

# How Living Cells Work in Health and Disease

## Mechanobiology: How do Cells Generate Force?

**Cell Division**

Ahna Skop, Wisconsin

**Cell Migration**

1. Traction  
2. Adhesion  
3. Propulsion

Tip adhesion  
Shaft adhesion  
Basal adhesion  
Lamellipodium  
Lamellum  
Actin bundle  
Stress fiber

**Mechanical sensing**  
JAS/Vinculin + Zyxin

Hoffman et al., 2006

**Research**

- Perform quantitative mathematical modeling in collaboration with experimental biologists.
- Response and generation of forces in migrating cells

**Cell Division**

5  $\mu$ m  
Fission yeast *S. Pombe*

drag force  
ring sliding  
constriction

Node  
Myo2  
Mcp1 cluster  
Katanin Cdc12 dimer  
Phospholipid bilayer  
Septin  
F-actin

RFP-Bgs4 Rlc1-GFP

2' 8' 12' 17'

Septum  
Ring

1  $\mu$ m

Wu et al., 2006

**Research**

- Fission yeast as a model to study animal cells
- Reveal mechanisms for tension production

Collaborators: Tom Pollard (Yale), Mohan Balasubramanian (Warwick)

## Cell Migration: Immune System, Cancer Metastasis

**Motility of cancer cells causes metastasis**

cells grow as a tumor  
break through basal lamina  
invade capillary  
adhere to blood vessel  
escape from blood vessel  
travel through bloodstream  
new cells (10,000 cells) will survive to form metastases  
proliferate to form metastases in liver

Figure 23-15 Molecular Biology of the Cell, 4th Edition.

Glannone et al, Cell, 2007

15.75  
13.5  
11.25  
9.0  
6.75  
4.5  
2.25  
0

100  $\mu$ m  $s^{-1}$   
100  $nm \cdot s^{-1}$

150  
66  
132  
198  
264

time (s)

**Research**

- Goal: understand why lateral waves are formed at the leading edge of migrating cells through mathematical modeling

## O'Shaughnessy Group Chemical Engineering, Columbia University, New York, NY

### Neurotransmission

- Quick communication between 100 billion neurons at the synapses
- Fundamental pathway of synaptic transmission: action potential gates  $Ca^{2+}$  channels
- SNARE Proteins: conserved core of cell's fusion machinery

VAMP  
Syntaxin  
SNAP-25  
Docking  
Fusion  
cis SNARE complex

NIH, Alzheimer's Disease, 1998

**Research**

- Neurotransmitter release machinery: integrated mathematical modeling, image analysis and experiment
- Unravel how information is processed in the brain

Organization of the presynaptic release machinery, Sudhof, 2013

Collaborators: James Rothman, Erdem Karatekin (Yale)

### Hormone Secretion

- Regulate and maintain various physiological functions
- The release rate of hormones is highly regulated.
- Medical applications: type II diabetes is caused by impaired insulin release

insulin  
ATP  
Syntaxin  
SNAP 25  
Fusion pore  
Amlylin  
Full fusion  
Barg and Coock, 2016

Membrane  
Interior  
Merge

**Research**

- Develop mathematical model to understand how vesicles evolve and how release is regulated.

Free energy  
Diameter  
Omega  
Lambda  
Bending  
Tension  
Bulk

$$F_{ves} = \int \frac{\kappa}{2} (2H)^2 dS + \gamma_{ves} A - \Delta p V$$

100 Pa  
200 Pa

500 nm

Collaborator: Ling-Gang Wu (National Institute of Health)

## Viral Infection: Influenza, Ebola

- Membrane enclosed viruses (e.g. Influenza, HIV, Ebola) infect cells by fusing with the host cell's membrane
- Thousands of deaths due to viral infection annually
- Long term goal: design anti-viral drugs

Ebola virus emerging from an infected cell. NIAID/NIH

Virus  
Cell nucleus  
RNA delivery  
Target membrane  
Influenza virus fusion protein (HA)  
Viral membrane

- Specialized fusion proteins release genomic material near cell nucleus

**Research**

- Combine mathematical modeling, theory and experiment to elucidate mechanism of infection

Collaborator: Erdem Karatekin (Yale)

## Membrane Fusion

- Possible pathway to fusion

A Initial contact  
B Contact between protein-depleted bilayer patches  
C Hemifusion stalk  
D Hemifusion diaphragm  
E Initial fusion pore  
F Post-fusion conformation

Lipid molecule  
Detailed CG

Yang et al., 2017

### Research

- Study synaptic transmission and viral infection using a coarse-grained molecular dynamics simulation

