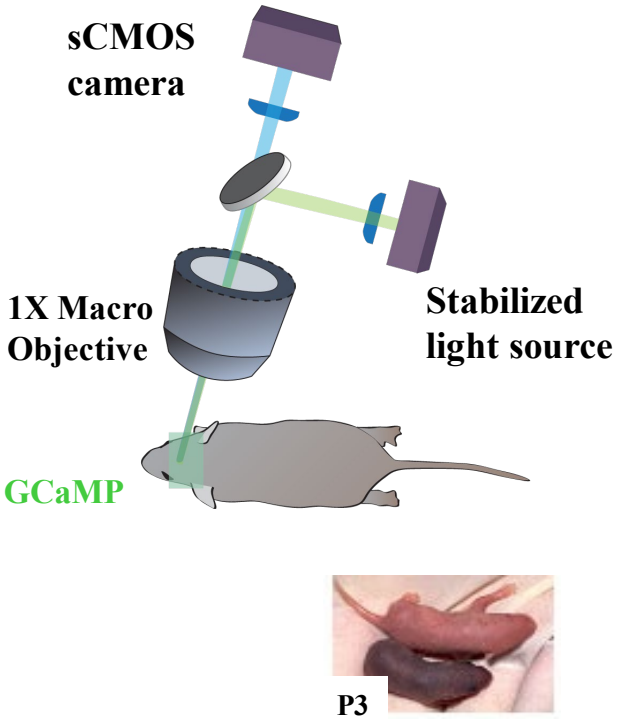
michael.crair@yale.edu

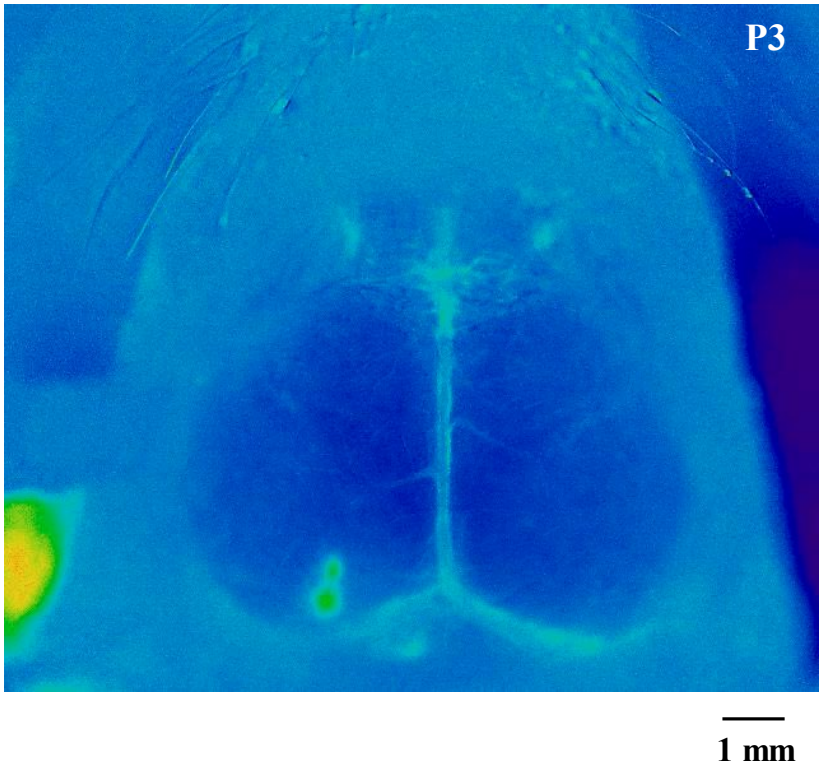
Crair Lab: Neural Circuit Development

Model System:

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

Michael C. Crair
Department of Neuroscience
SHM B301



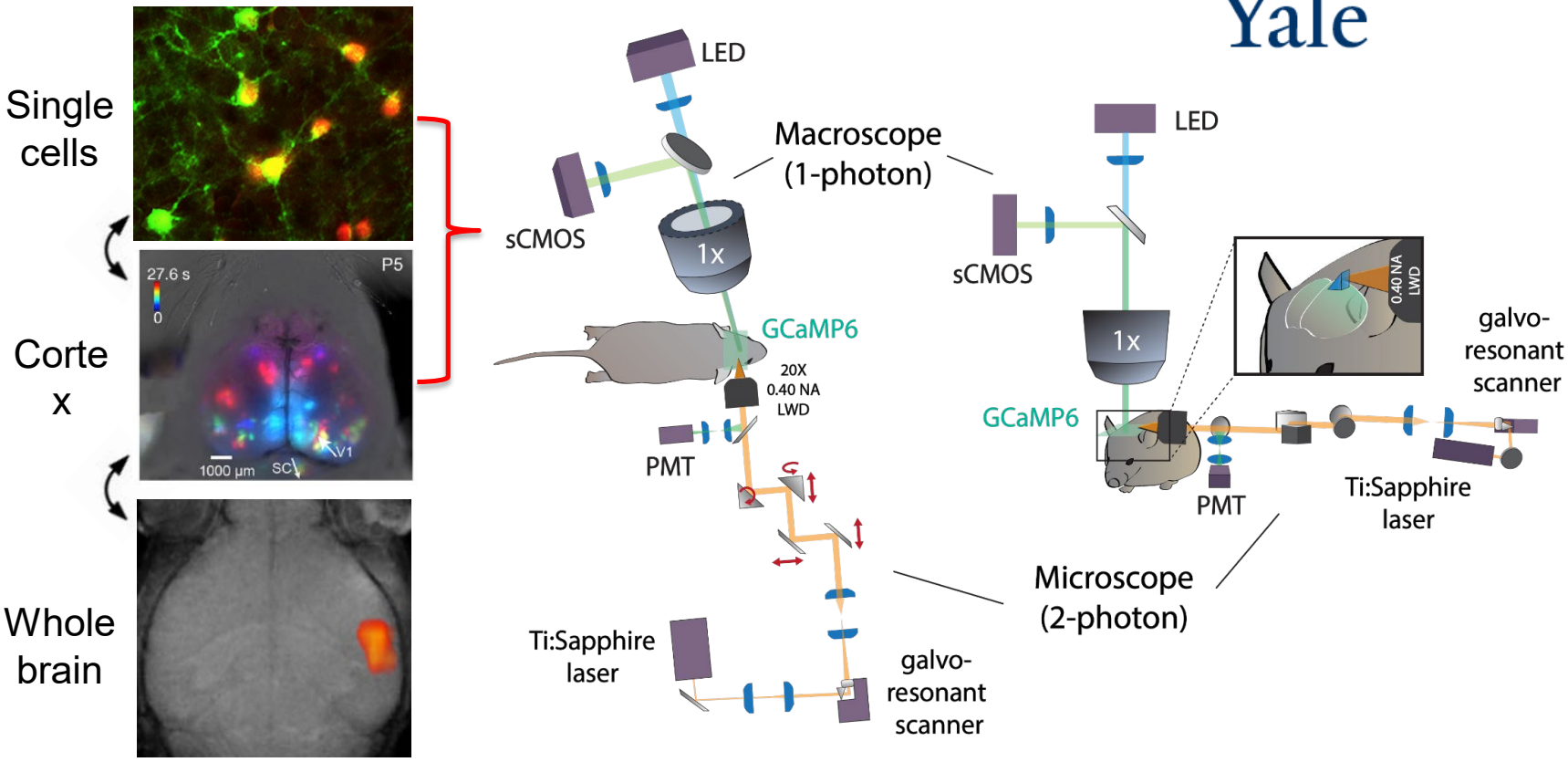


Crair Lab: Neural Circuit Development

Michael C. Crair
Department of Neuroscience
SHM B301
Yale

Experimental Approaches:

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



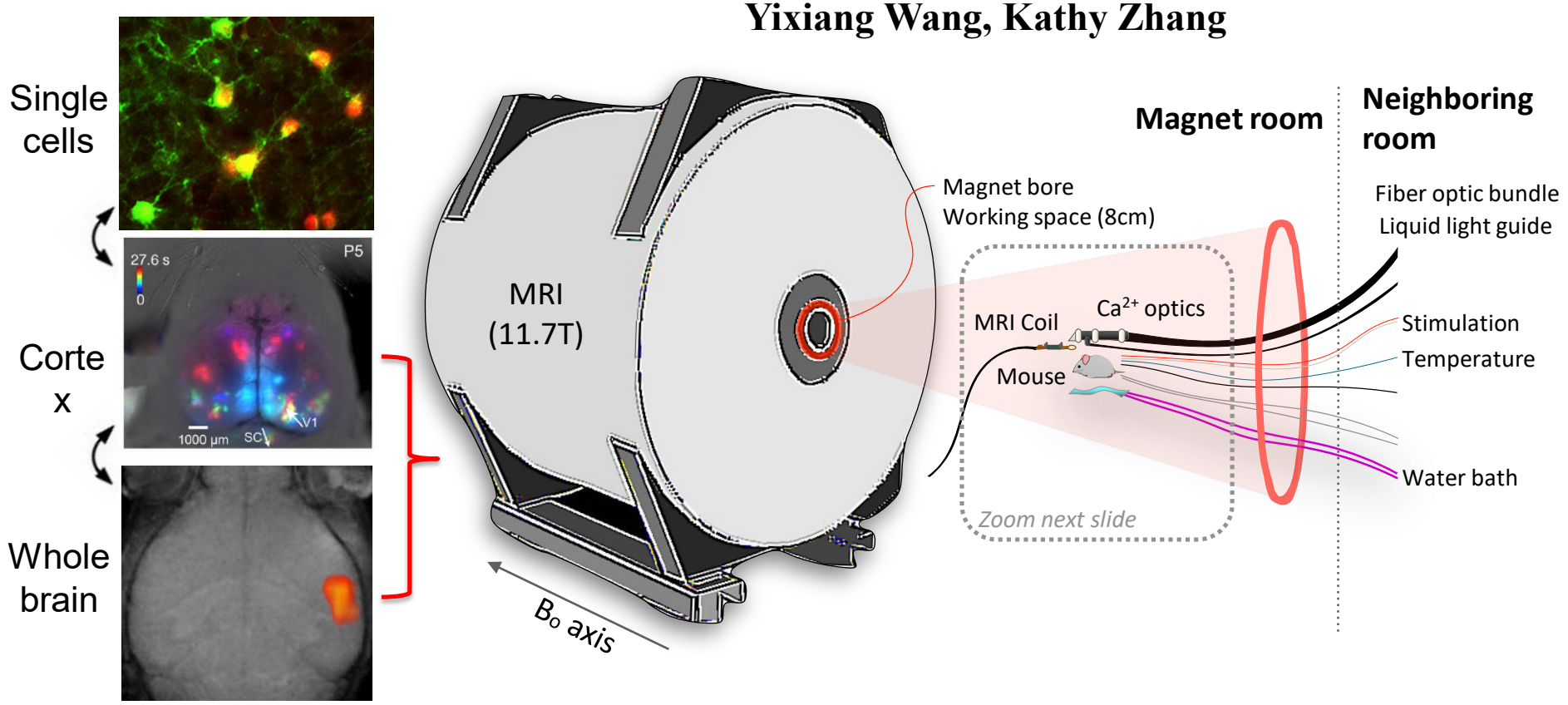
Crair Lab: Neural Circuit Development

Lab Style:

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

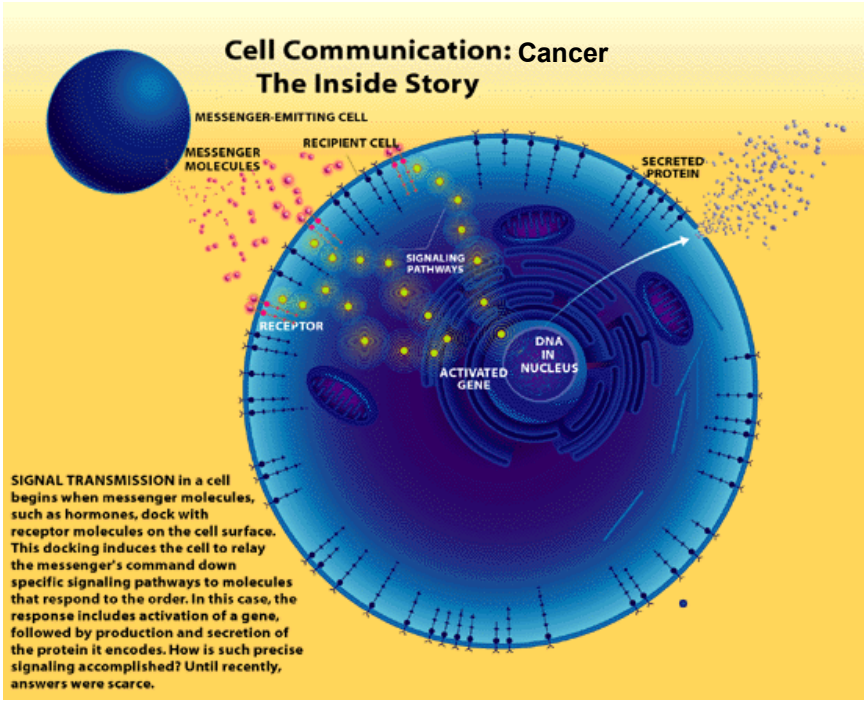
Current Yale Neuroscience Undergrads and Grads:

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

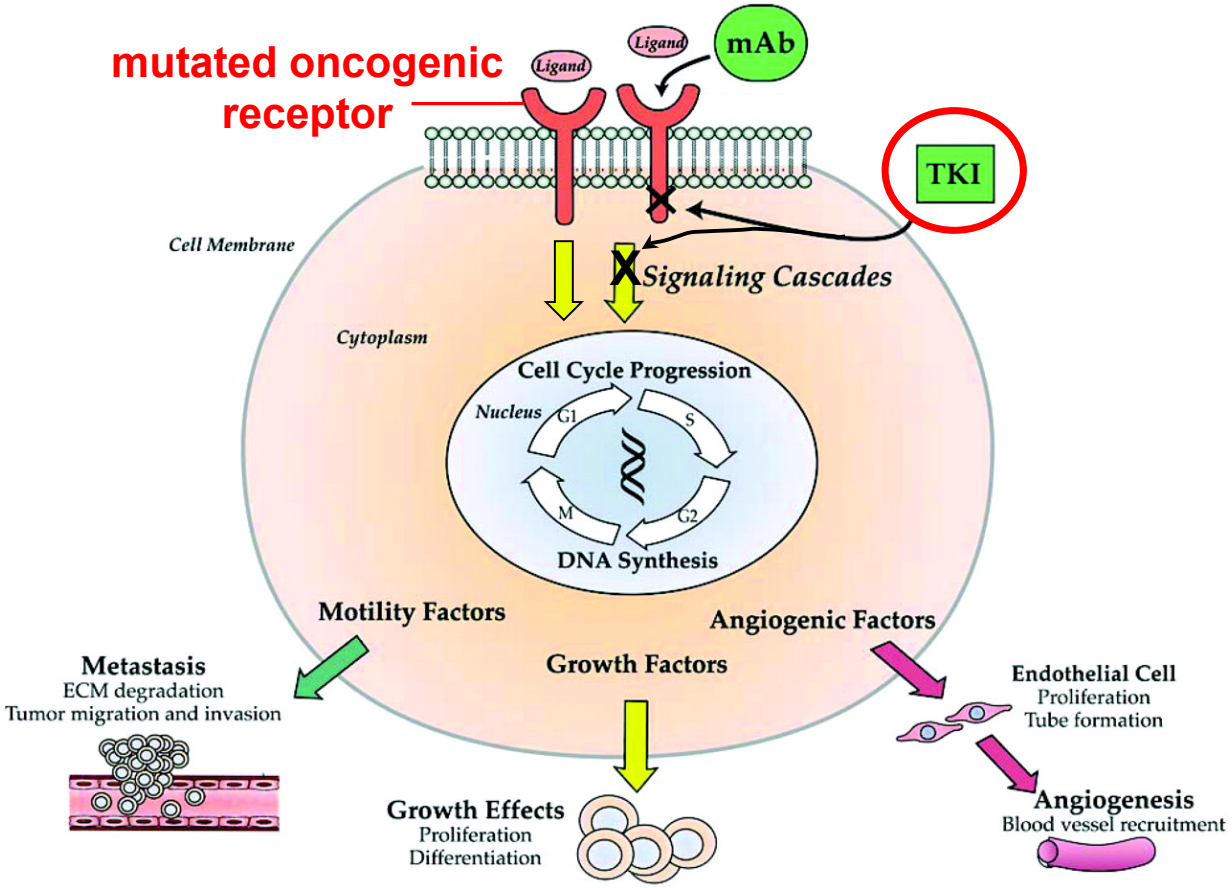


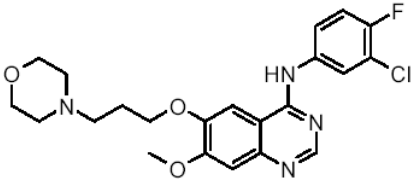
Yale *Cancer Biology Institute*

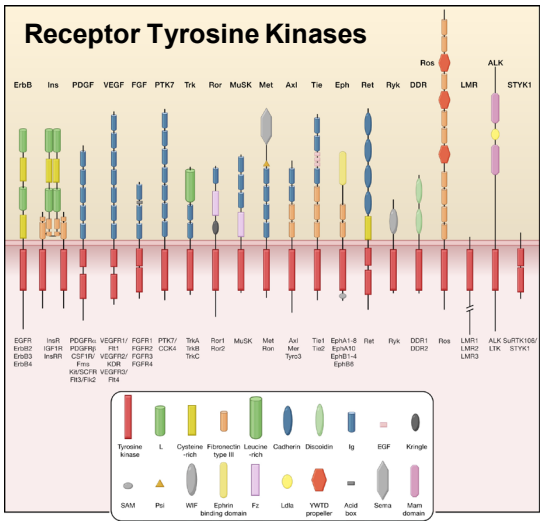
Signaling by cell-surface growth factor receptors: in biology and disease (cancer)

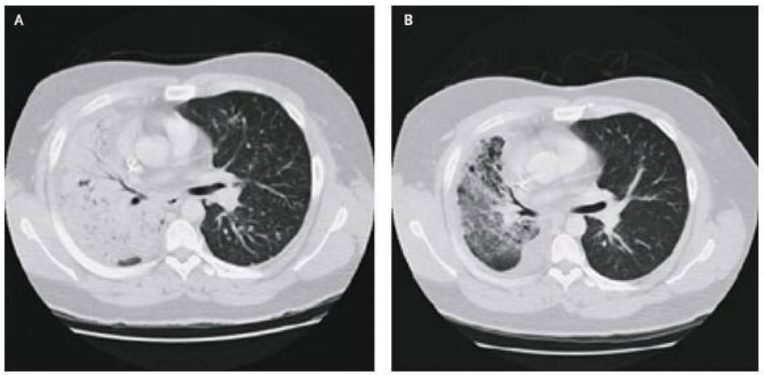


Mark A. Lemmon: Yale Cancer Biology Institute
Department of Pharmacology, YSM
mark.lemmon@yale.edu

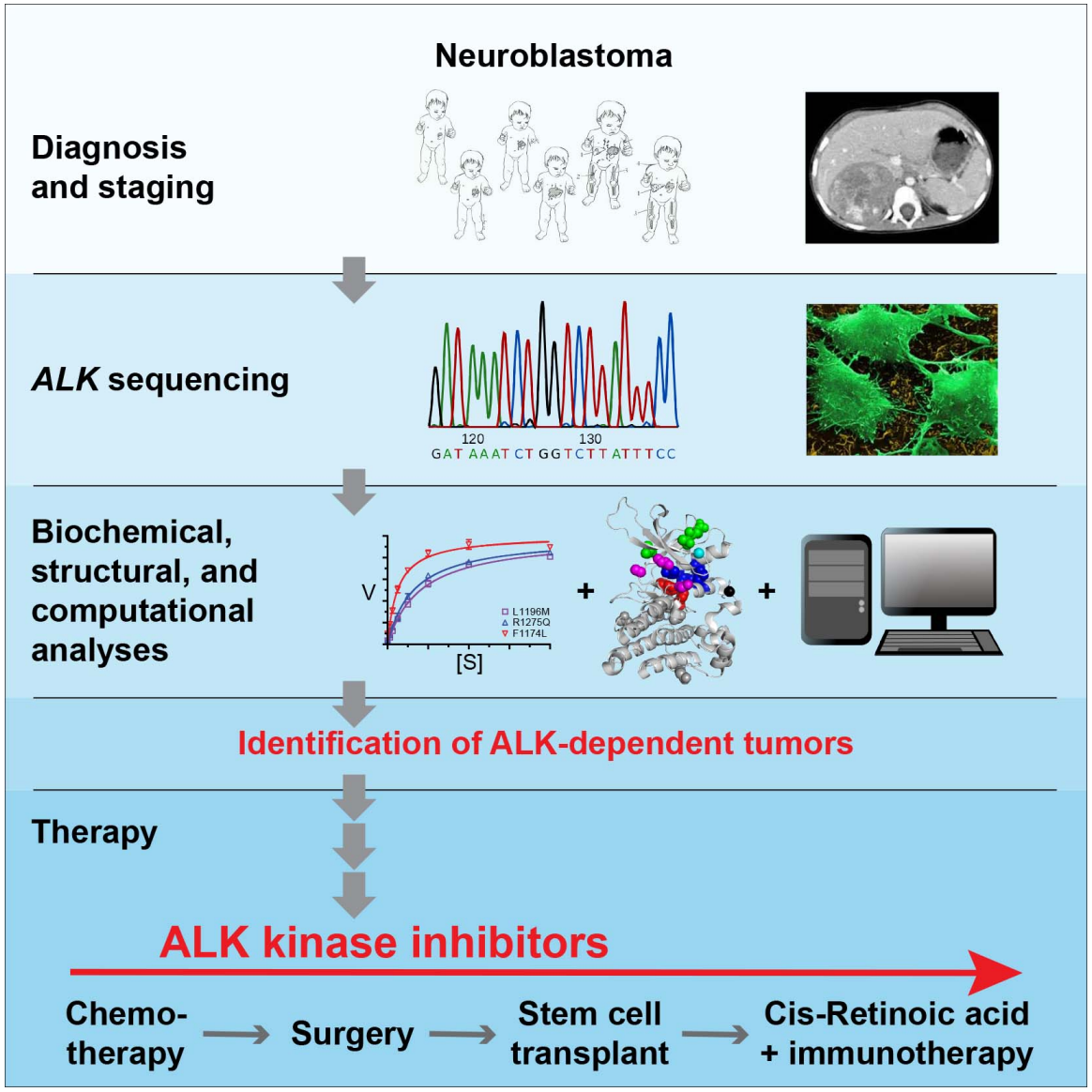








Lynch *et al., N.E.J.M.* **350,** 2129 (2004)



- 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

Rothlin-Ghosh Lab

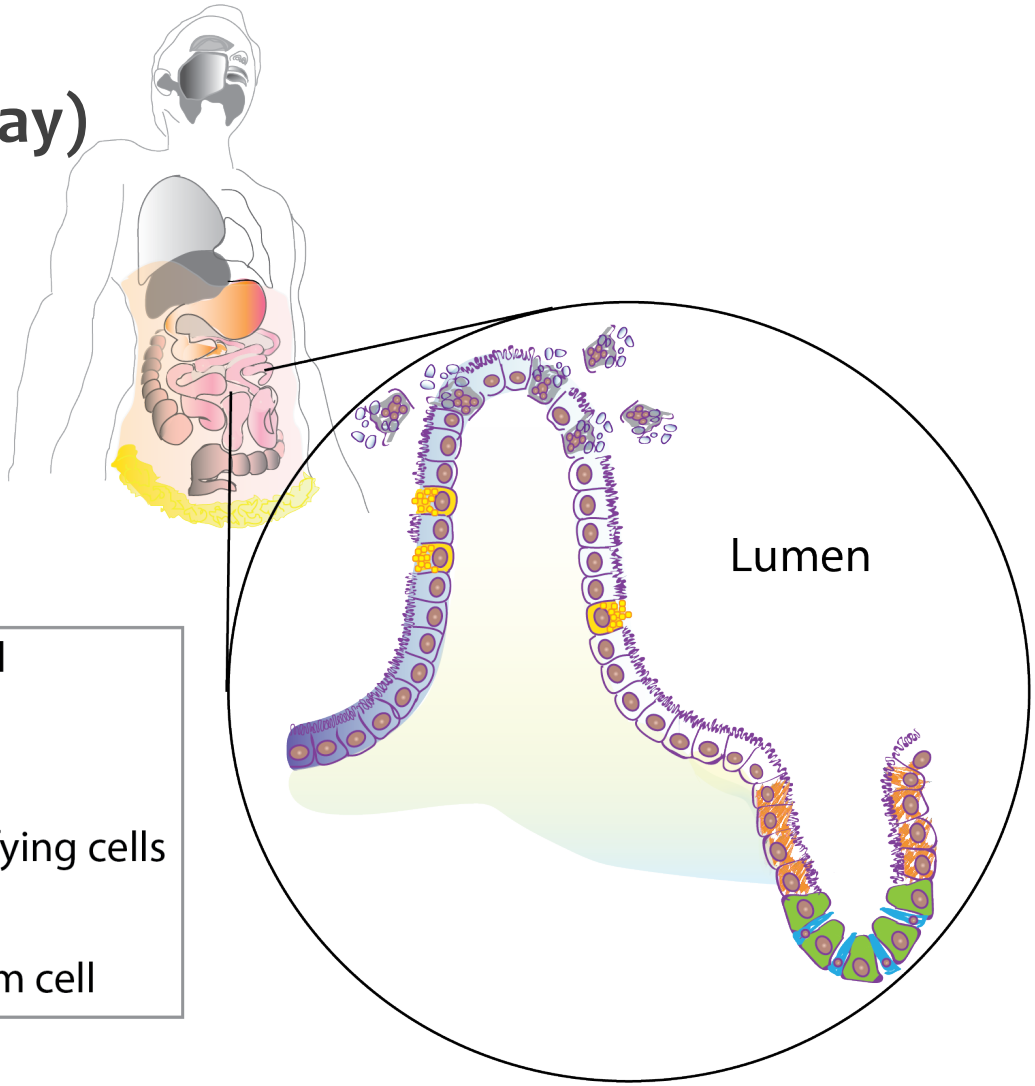
Carla Rothlin, Ph.D. and Sourav Ghosh, Ph.D.

carla.rothlin@yale.edu

What happens after ..... death?

What happens after cell death?

Adulthood
(>10^9 cells die per day)



Development

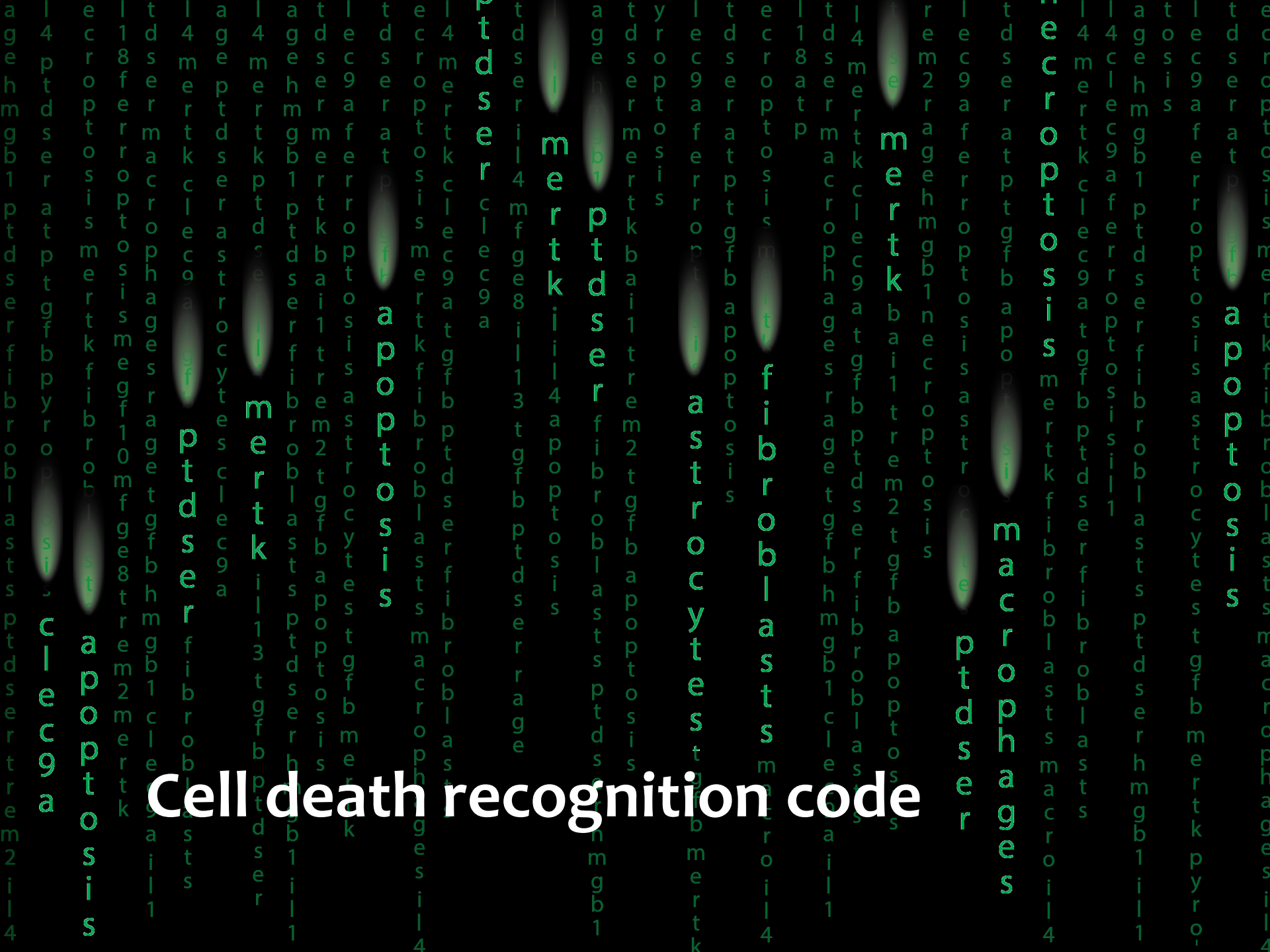
Injury

Homeostasis

Degeneration

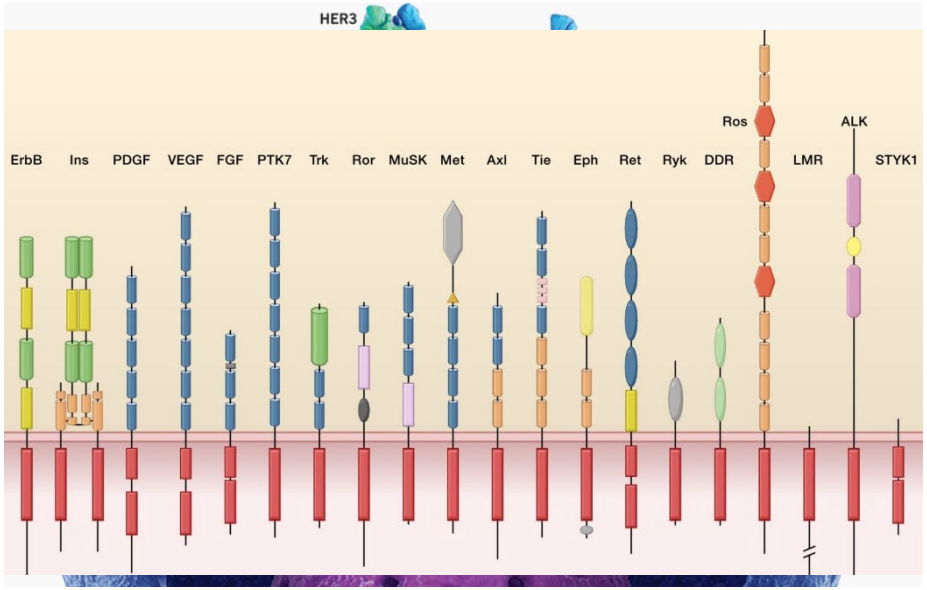
Infection


?
cell death
output1,2,3,4.....n


Cell death recognition code

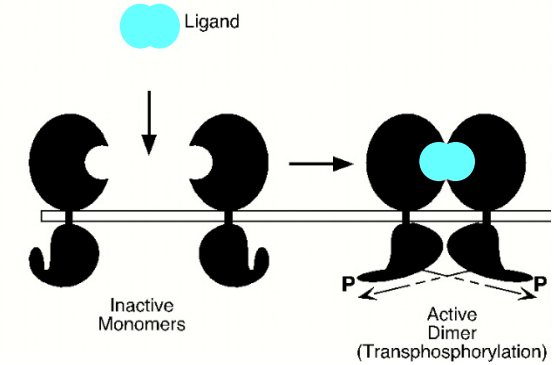
Yale *Cancer Biology Institute*

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



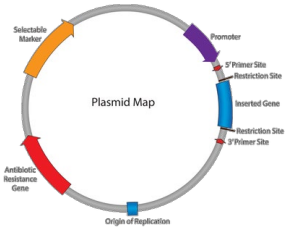
Elegant, but **it's more complex** for many of the 20 families of RTKs –
larger oligomers, lifetimes, co-receptors

Kate Ferguson

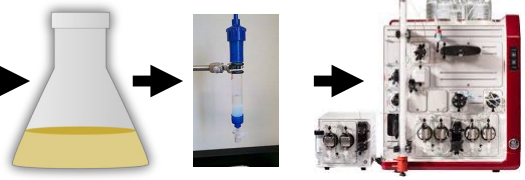
Yale Cancer Biology Institute & Department of Pharmacology,
Advanced Biosciences Building, Yale West Campus
kathryn.ferguson@yale.edu

Yale University
School of Medicine

Research Projects



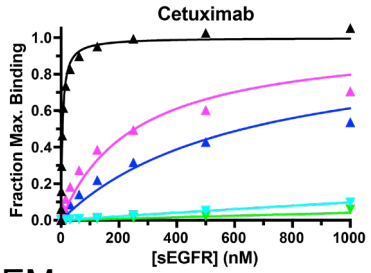
Generate/alter plasmids for protein expression



Recombinant protein purification

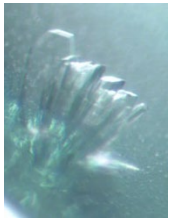
Expression in mammalian cell

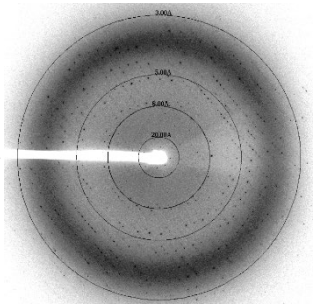
Quantitative Biophysical Experiments – oligomerization, ligand binding analysis

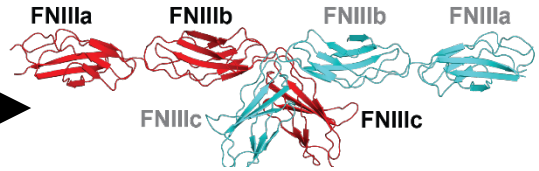


Low resolution shape information – SAXS, EM

Atomic resolution structure determination: X-ray crystallography, EM

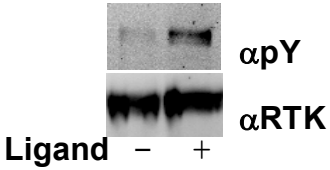






Predict mechanism and test hypothesis in cellular assays

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

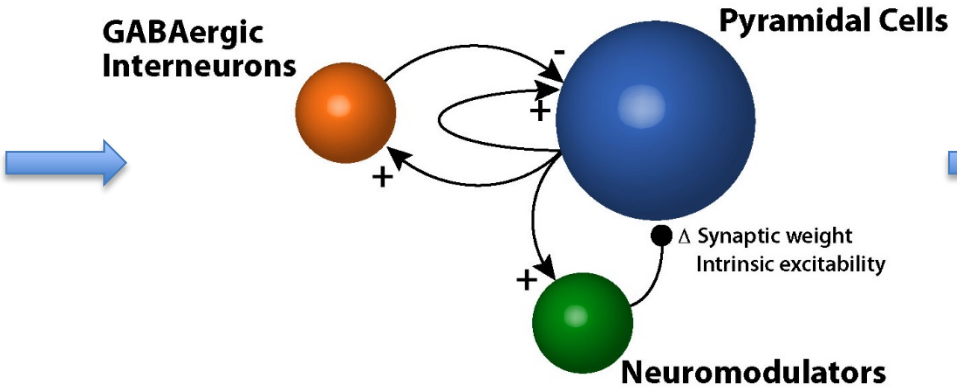
Investigating the functional architecture of cortical circuits

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



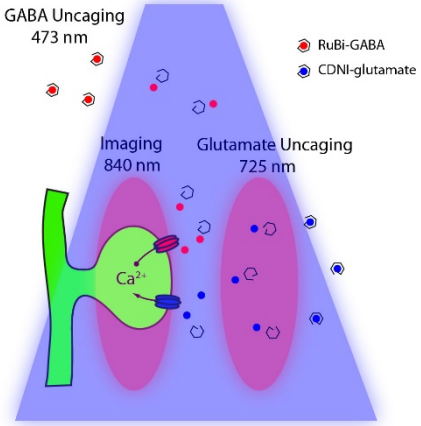
Behavior!

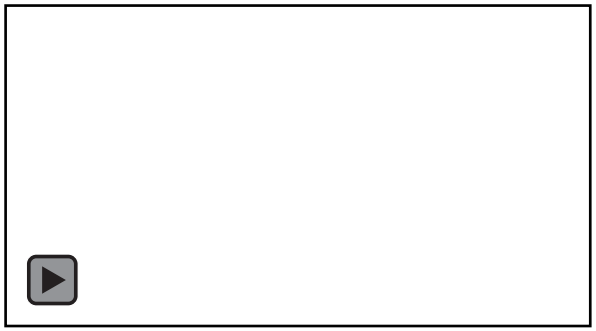
…electrophysiology, 2-photon imaging, photo-uncaging, optogenetics, viral tracing, CRISPR, behavior…

Function and plasticity of GABAergic synaptic inhibition

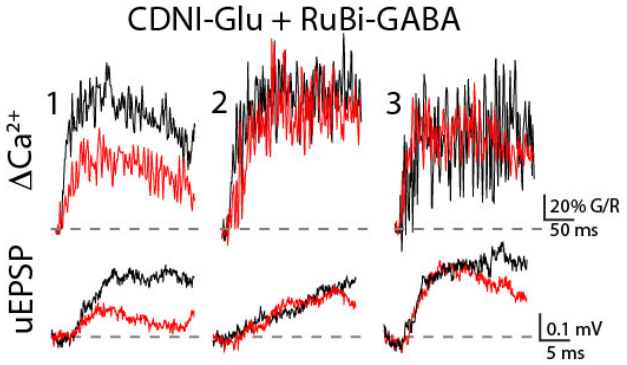
Chiu et al., *Science*, 2013
Lur and Higley, *Cell Reports*, 2015
Kannan et al., *J. Neurosci.*, 2016
Chiu et al., *Neuron*, 2018

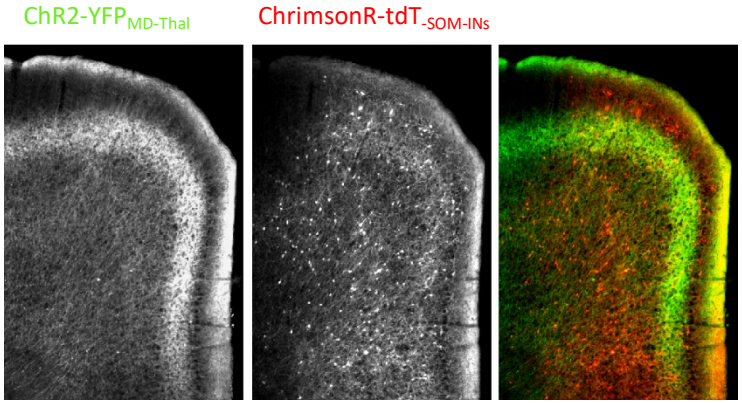
Dual glutamate & GABA uncaging

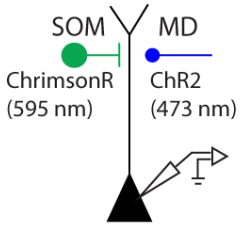


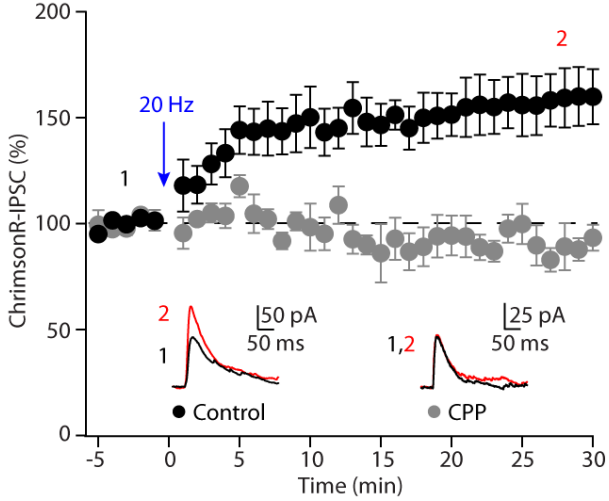


1 micron



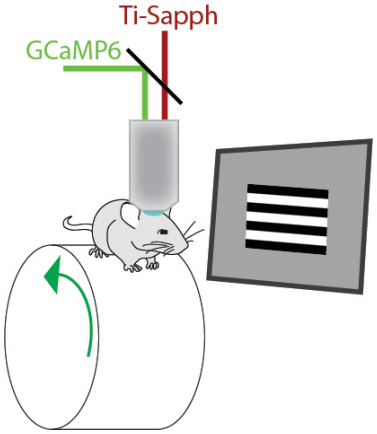


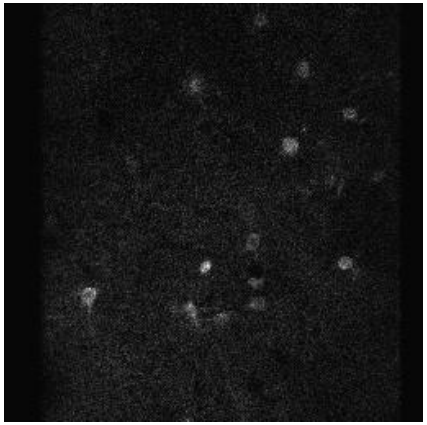


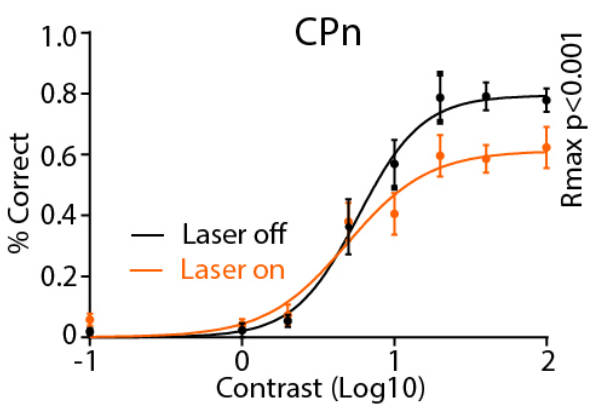


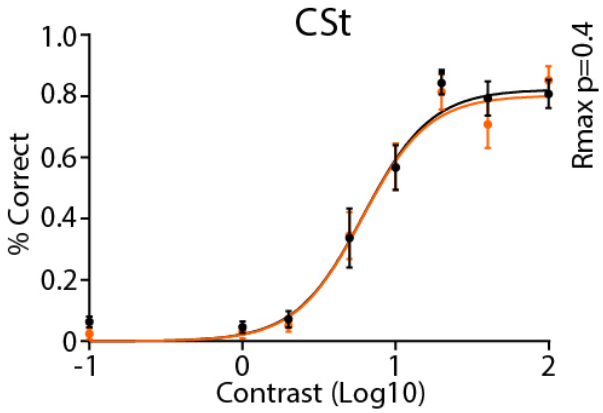
Circuits underlying visual perception and behavior

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









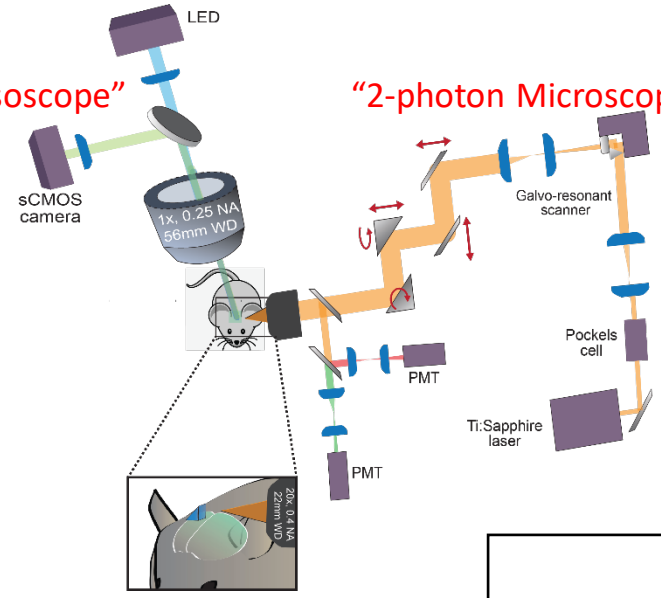
Simultaneous imaging of local and global cortical dynamics

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

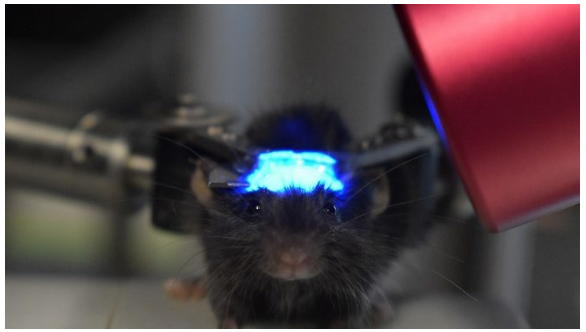
With labs of M. Crair, T. Constable, J. Cardin

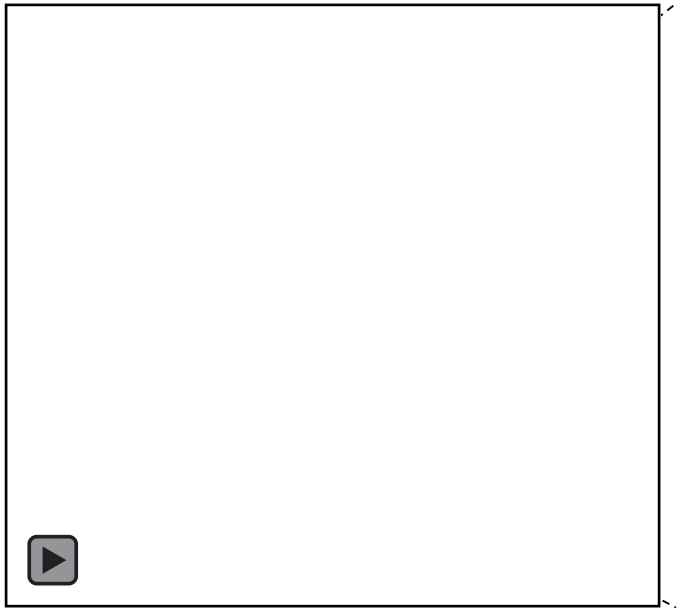
"Mesoscope"

"2-photon Microscope"

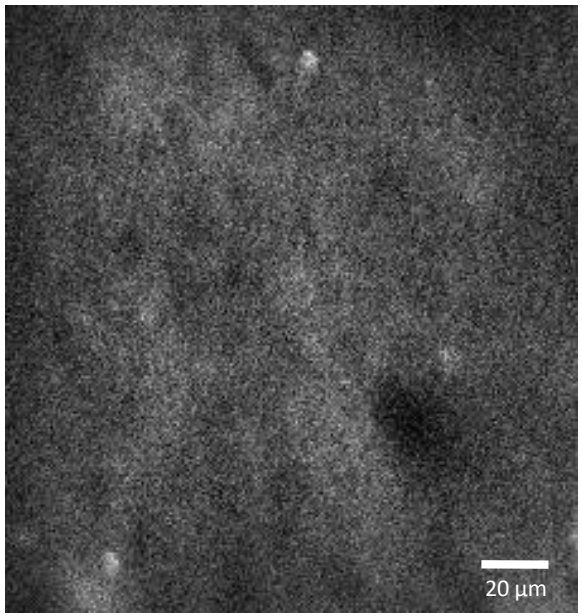


"GCaMP6-expressing mouse"





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)

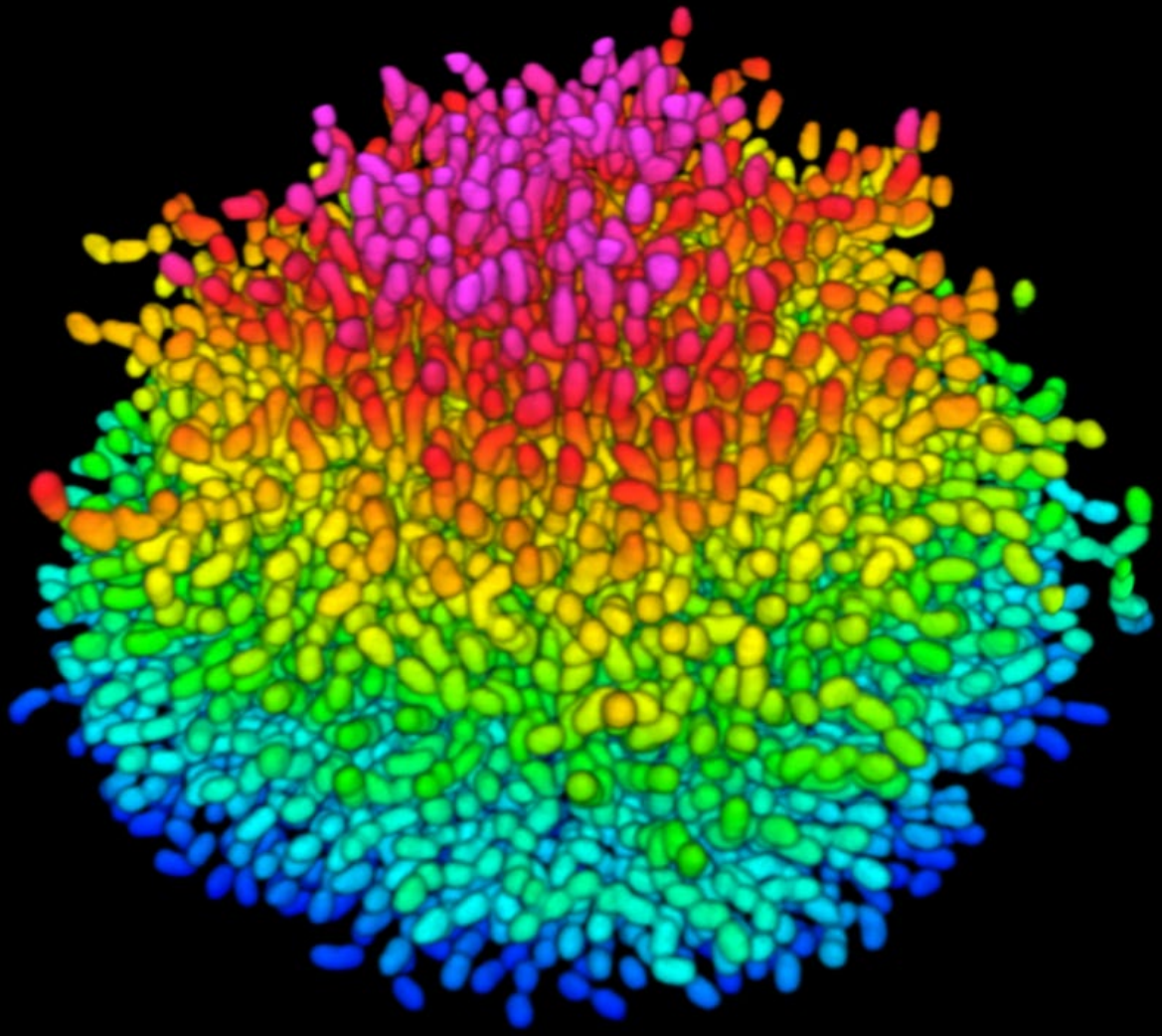
Funding Sources

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

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

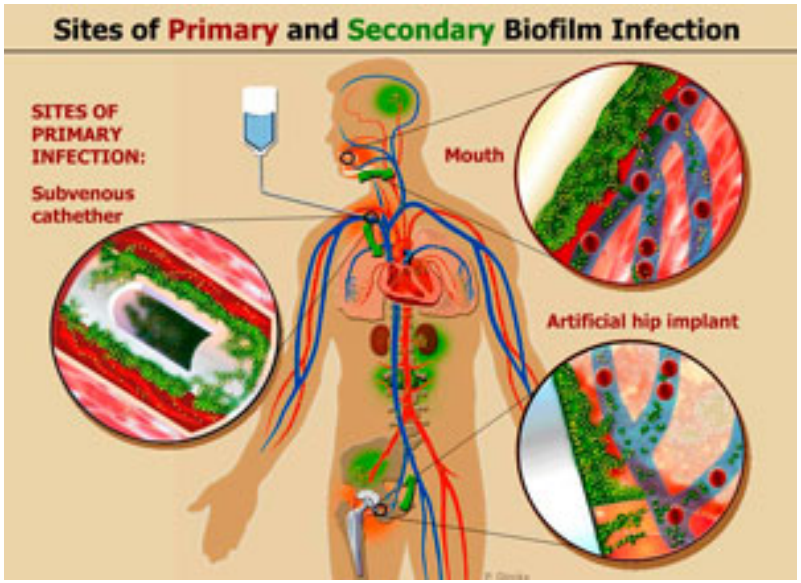
m.higley@yale.edu @mjhigley http://higleylab.org

How Do Bacteria Build Their Home?

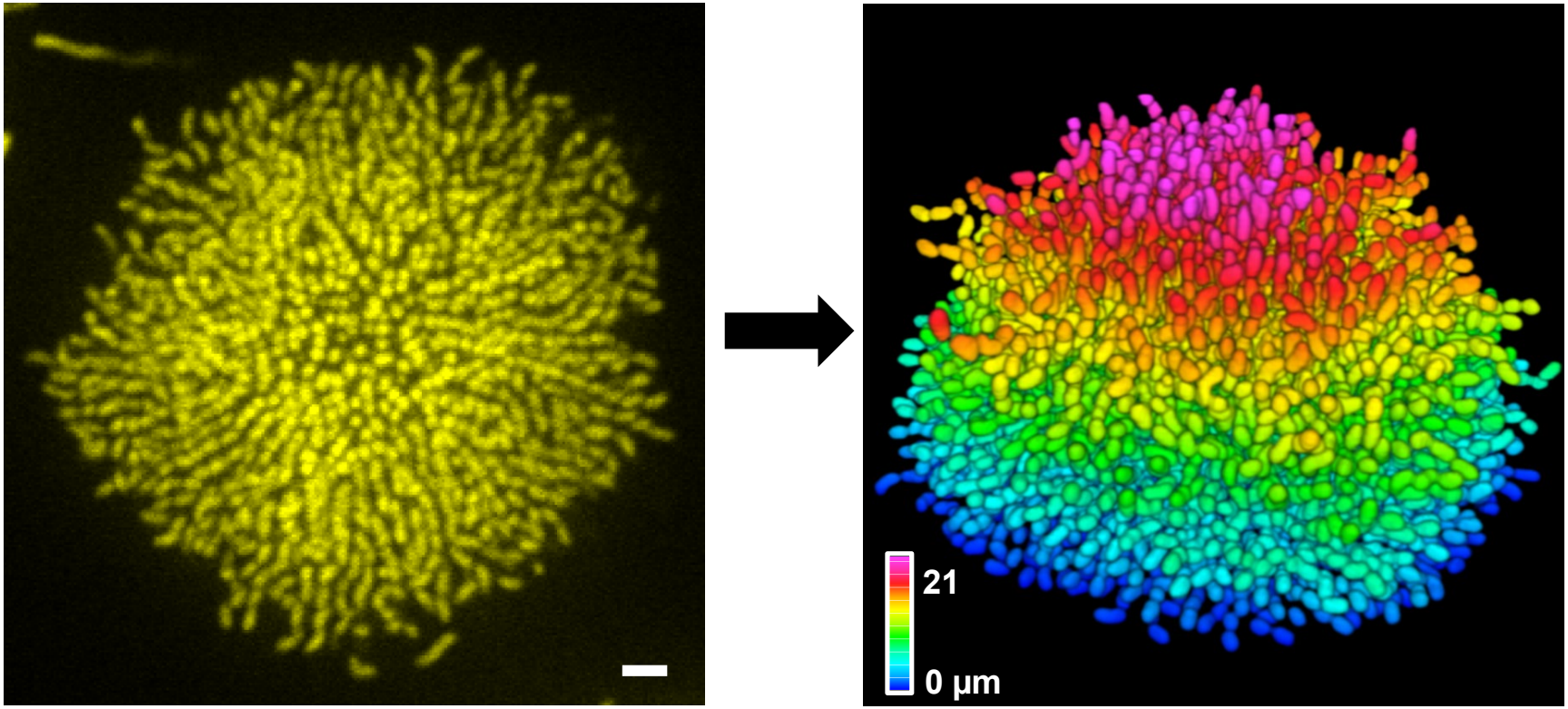


Jing Yan
Quantitative Biology Institute
Department of Molecular, Cellular and Developmental Biology

Bacterial Biofilms Are Everywhere



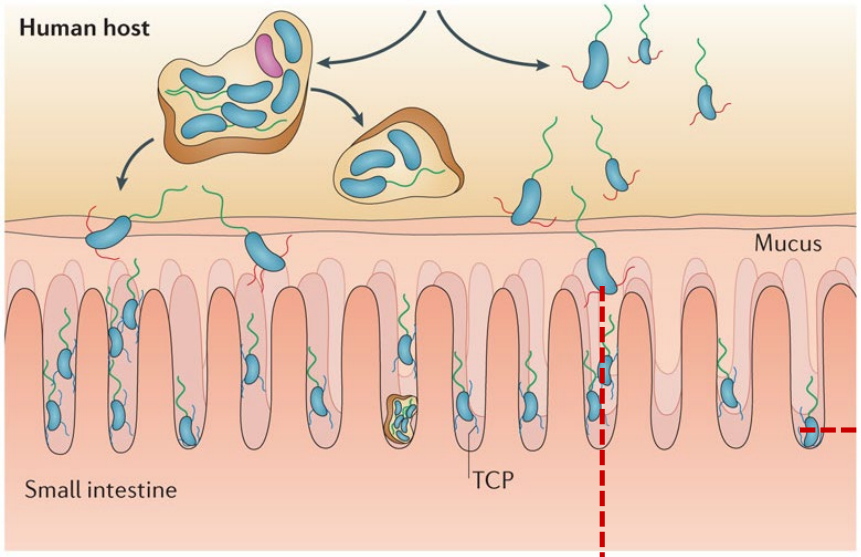
Single-Cell Resolution Imaging of *Vibrio cholerae* Biofilms

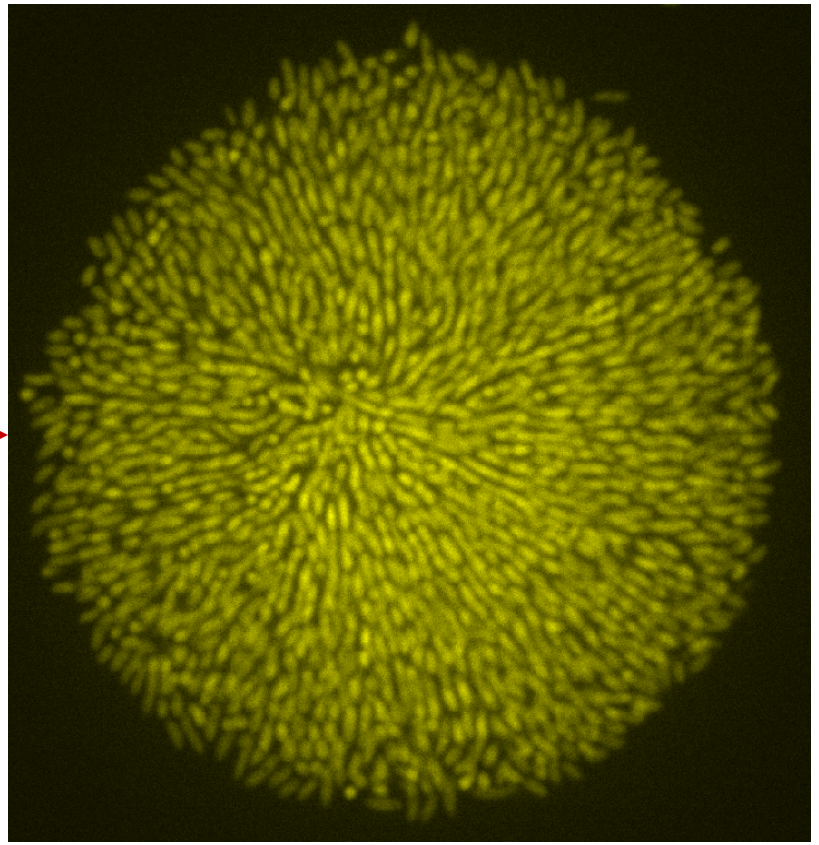


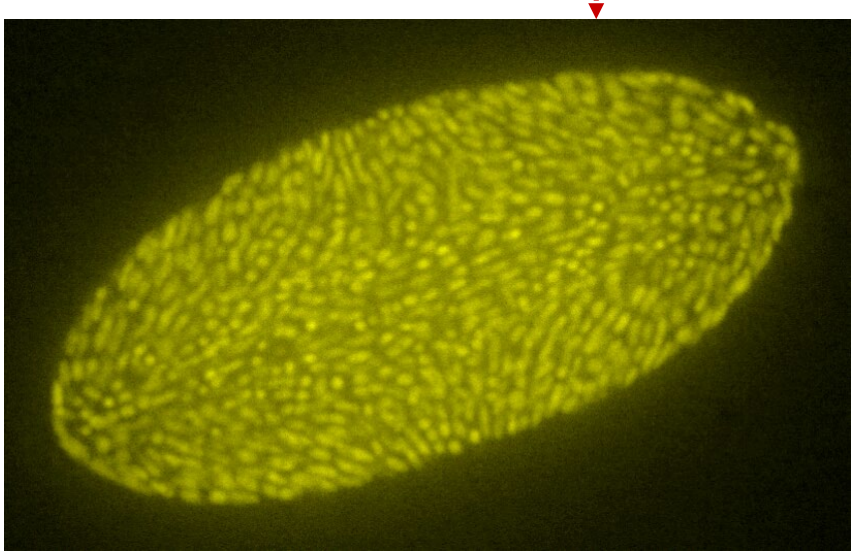
Scale bar: 3 µm

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

Dieter Söll Lab

Jeffery Tharp

Natalie Krahn

Jonathan Fischer

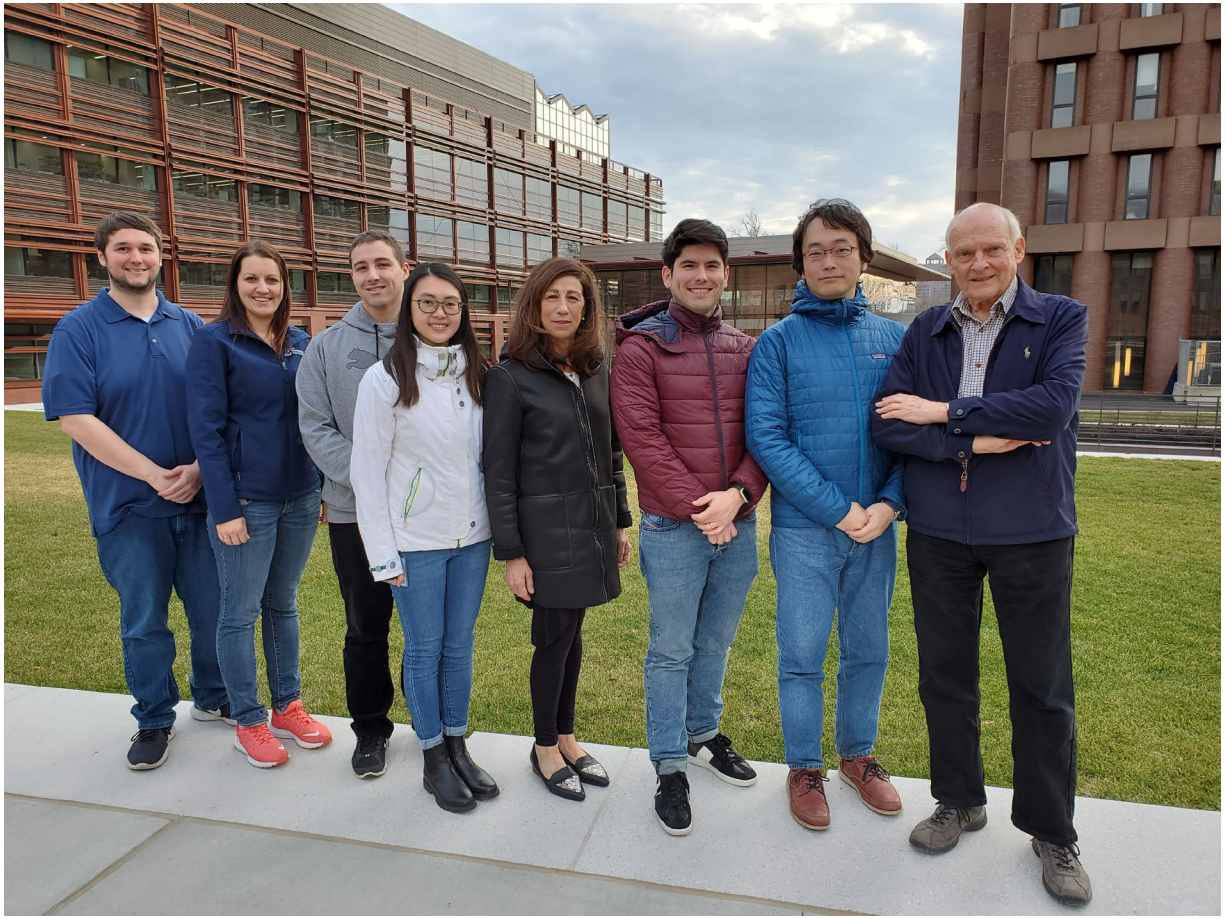
Christina Chung

Ava Artaiz

Oscar Vargas-Rodriguez

Kazuaki Amikura

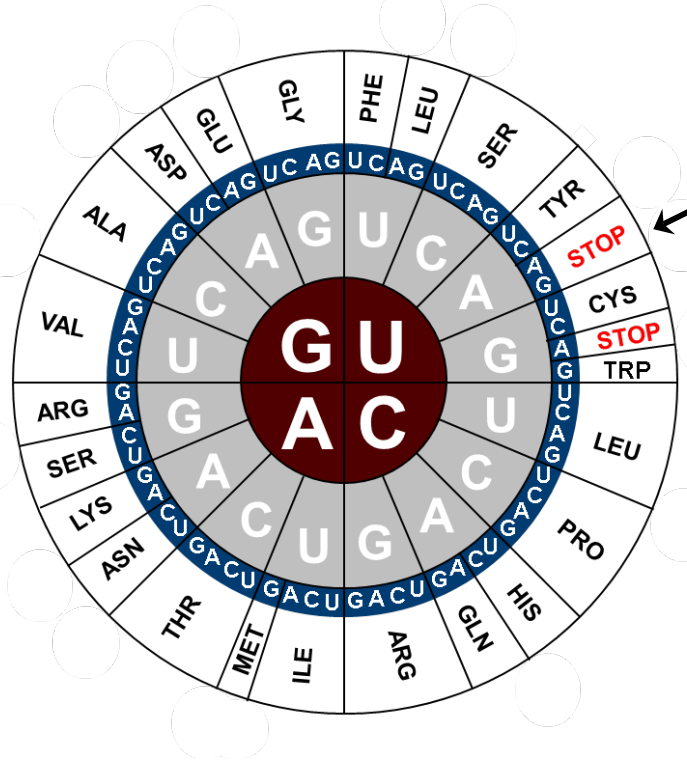
Dieter Söll

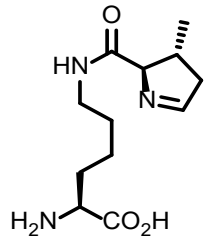


dieter.soll@yale.edu

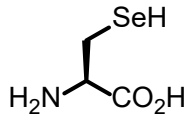
Genetic Code Expansion

The Standard Genetic Code





Pyrrolysine
UAG

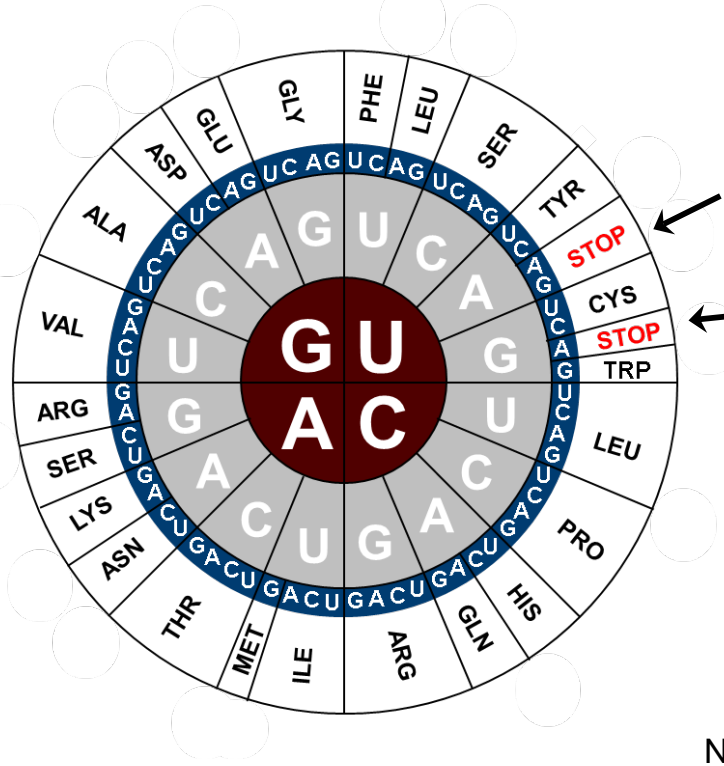


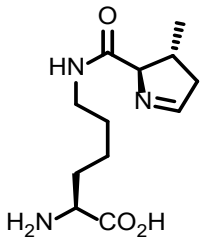
Selenocysteine
UGA

Tharp et al., *RNA Biol.*, **2017**, *14*, 1-12.
Wan et al., *Biochim. Biophys. Acta.*, **2014**, *1844*, 1059-1070.

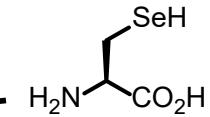
Genetic Code Expansion

The Standard Genetic Code





Pyrrolysine
UAG

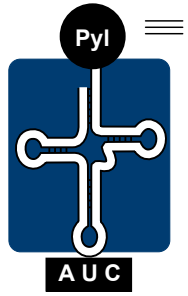


Selenocysteine
UGA

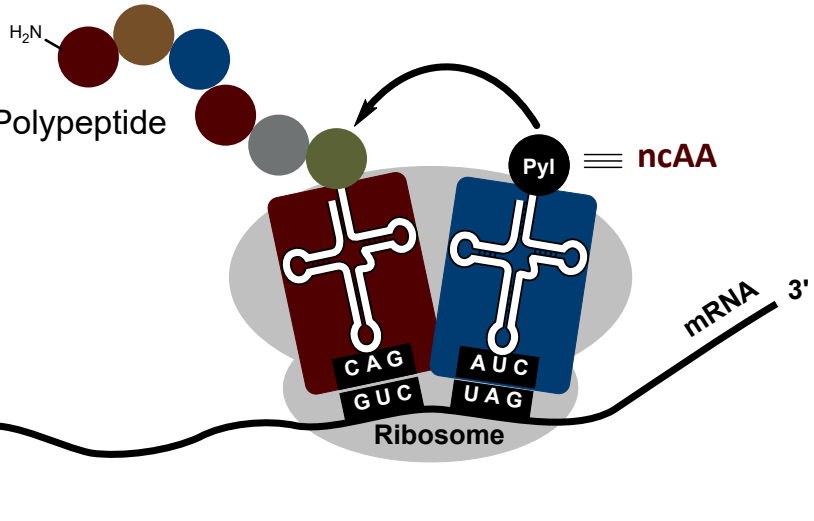
$tRNA^{Pyl}$

ATP + Pyl ≡ ncAA + PPi → AMP

Pyrrolysyl-tRNA Synthetase **Mutant**



ncAA



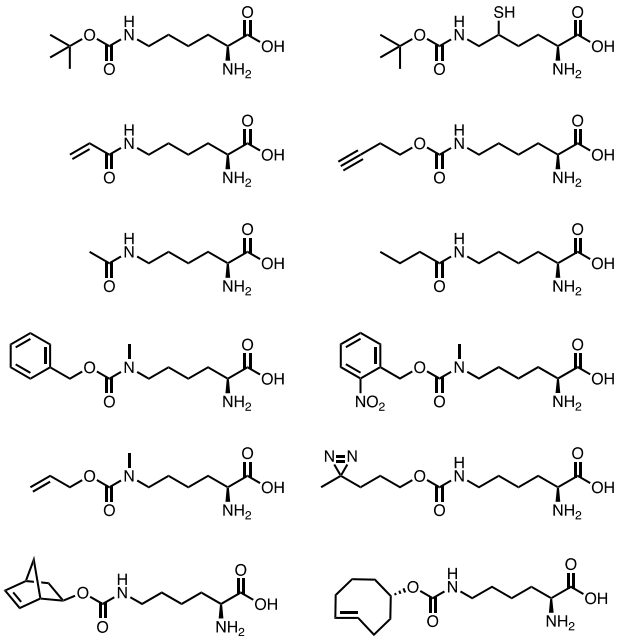
Tharp et al., *RNA Biol.*, **2017**, *14*, 1-12.
Wan et al., *Biochim. Biophys. Acta.*, **2014**, *1844*, 1059-1070.

Pyrrolysyl-tRNA Synthetase

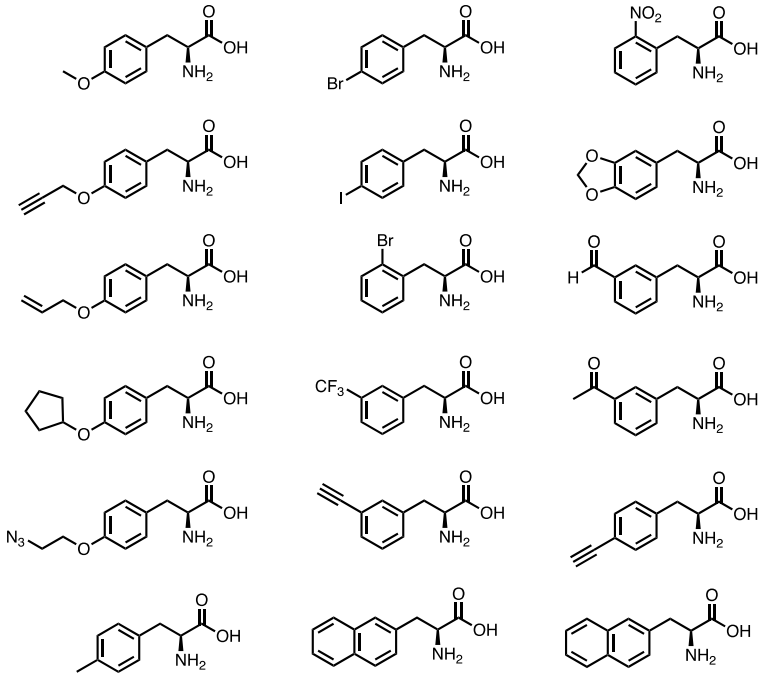
The pyrrolysyl-tRNA synthetase has been used to genetically encode >150 non-natural amino acids which have numerous purposes.

We are engineering this enzyme to 1) improve its activity and 2) encode new non-natural amino acids

Lysine Derivatives



Phenylalanine Derivatives

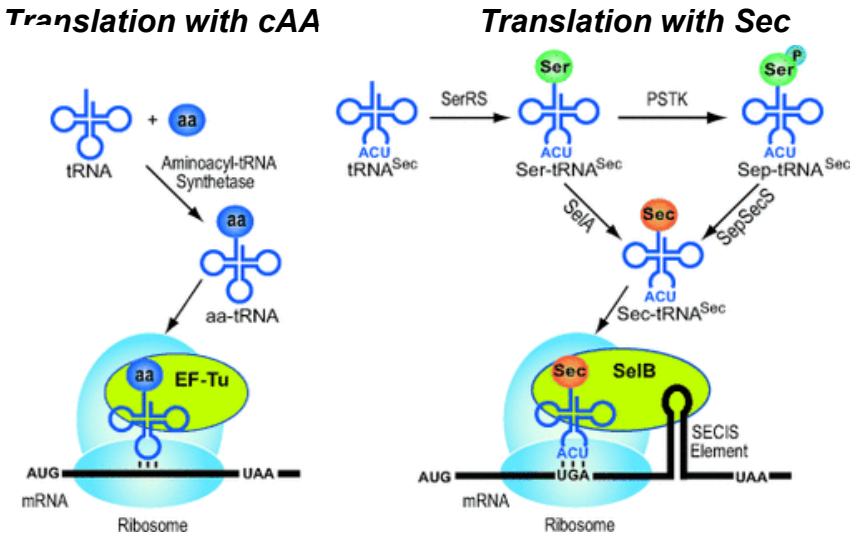


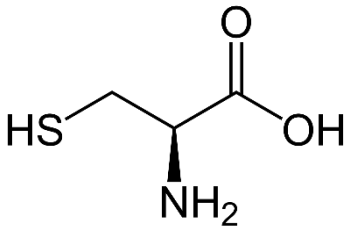
Tharp *et. al*, *RNA Biol.*, **2017**, *14*, 1-12.
Wan *et. al*, *Biochim. Biophys. Acta.*, **2014**, *1844*, 1059-1070.

Rewiring translation for selenocysteine incorporation

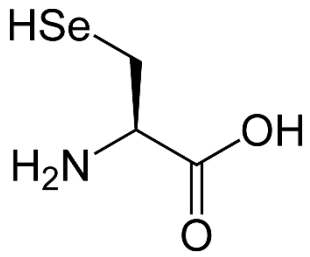
Humans have at least 25 selenoproteins which provide us with the essential micronutrient selenium

Selenocysteine incorporation in proteins is complicated and not fully understood





Cysteine
pKa=8.18



Selenocysteine
pKa=5.47

Aldag *et. al,* Angew Chem Int Ed. **2013**, 52, 1441-1445

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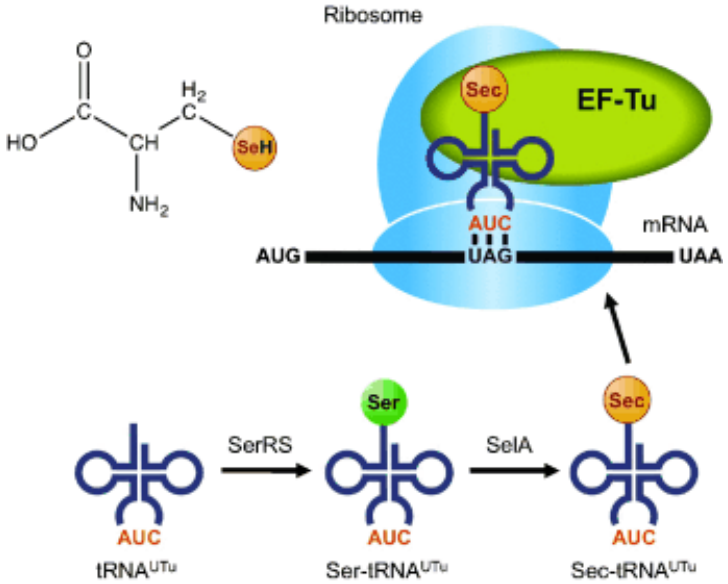
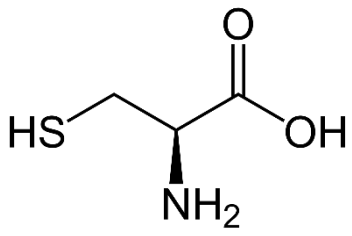
Rewired translation with Sec





Cysteine
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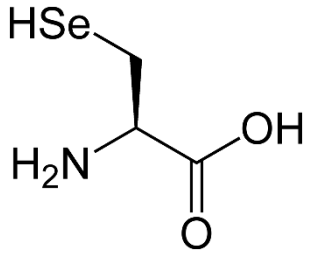
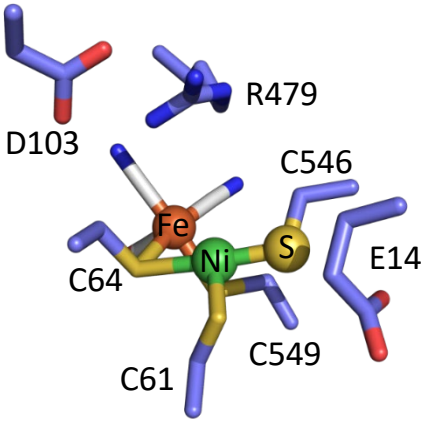
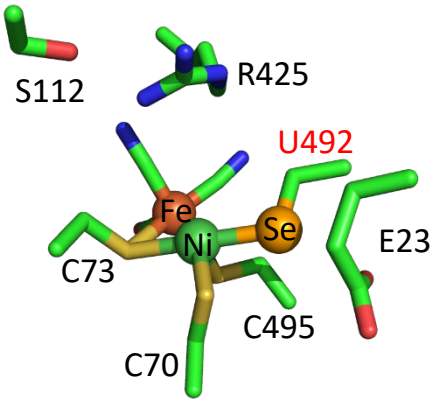


Selenocysteine
pKa=5.47





up to 1000x activity

Aldag *et. al,* Angew Chem Int Ed. **2013**, 52, 1441-1445

Bleichert Lab

Molecular Mechanisms of Chromosome Duplication

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

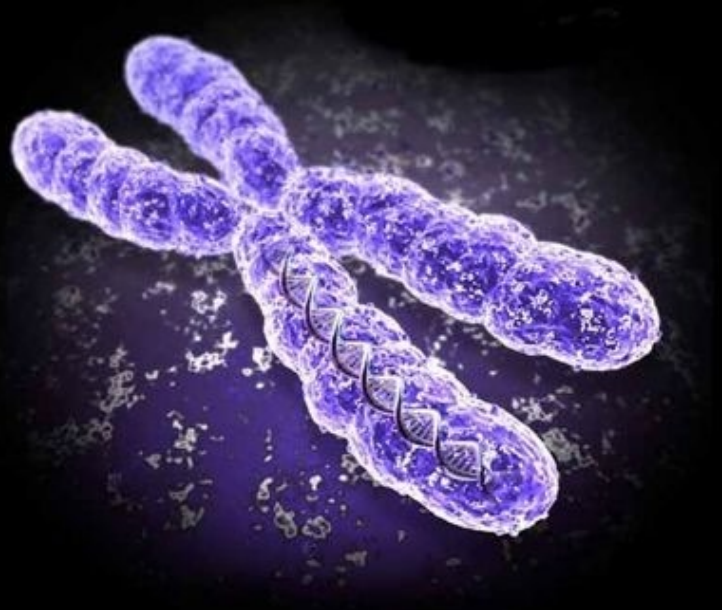


Image credit: Los Alamos National Laboratory

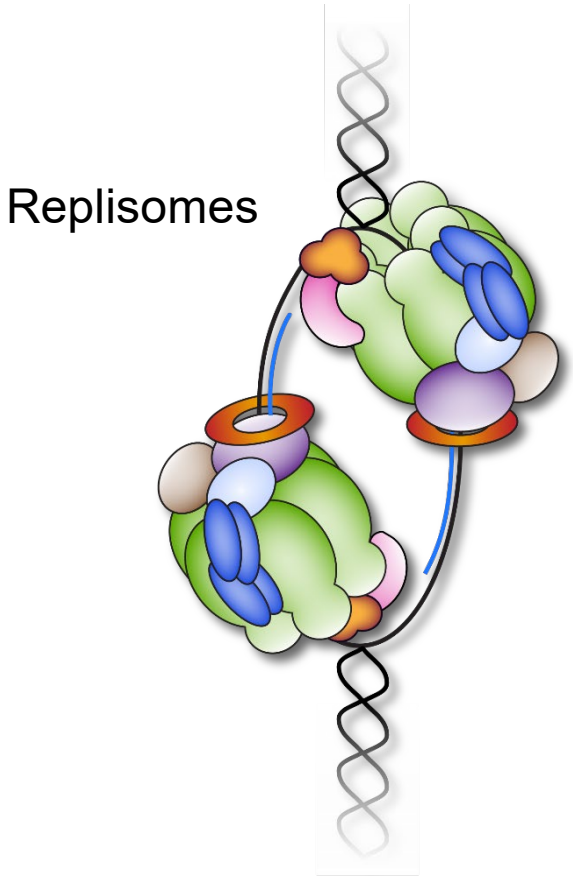
Every human synthesizes ~2 light years of DNA during their lifetime

< 1 mistake per 100 million nucleotide incorporation events

Bleichert Lab – Our scientific questions

franziska.bleichert@yale.edu

www.bleichertlab.org



How are DNA replication machineries assembled?

How does chromatin structure influence DNA replication?

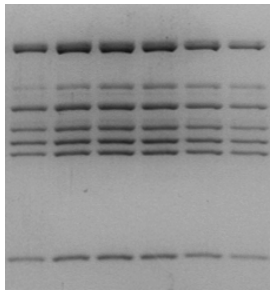
How is dysregulation of these events linked to human diseases?

Bleichert Lab – Our approaches

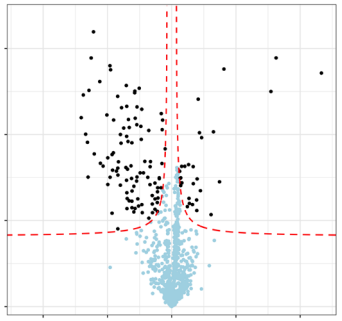
franziska.bleichert@yale.edu

www.bleichertlab.org

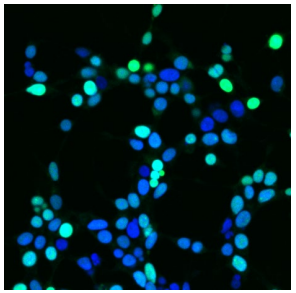
Reconstitution biochemistry



Proteomics

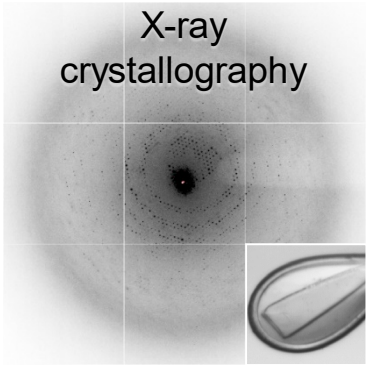


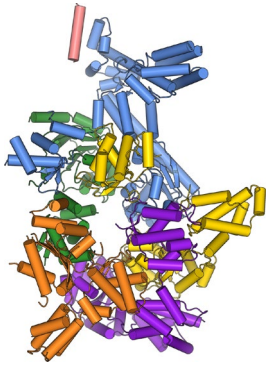
Cell-based

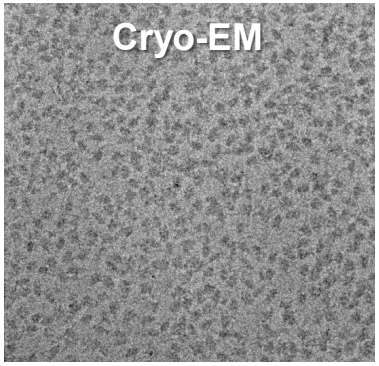


Structural biology

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

Bergwitz Lab information

Lab Head (top photo third from left):

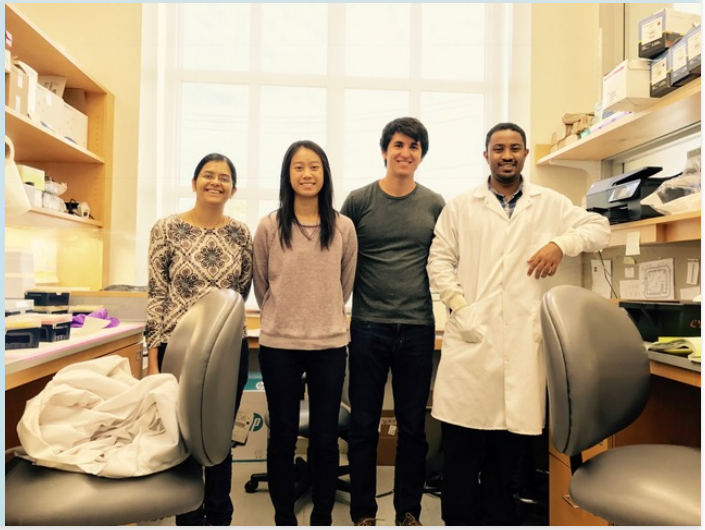
Clemens Bergwitz, M.D.

website:

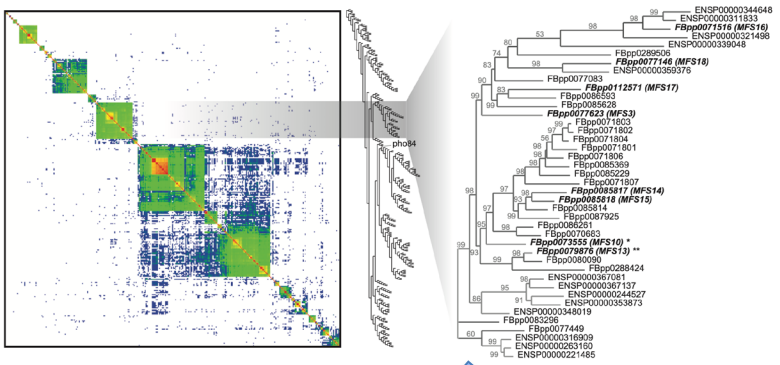
http://medicine.yale.edu/lab/bergwitz/

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

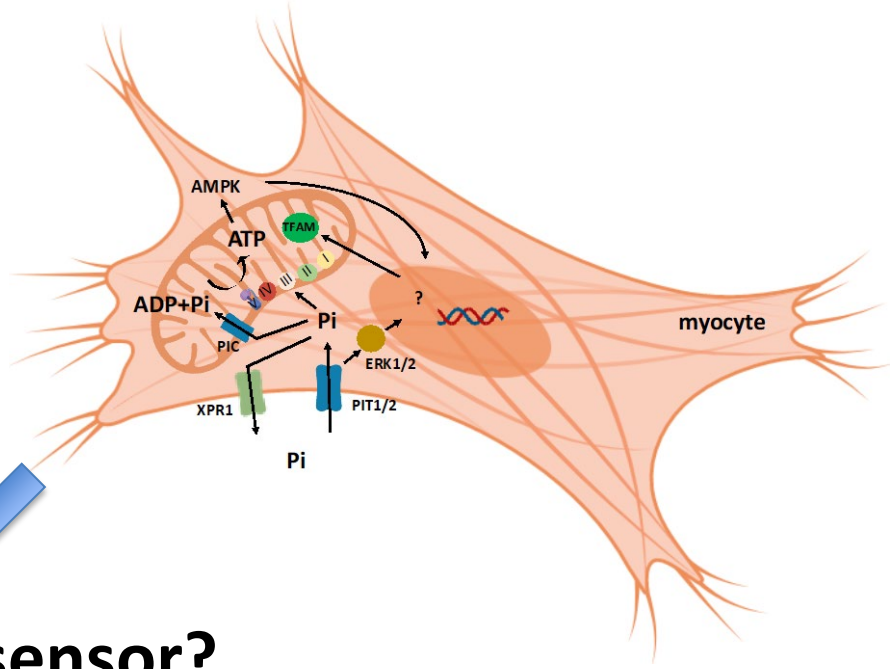
Work Phone: 203-737-5450
Work Fax: 203-785-5535
email: clemens.bergwitz@yale.edu



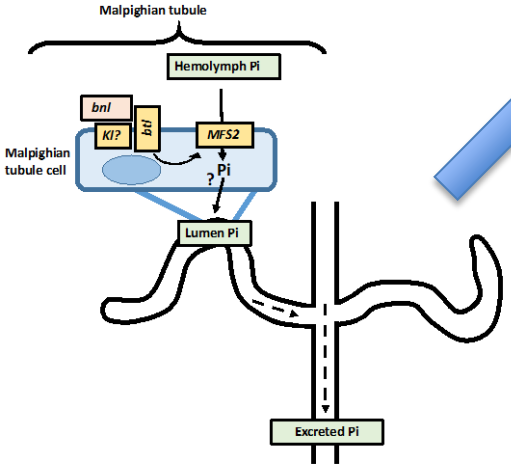
Homologs of bacterial and yeast Pi sensors

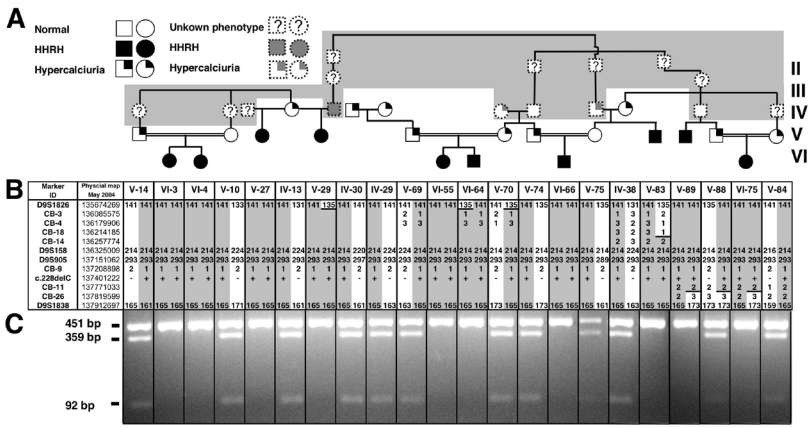


Metabolic Pi sensors in skeletal muscle



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

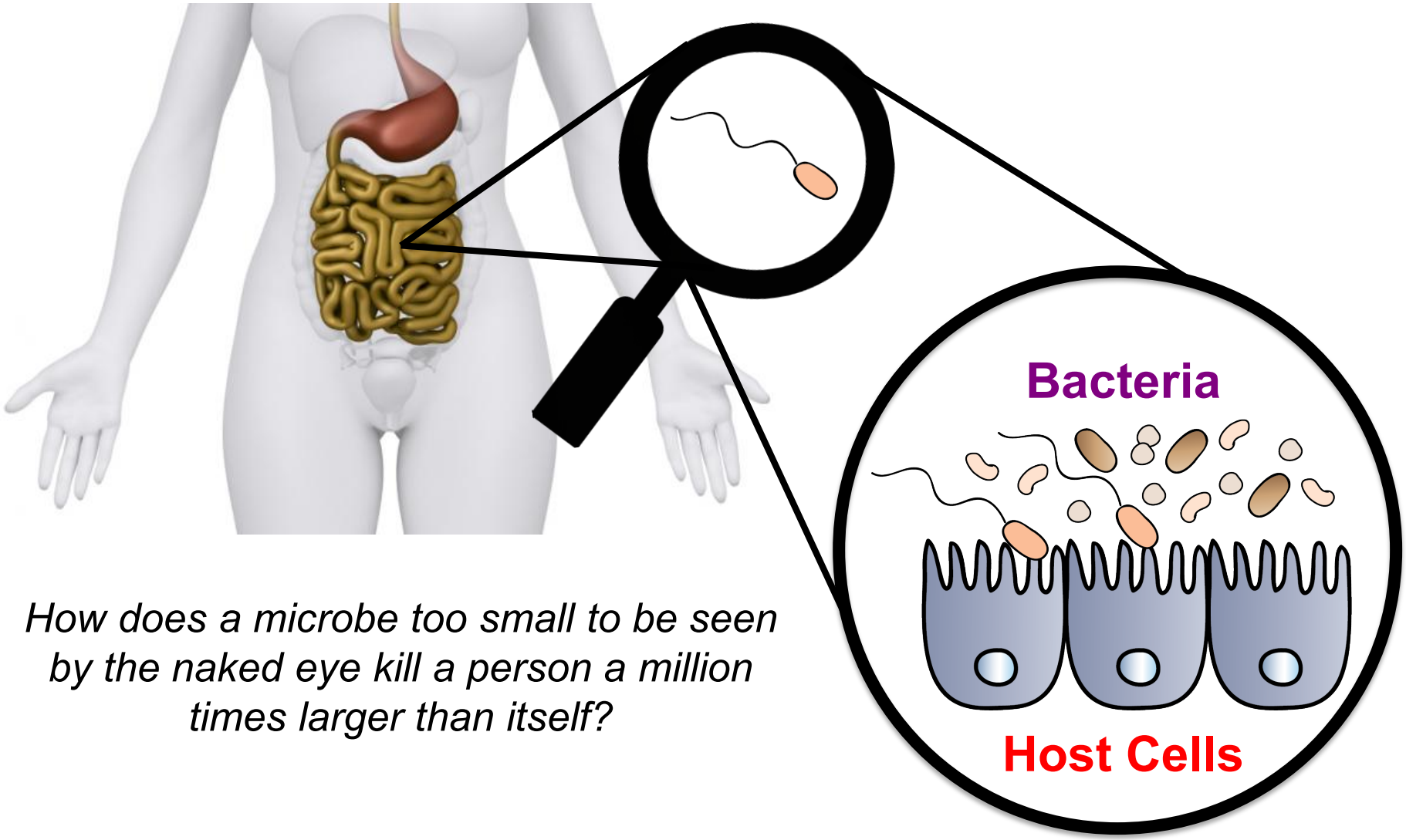
June-August 2020: Provide written protocols and one-on-one supervision by PI or postdoc during 12 week summer internship, which enables students to independently conduct a small project, which will - if successful - earn them a co-authorship in a line of research that is close to publication

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).

Hatzios Lab

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

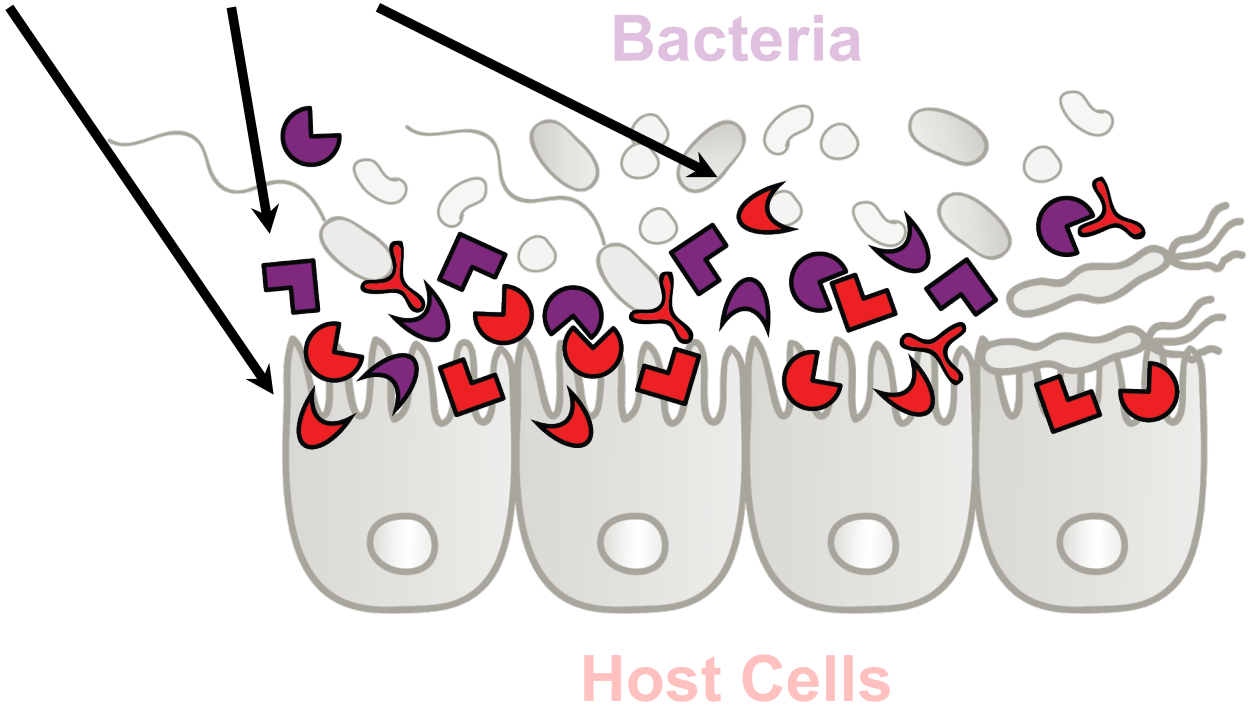


How does a microbe too small to be seen by the naked eye kill a person a million times larger than itself?

Central questions

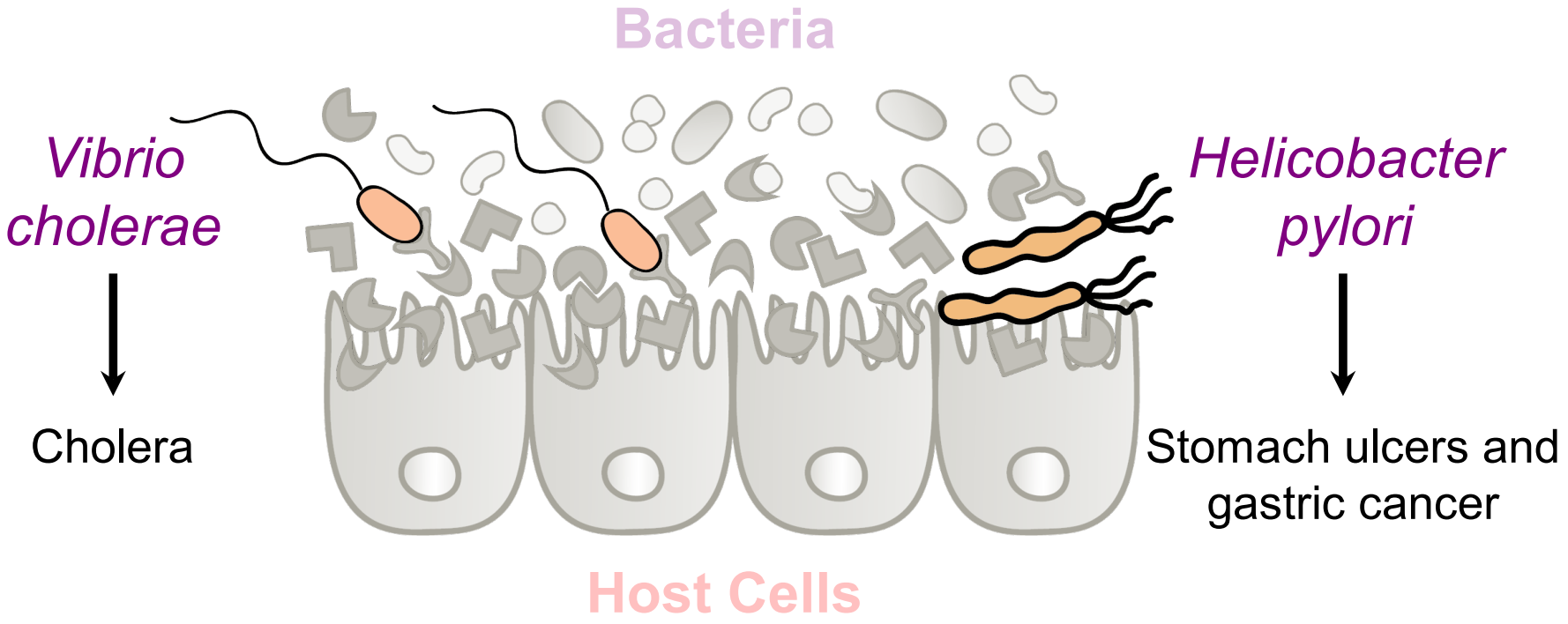
What proteins are functional at the host-microbe interface?

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

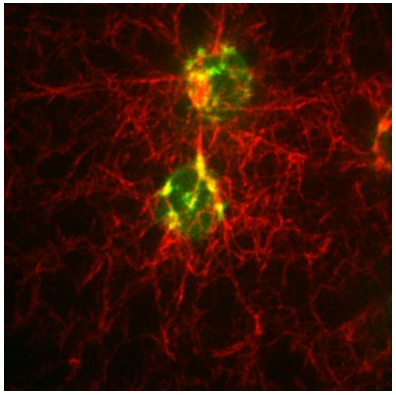


We use chemical biology, genetics, and microbiology to study bacterial and host proteins that contribute to infection

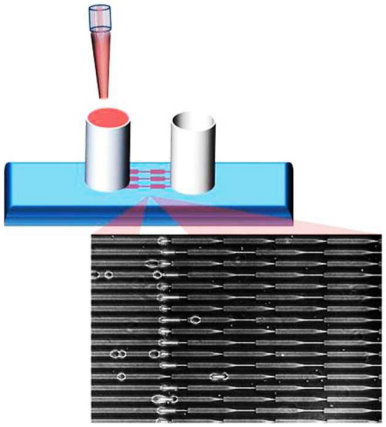
To learn more: Visit hatzioslab.yale.edu
Contact Postdoc Alicia DeColli (alicia.decolli@yale.edu) or
Prof. Stavroula Hatzios (stavroula.hatzios@yale.edu)

Multiscale Mechanobiology Lab

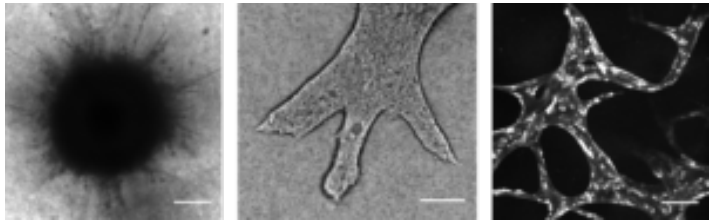
Cell-Matrix Interactions



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.

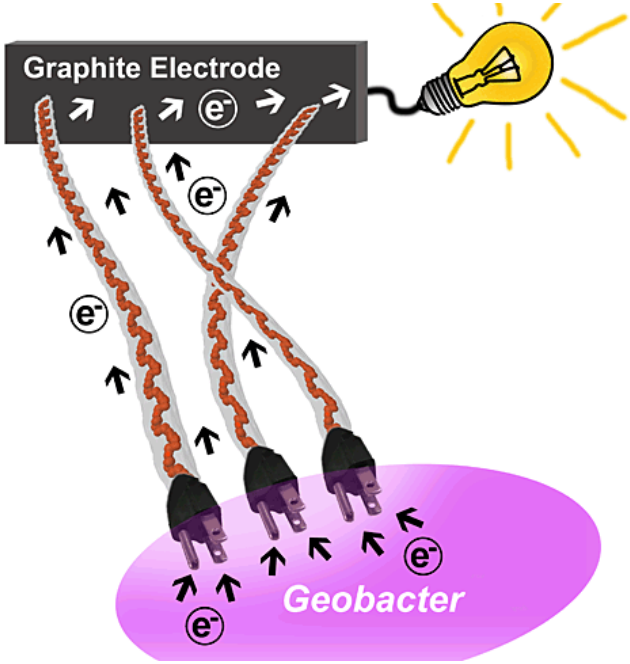
Activities

- 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.

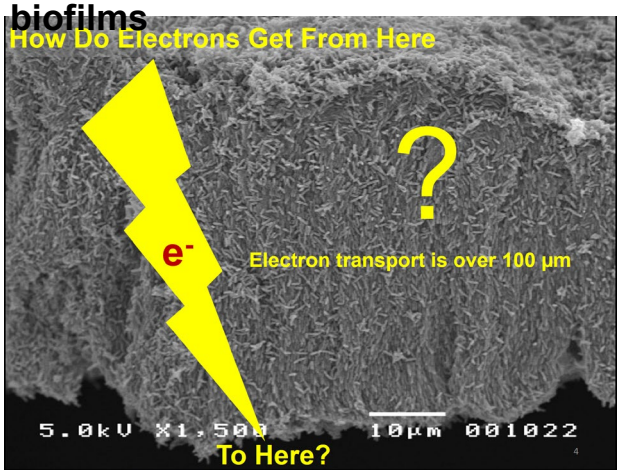
Nikhil Malvankar Lab

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.

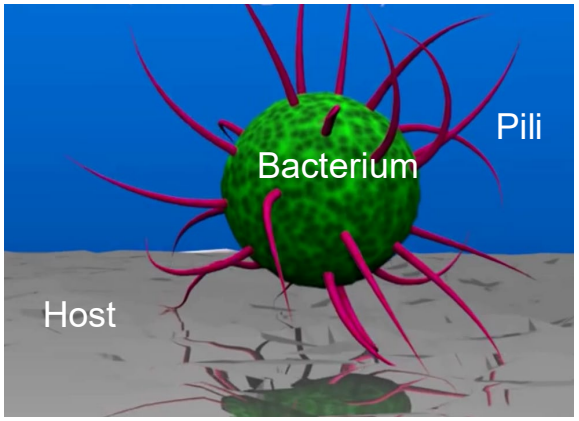
Electric Bacterial Nanowires



Bacterial communities in biofilms

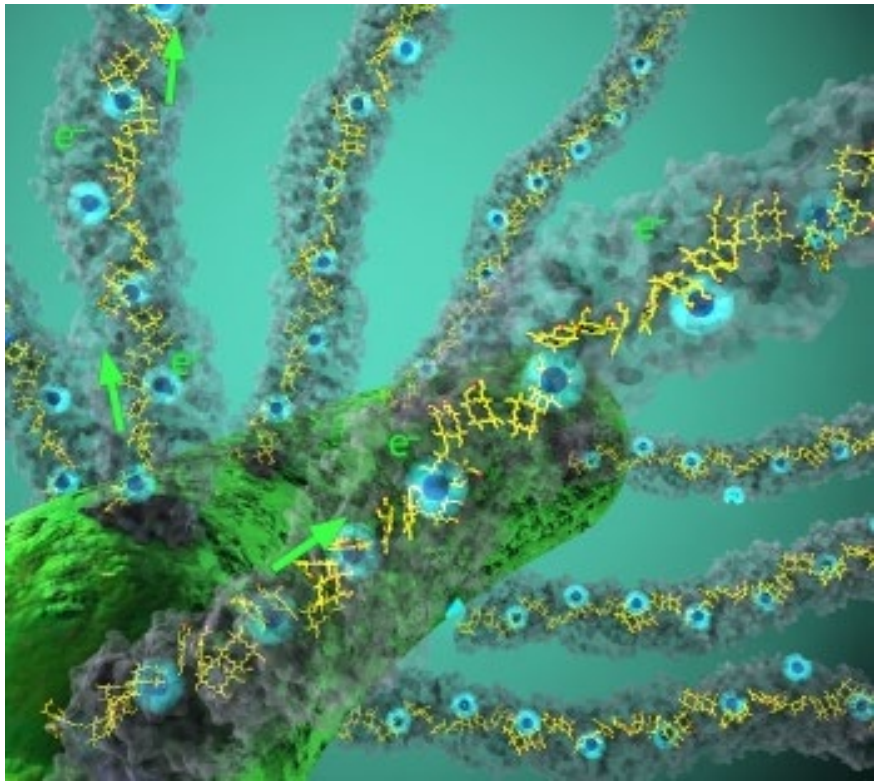


Host-pathogen Interactions in single cells and biofilms



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."

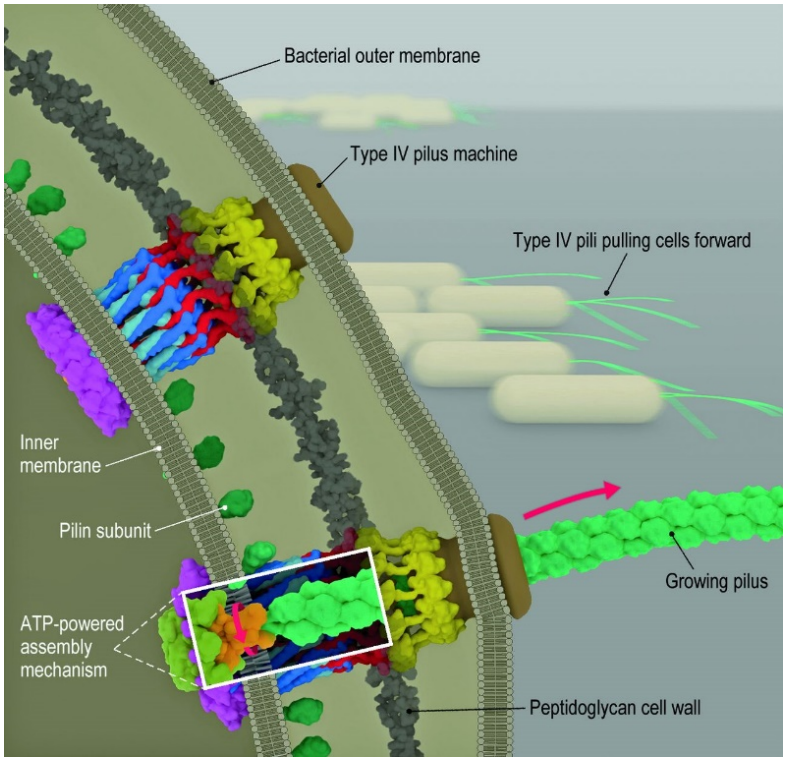
Among Highest Impact Structures of the Century

21st Century

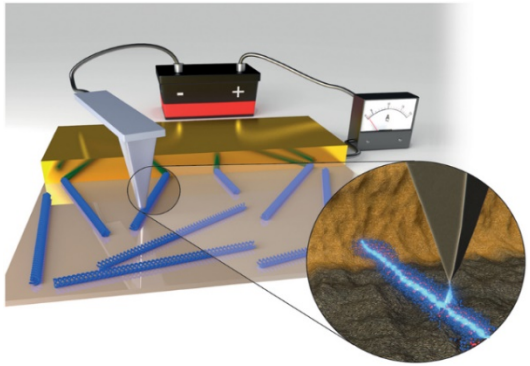
- **2000 - Ribosome**: This structure surprised almost everyone by showing that peptidyl transferase is a ribozyme, rather than a protein enzyme. It won the 2009 Nobel Prize in Chemistry.
- **2007 and 2011 - G protein-coupled receptor**: In 2007 the structure of the first ligand-activated G protein-coupled 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.

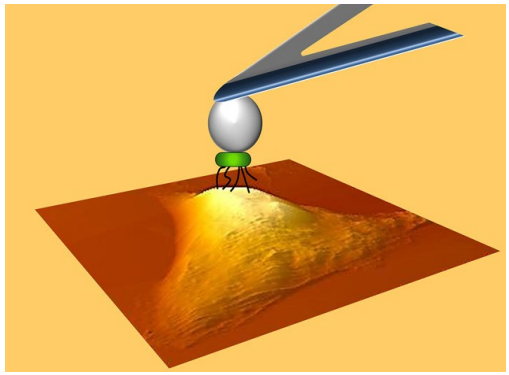
Student Projects – Physics, Chemistry, Biology & Engineering

Cryo Electron Microscopy & Tomography of bacterial nanowires and assembly

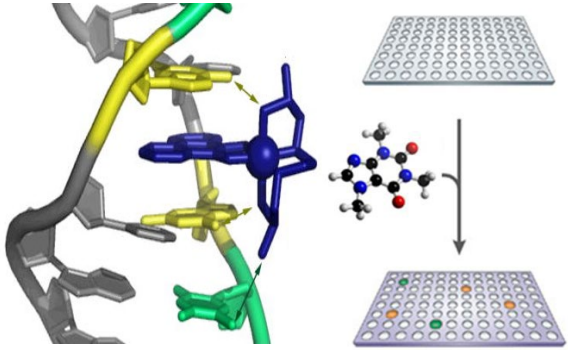


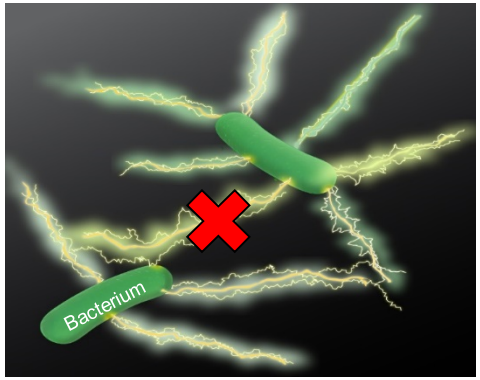
Targeting bacterial survival mechanisms





Novel drugs to neutralize host-pathogen interactions





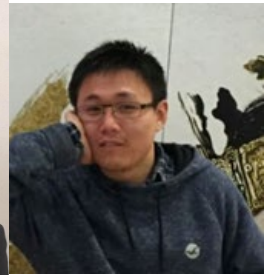

Sibel Yalcin


Catharine Shipps


Sophia Yi

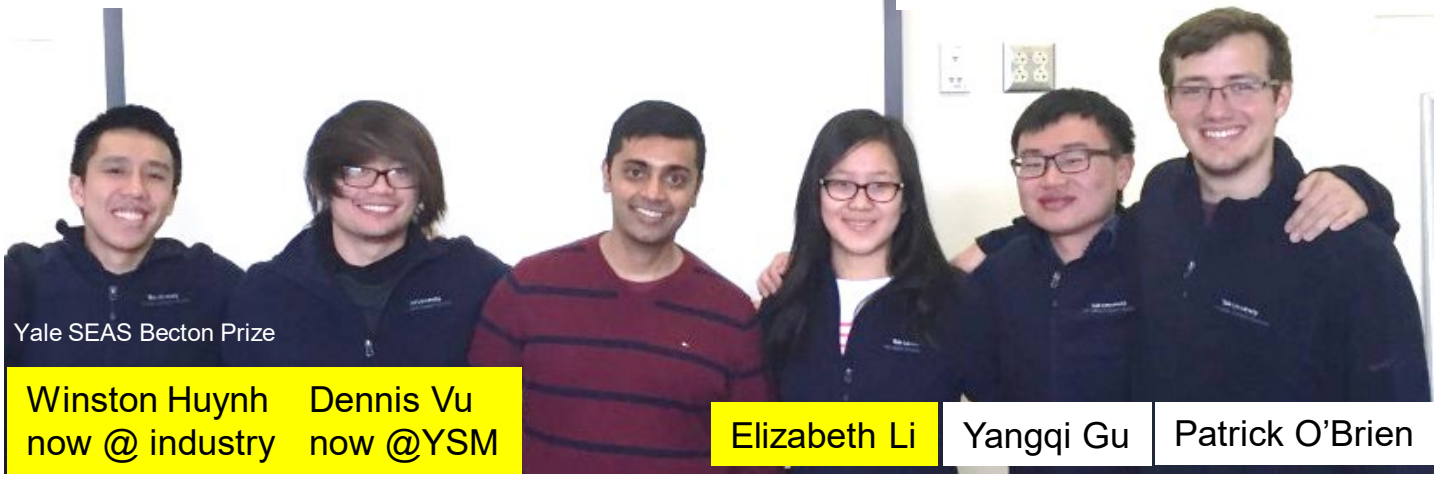

Peter Dahl


Vishok Srikanth


Cong Shen


Jens


Dan Shapiro (now @ Duke)




Claire Sheen Mitchell Lee

Winston Huynh now @ industry

Dennis Vu now @YSM

Elizabeth Li

Yangqi Gu

Patrick O'Brien

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

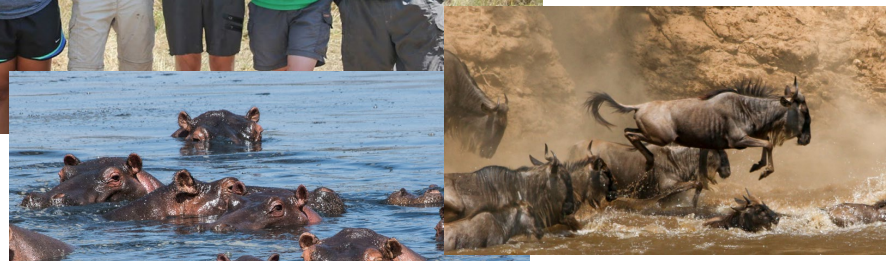
THE HARTWELL FOUNDATION

Charles H. Hood FOUNDATION

NSF GRFP

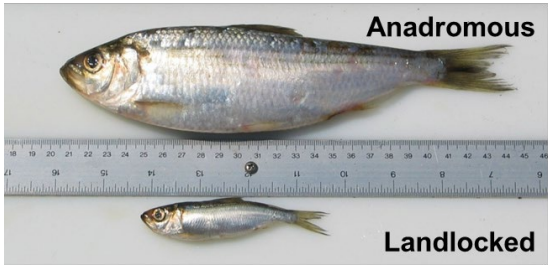
Post Lab

david.post@yale.edu



Connecticut: eco-evolutionary interactions in lakes

- Interactions between ecology and contemporary evolution in lake food webs

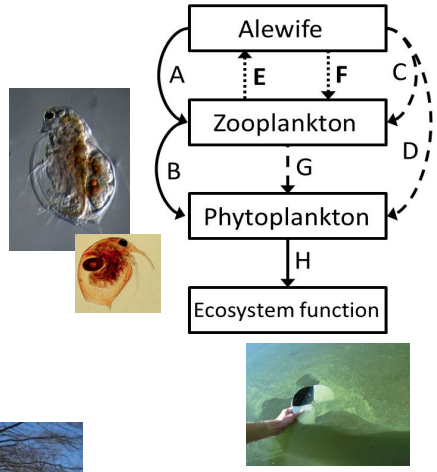


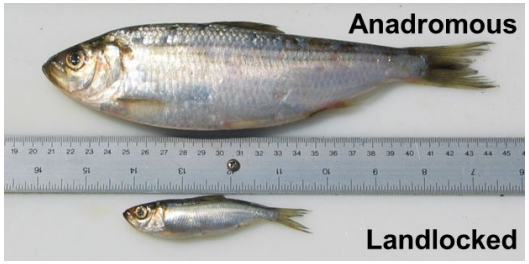
- Alewife (Alosa pseudoharengus)
  - Two life history forms

- 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

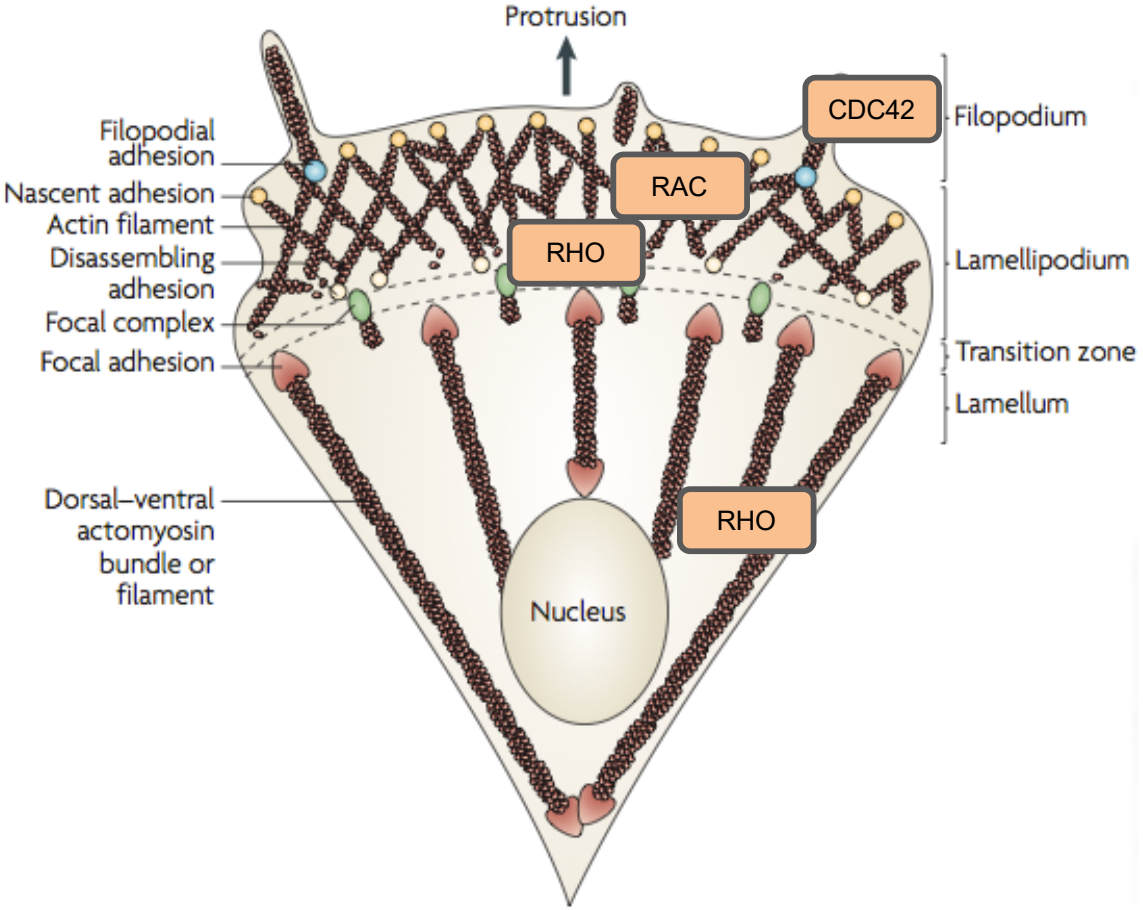
Outreach and Education

- Short Courses for US and East African Students

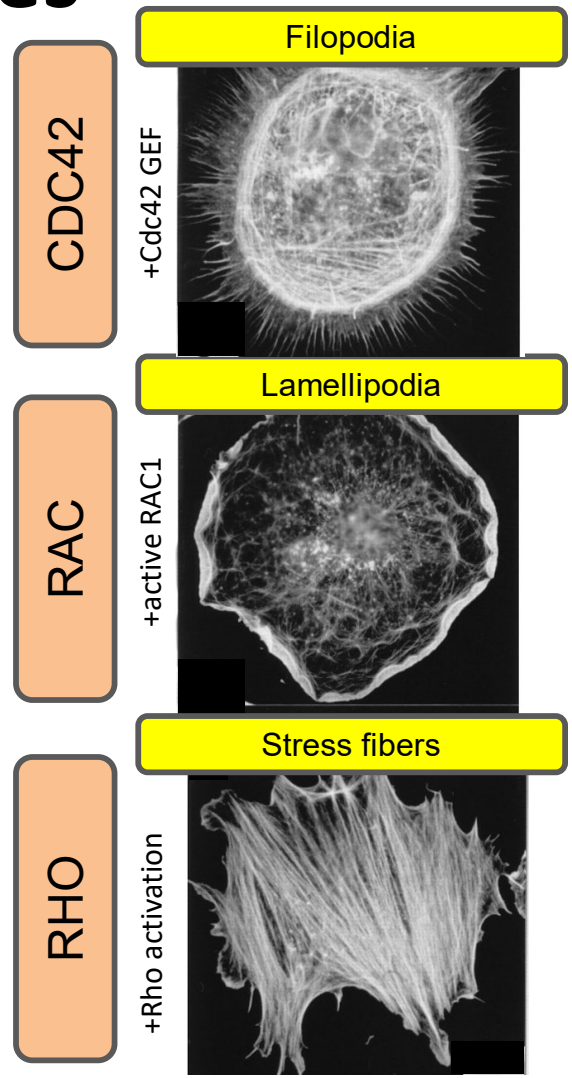
Boggon Lab

Structural biology of Rho Signaling cascades

titus.boggon@yale.edu

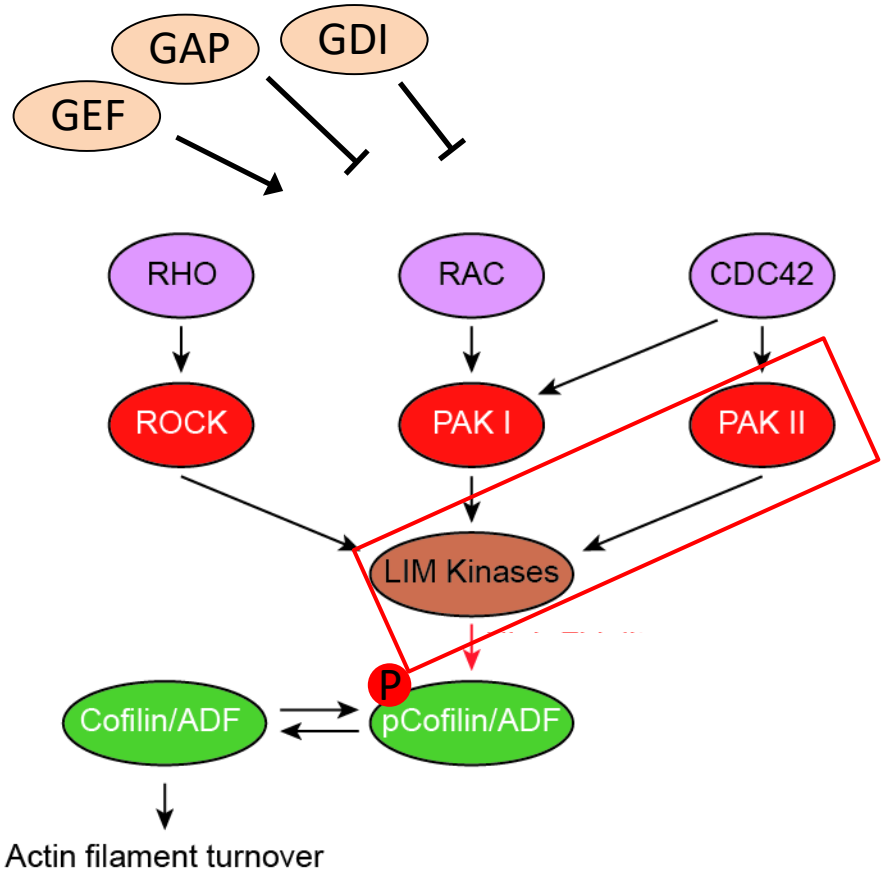


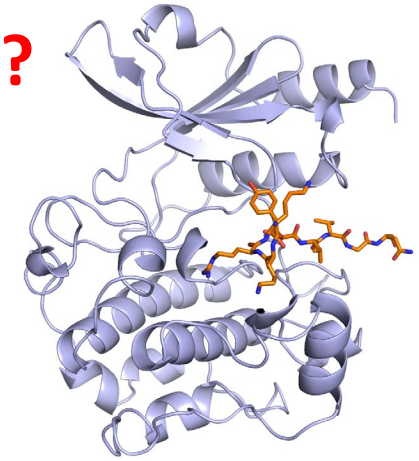
Parsons *et al.*, *Nature Reviews MCB*, 2010



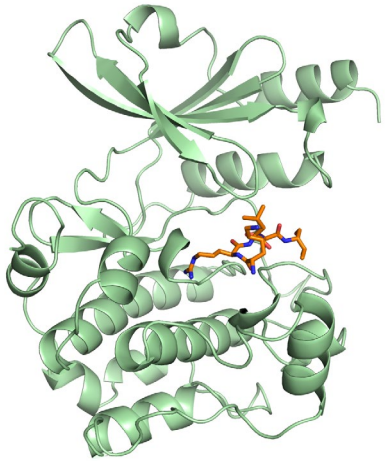
Hall, *Science*, 1998

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

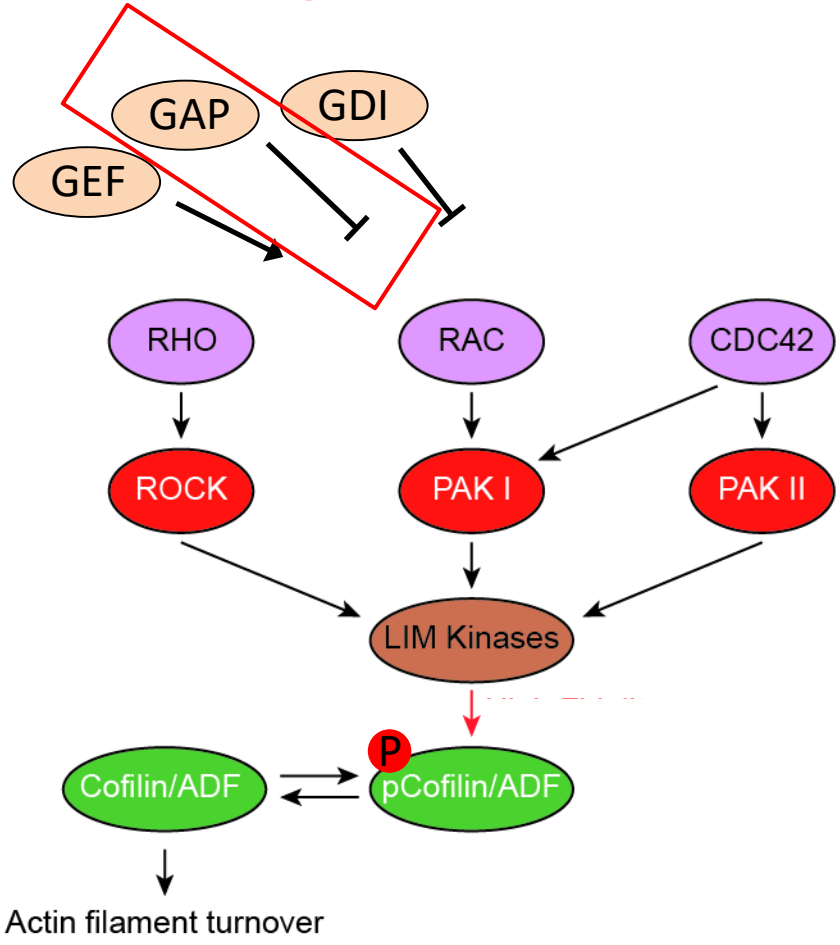
journal homepage: www.elsevier.com/locate/bbapap

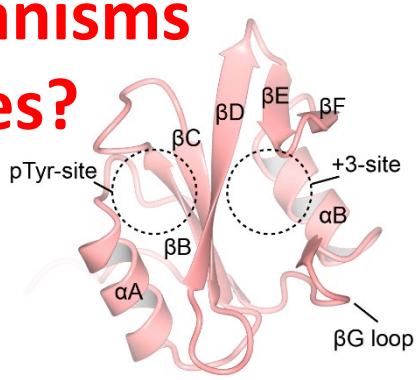
PAK4 crystal structures suggest unusual kinase conformational movements

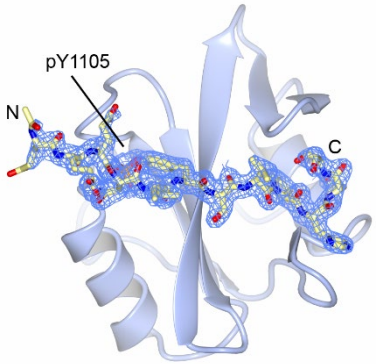
Eric Y. Zhang[a], Byung Hak Ha[a], Titus J. Boggon[a,b,*]

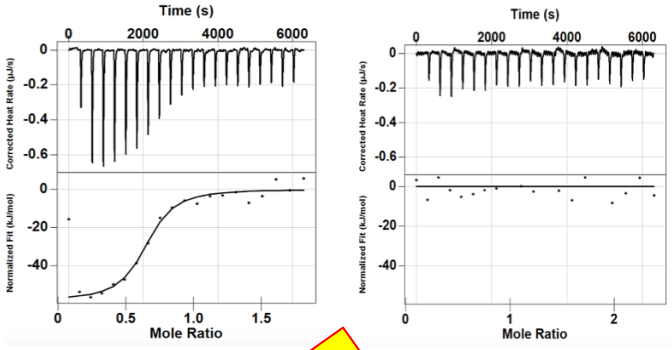
Eric Zhang
MB&B 2017

What are the molecular mechanisms that regulate these cascades?









Rachel Jaber Chehayeb MB&B Senior

Jessica Wang
MB&B 2019

PLOS ONE

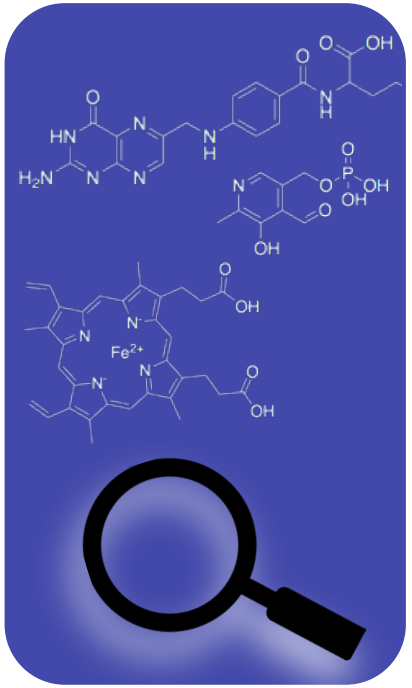
Crystal structures of p120RasGAP N-terminal SH2 domain in its apo form and in complex with a p190RhoGAP phosphotyrosine peptide

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

Solving the puzzles in cellular metabolism

"de-orphan" metabolic enzymes & transporters

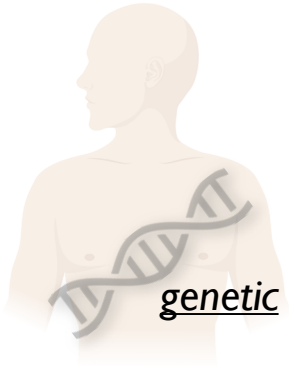
cell biology of micronutrients and cofactors



new tools for metabolite sensing at cellular level

The Shen lab

Cellular & molecular physiology
Systems Biology Institute, Yale West Campus



"De-orphan" the metabolic genes underlying genetically influenced nutrient metabolism

healthy → *sick*

GWAS of intermediate metabolites level - heritability

inborn errors of metabolism

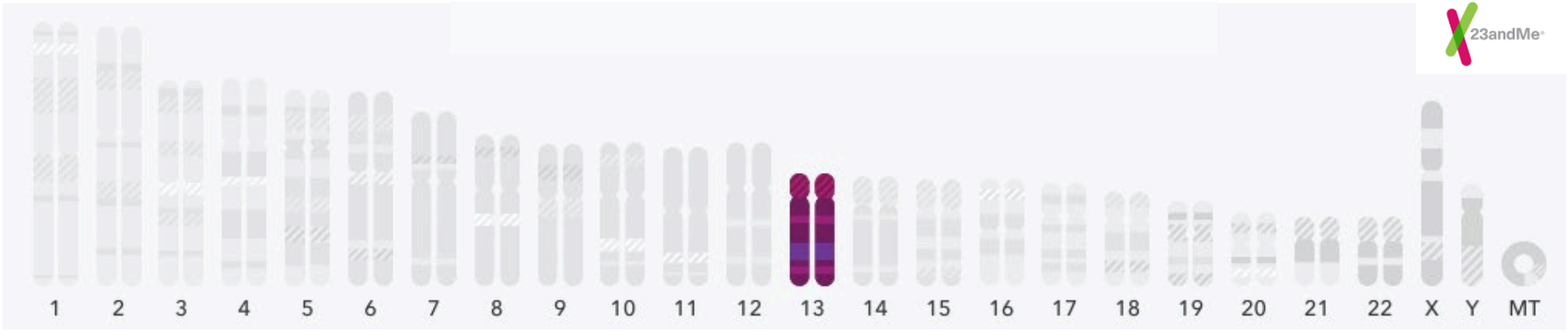
genes ↔ **metabolites** ↔ **traits/diseases**

"unknown" gene sequences for enzymes/transporters

"orphan" biochemical activities

~ 2,000/ 20,000

CLYBL, an orphan mitochondrial enzyme

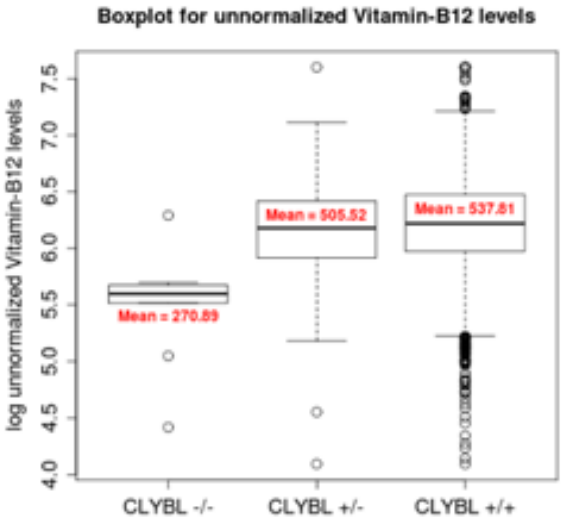


- CLYBL is a human “knockout” gene, with the LoF allele found in ~ 3 % all human chromosomes

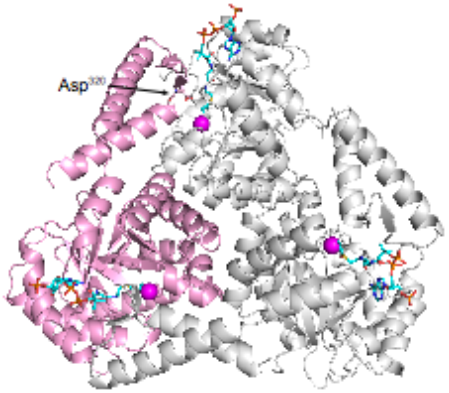
- CLYBL loss is associated with vitamin B_{12} deficiency

rs41281112

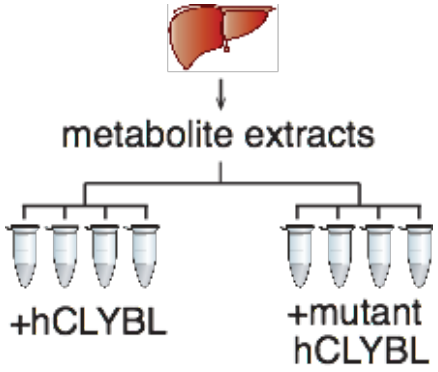
CGA→TGA
R259 OPA



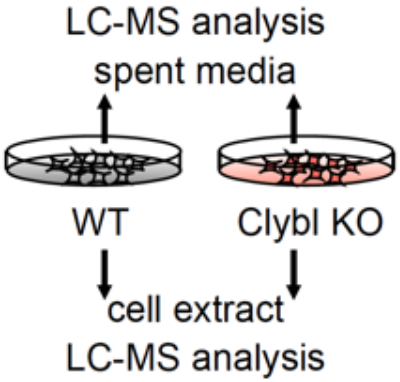
An integrated strategy to deorphanize CLYBL linking vitamin B_{12} and immunometabolism



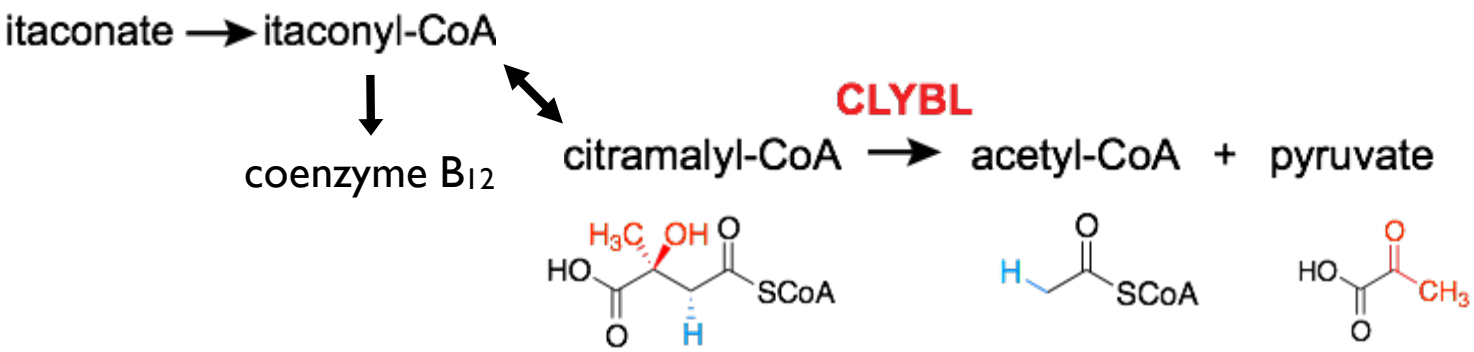
X-ray crystallography



***in vitro* activity-based metabolite profiling**



CRISPR engineering & high-resolution mass spec metabolomics



Shen et al. *Cell* 2017; *Reutz … Shen et al., Science, 2019;* unpublished

We are recruiting!

The Shen lab

Cellular & molecular physiology
Systems Biology Institute, Yale West Campus

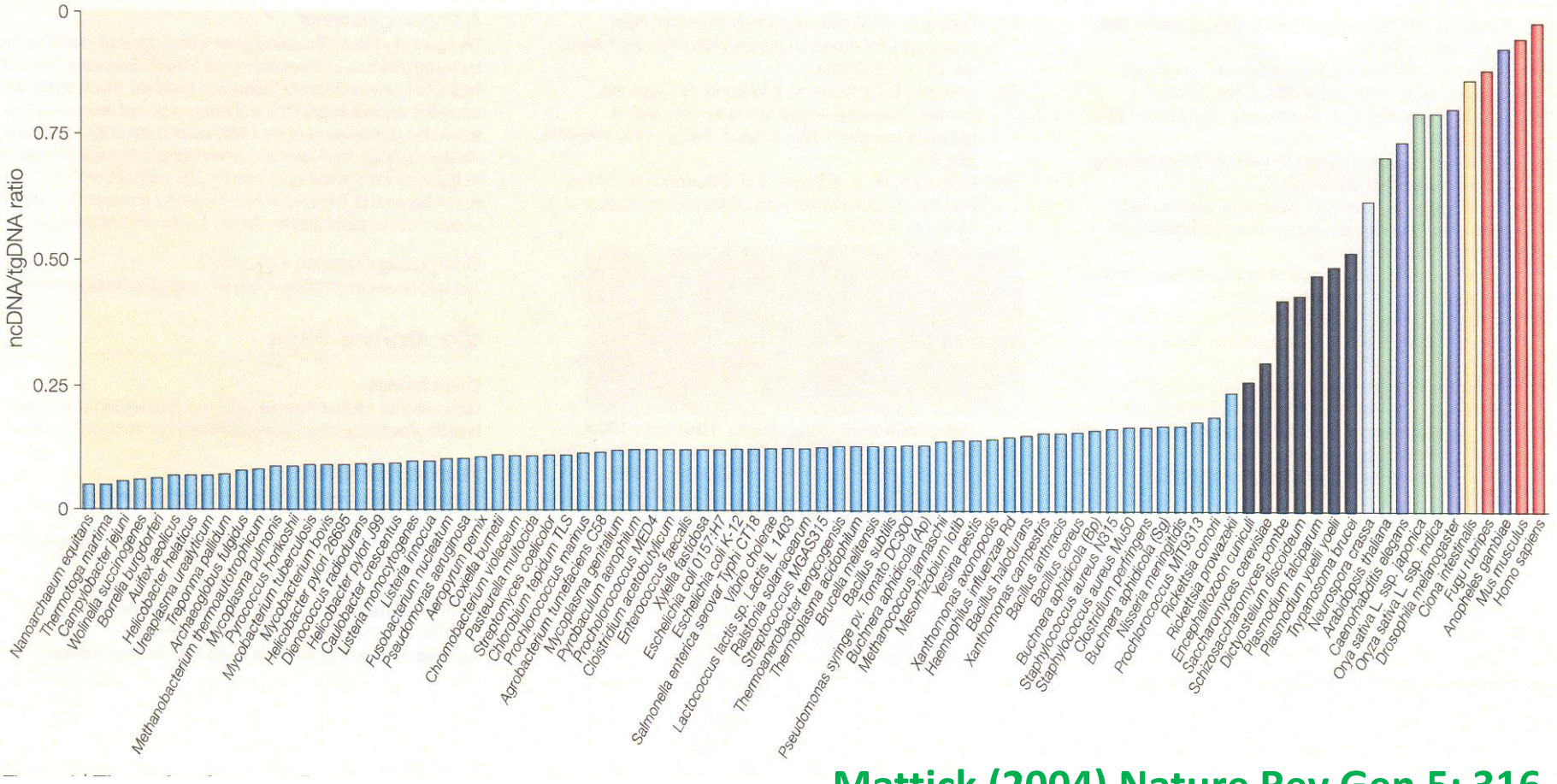
hoyshenlab.org

hongying.shen@yale.edu

@hoy_Shen


Joan Steitz Lab
YALE

The Ratio of Non-coding to Protein-coding DNA Rises as a Function of Developmental Complexity



Mattick (2004) Nature Rev Gen 5: 316.

Viral non-coding RNAs:

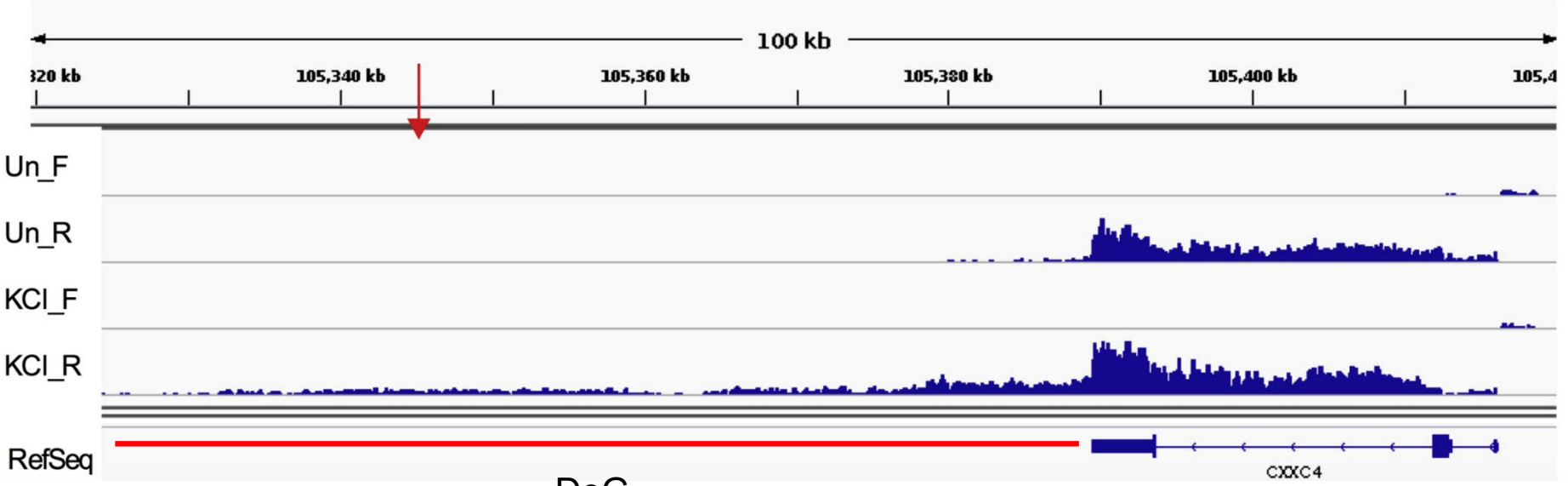
	virus	*function*
HSUR 1 - 7 snRNPs 1986	Herpesvirus saimiri (HVS)	upregulation of T-cell activation host genes via host miR-27 degradation additional mechanisms?
HVS-encoded microRNAs 2010		target host cell cycle regulators
EBER 1 and 2 snRNPs 1981	Epstein-Barr (EBV)	EBER2 enables viral replication mechanism? EBER1?
EBV sisRNAs 2013		stable intronic sequences function?
EBV- and rLCV-encoded microRNAs 2005		collaborate with host oncogenic and apoptotic microRNAs during latency
PAN (polyadenylated nuclear) RNA 1996	Kaposi Sarcoma associated Herpesvirus (KSHV)	enables late protein synthesis and virus production mechanism?

Target-Directed MicroRNA Degradation

Viral RNA-RNA interactions of EBERs

RNA triple helix function in transcript stabilization

Stress-induced readthrough transcripts



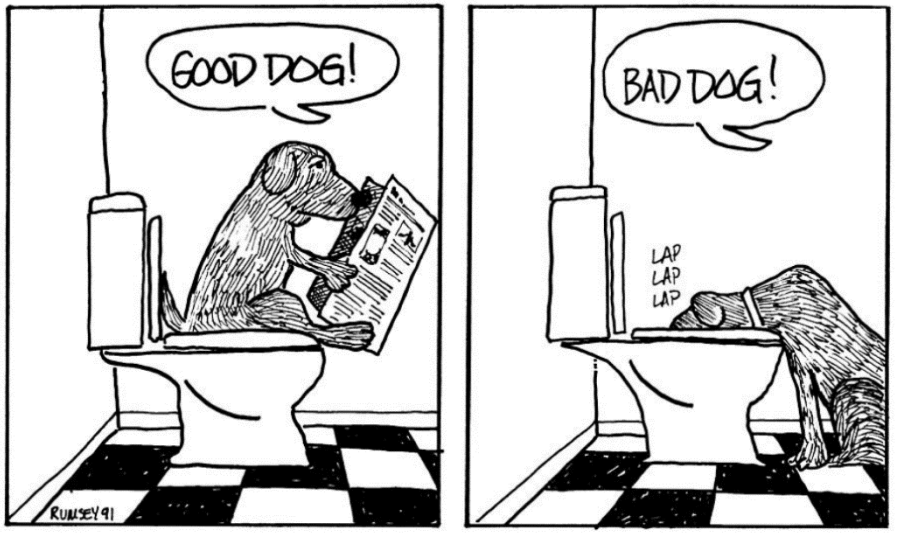
DoG

- Induced minutes after stress and return to base levels after 3.5 hour of recovery.
- Continuous with the upstream mRNA and can be over 200 kb in length.
- Arise from ~20% of protein-coding genes.

Vilborg et al. 2015

Stress-induced readthrough transcripts

- How are DoGs made?
- What do DoGs do?
- Are DoGs important in a disease context?



Are DoGs helping the cell?

Are DoGs hurting the cell?

Internal representation of the spatial world

George Dragoi, MD PhD

george.dragoi@yale.edu

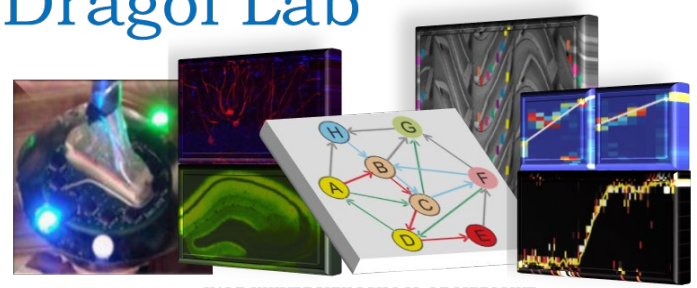
Interdepartmental Neuroscience Program
Departments of Psychiatry and Neuroscience

Yale University

LUX ET VERITAS

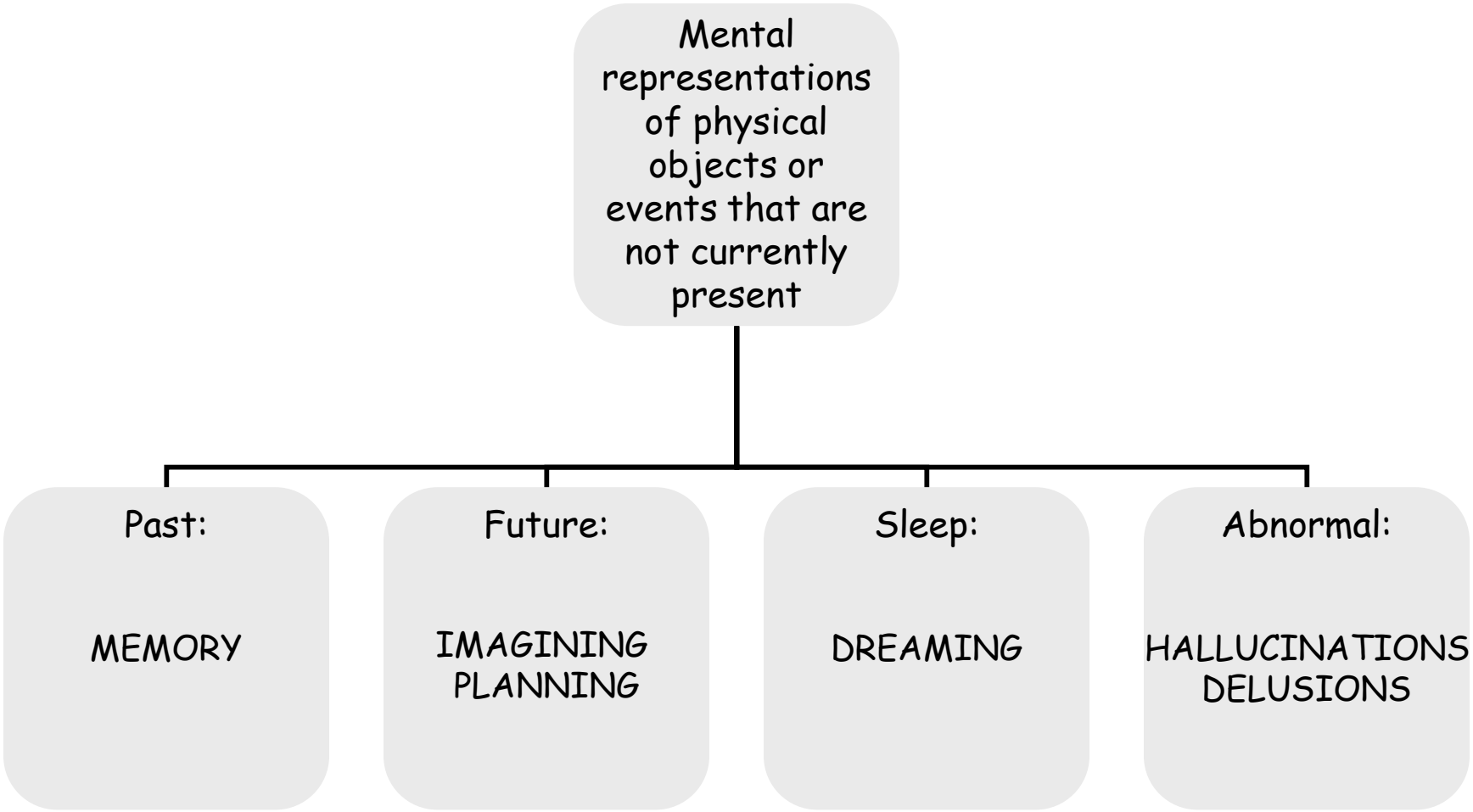
Yale University
School of Medicine

Dragoi Lab

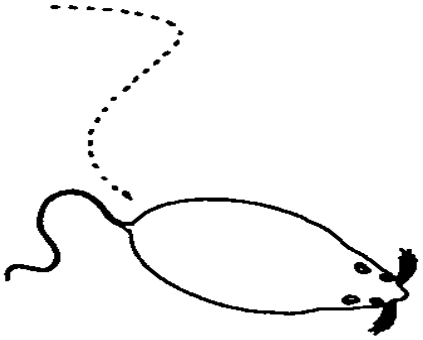


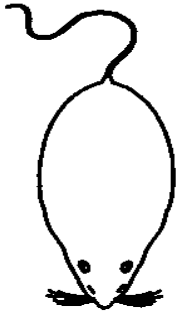
https://medicine.yale.edu/lab/dragoi/

Internally-generated representations



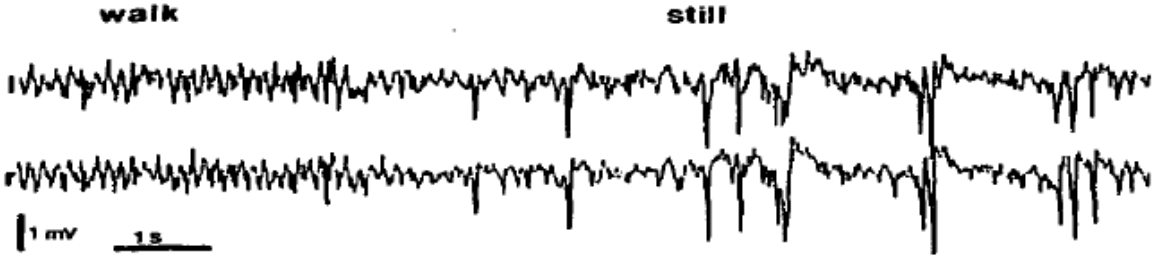
Two stage model of memory formation

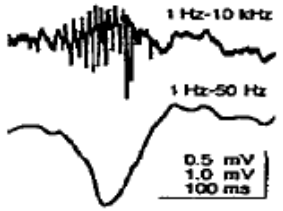




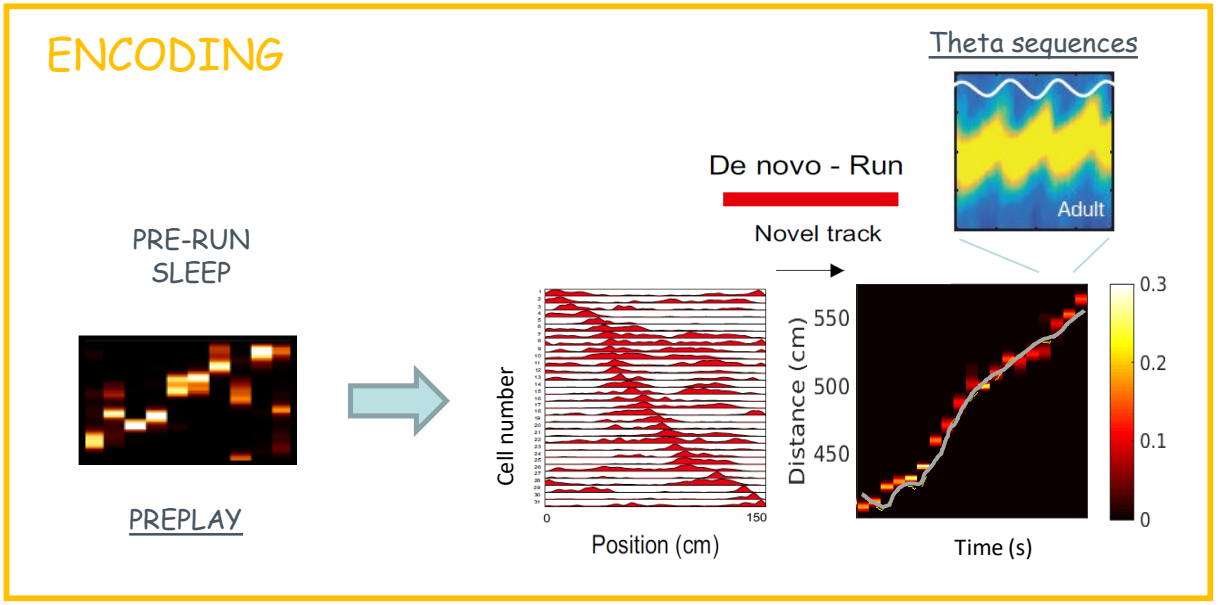
Stage 1 - Encoding
Exploration
Theta oscillation

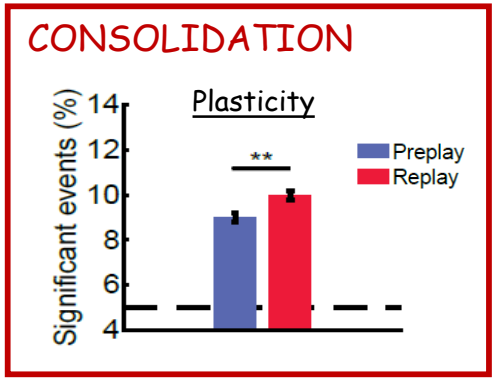
Stage 2 – Consolidation
Sleep (NREM) or rest
Ripple oscillation





Hippocampal temporal sequences in service of memory formation



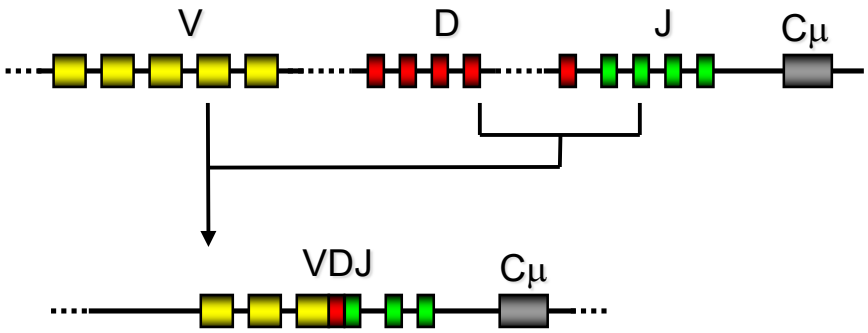


- What is their developmental timeline?
- What is their role in memory and planning?
- What is the neural 'syntax' underlying memory processing?

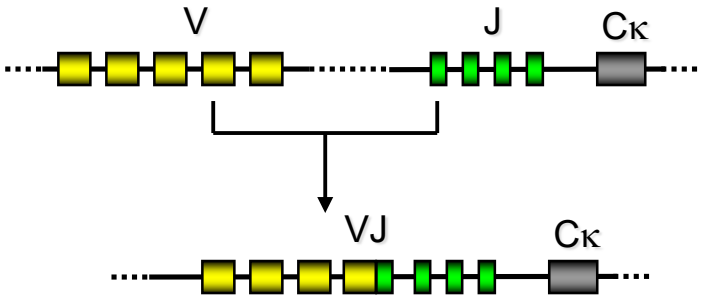
- Methodology: large-scale electrophysiological recordings of brain activity in freely behaving and sleeping rodents and computational methods for data analysis

VDJ Recombination

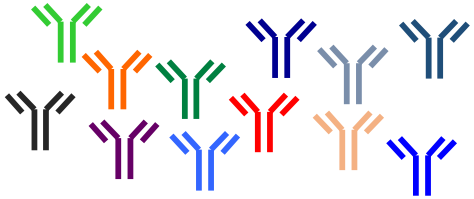
Ig heavy chain gene (Igh)



Ig kappa light chain gene (Igκ)



Billions of antibodies
(B cells)



Billions of T cell receptors
(T cells)

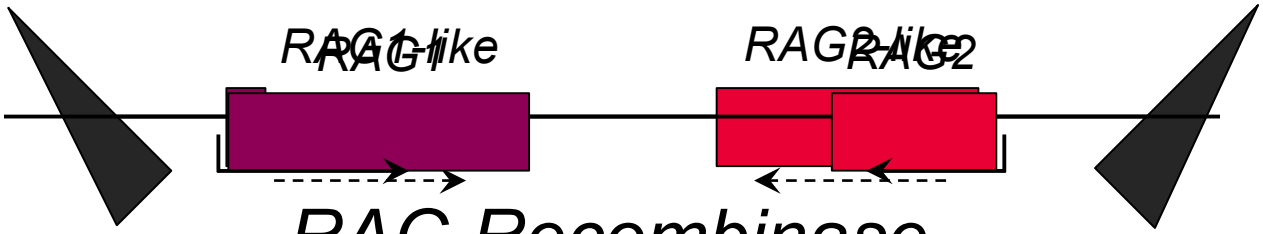
What are the evolutionary origins of V(D)J recombination?

David Schatz david.schatz@yale.edu

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?

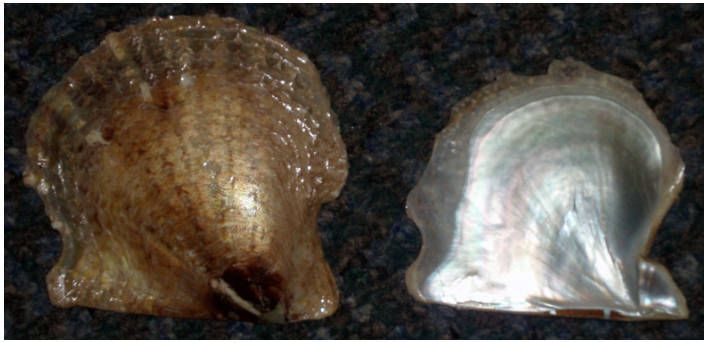
Hundreds of millions of VDJ recombination events each day per person

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

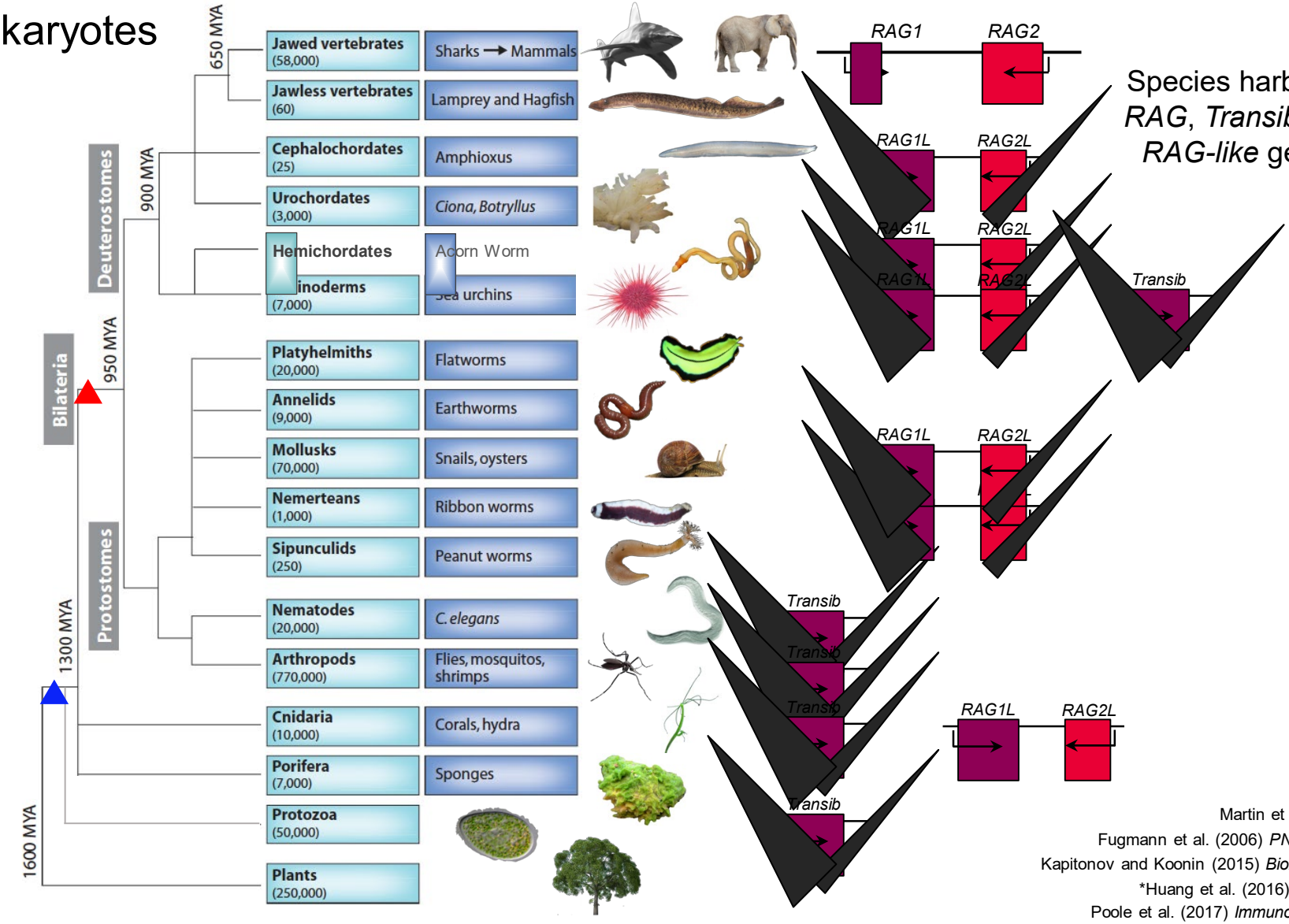
Nemertea

Ribbon worm
Notospermus geniculatus
(Nimrod Shai)

Cnidaria

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

Eukaryotes

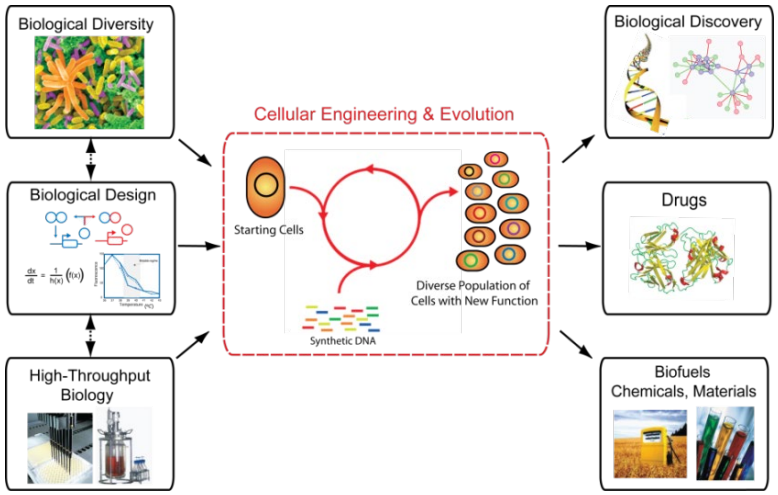


Martin et al., submitted.
Fugmann et al. (2006) *PNAS 103*:3728.
Kapitonov and Koonin (2015) *Biol Direct 10*:20.
*Huang et al. (2016) *Cell 166*:102.
Poole et al. (2017) *Immunogen. 69*, 391.

Synthetic Biology @ Yale

Farren Isaacs
Associate Professor & DGS
Molecular, Cellular & Developmental Biology
Biomedical Engineering
Systems Biology Institute
Yale University

Isaacs Lab



- Invent new genome engineering technologies
- Construct organisms with new genetic codes
- Engineer novel proteins & biomaterials
- Develop biological safeguards

➢ **Undergrads publish papers!** **Isaacslab.org**

iGEM

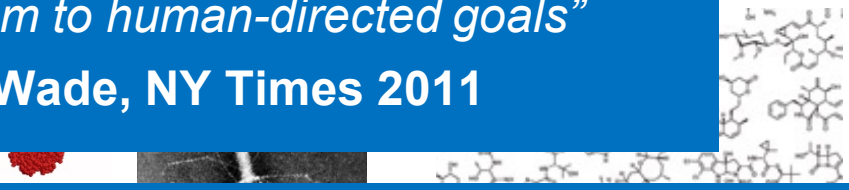
- **I**nternational **g**enetically **e**ngineered **m**achines
- Multidisciplinary teams work together to build, design, and test novel biological systems
- Push the boundaries of science by tackling real-world global problems

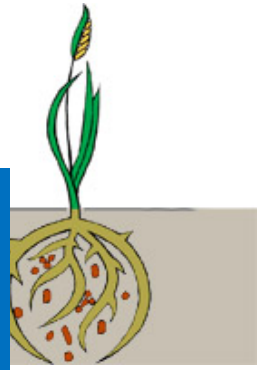
➢ Compete against 6,000 people from around the world at annual Jamboree @ MIT **igem.org**

Synthetic Biology: **a new approach for meeting grand challenges and societal needs**

"the quest to hijack living systems and convert them to human-directed goals"

-Nicholas Wade, NY Times 2011

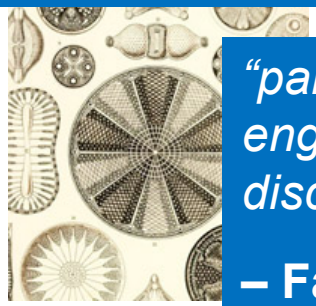




"By combining elements of engineering, chemistry, computer science, and molecular biology, synthetic biology seeks to assemble the biological tools necessary to redesign the living world."

– New Yorker 2009

ricultural



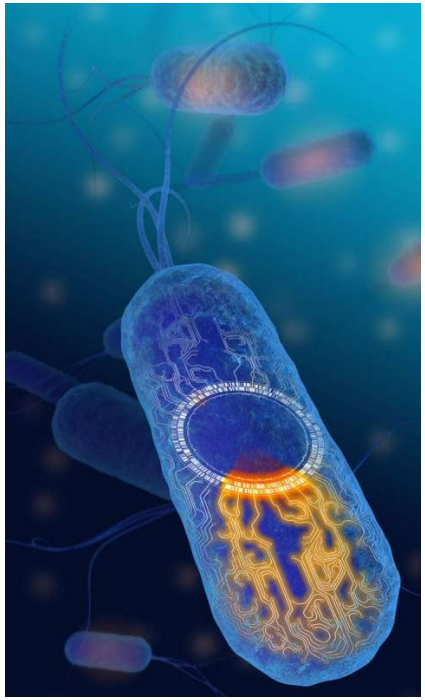
"part of the natural maturation of biotechnology, in which the engineering of biological systems is becoming a formal discipline"

– Farren Isaacs & Lingchong You, Genome Biology 2009

Materials **Energy** **Global Health**

Synthetic Biology is "Engineering Biology"

- the design and construction of new biological parts, devices, and systems
- the re-design of existing, natural biological systems for useful purposes



Medicine

Food

Energy

Chemicals

Materials

iGEM at Yale

Team History

Yale iGEM was **founded in 2009** by a group of undergraduates passionate about the **potential of synthetic biology**. Inspired by the iGEM foundation mission, they set out to make their own contributions, completing their first project in 2010.

Nature's Antifreeze: Microbial Expression and Characterization of a Novel Insect Antifreeze Protein for De-Icing Solutions

Developing a Framework for the Genetic Manipulation of Non-Model and Environmentally Significant Microbes

Publications

- Journal of Biological Chemistry (cover)
- Nature, eLife, ACS-Synthetic Biology, Nucleic Acids Research

Team Awards

- Food/Energy Project Grand Prize
- Best Natural Biobrick
- Gold Medal
- Grand Finalist

Individual Awards

- Gates Fellowship
- Hertz Fellowship
- Goldwater Award
- Beckman Scholar
- Schwartzman Scholarship

iGEM Alumni

- Grad School @ Yale, Duke, Stanford, Harvard, Princeton
- Regeneron
- NIH
- Microsoft
- Promega
- McKinsey & Co., BCG

Recent Project

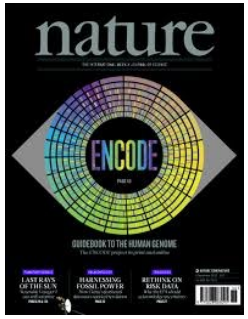
"its all about plastics"

To mitigate PET microplastic waste build-up, the Yale iGEM team has been working to engineer a strain of *Chlamydomonas reinhardtii,* a freshwater green algae, with the ability to secrete proteins capable of breaking down plastics.

THE iGEM TEAM SEEKS A FEW GOOD **YALIES** …
… TO CHANGE THE WORLD

farren.lsaacs@yale.edu

Gerstein Lab @ Yale (gersteinlab.org)



Program in Computational Biology & Bioinformatics (CBB)
Department of Biophysics & Biochemistry (MBB)

Lab focuses on **biological data sciences**

- Human Genomics
- Human Genetic Variation
- Functional Genomics

Participate in many big genomics consortia: **ENCODE, PsychENCODE, TCGA, exRNA** …

Contact: **joel.rozowsky@yale.edu** or **mark@gersteinlab.org**

Projects in Gerstein Lab

- Human Genomics (ENCODE + exRNA)
- Cancer Genomics & Human Variation (TCGA + ENCODE)
- Brain Genomics (PsychENCODE)
- Specific Topics: Biological Networks, Machine Learning Approaches, Genome Annotation, Pseudogenes, Protein Structure, Structural Variation, Functional Genomics, Tool Development, Genomic Privacy

Contact: **joel.rozowsky@yale.edu** or **mark@gersteinlab.org**

Gerstein Lab undergrad research experience

- Initially meet with MBG (will direct to potential mentors)
- Mentored by graduate students + postdocs + assoc. res. Scientists
  - big lab ~30 people + undergrads (5+ for summer)
- Weekly group meetings, journal clubs + subgroup meetings
- Lab Presentation (JC or GM) sometime during the summer presenting either a paper or summer work
- Many summer undergrad continue to work in the lab
- Many undergrads are included as authors on lab publications

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

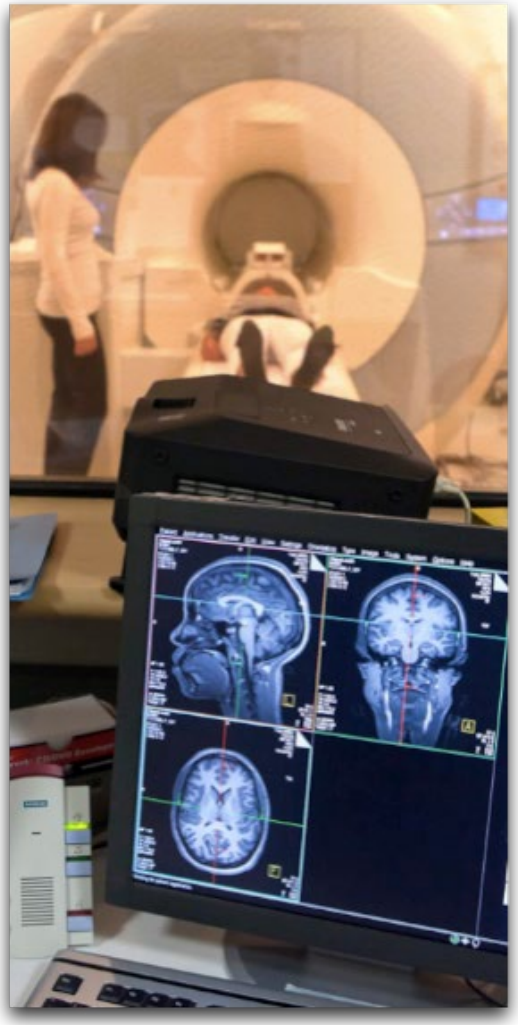
Interested in **Mindfulness**? **Substance Use Disorders**? **Eating Disorders? Emotion Regulation**?

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...

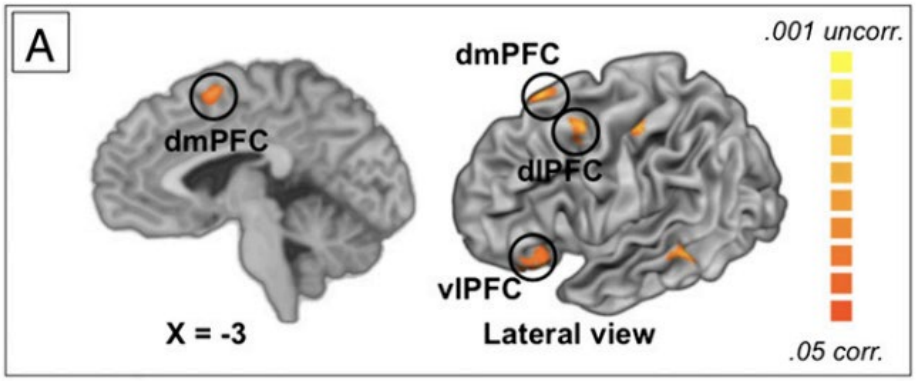
...in just a **short training period** on **regulating your cravings**?

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

hedy.kober@yale.edu