

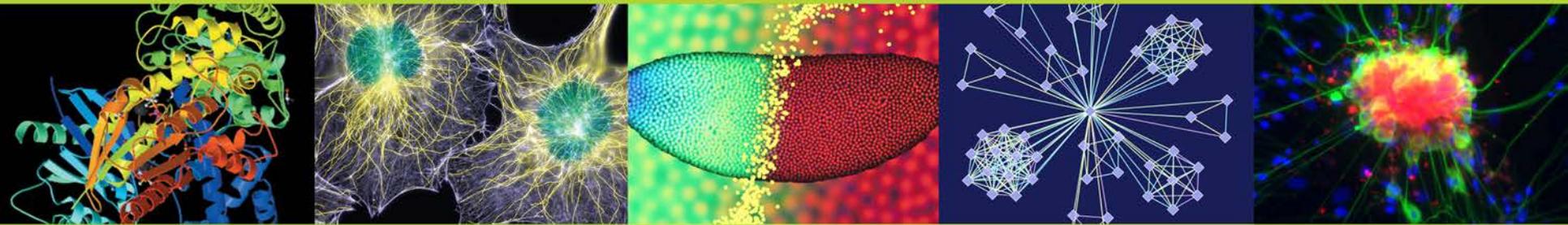


National Institute of  
General Medical Sciences



# Recent Research Advances Supported by NIGMS

Jon Lorsch  
Director, NIGMS



# NIGMS Mission

- Promote fundamental research on living systems to lay the foundation for advances in disease diagnosis, treatment and prevention.
- Enable the development of the best trained, most innovative and productive biomedical research workforce possible.

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# NIGMS Program Divisions



Cathy Lewis

Cell Biology  
and  
Biophysics

Genetics and  
Developmental  
Biology



Judith Greenberg



Mike Rogers

Pharmacology,  
Physiology and  
Biological  
Chemistry

Training,  
Workforce  
Development  
and Diversity

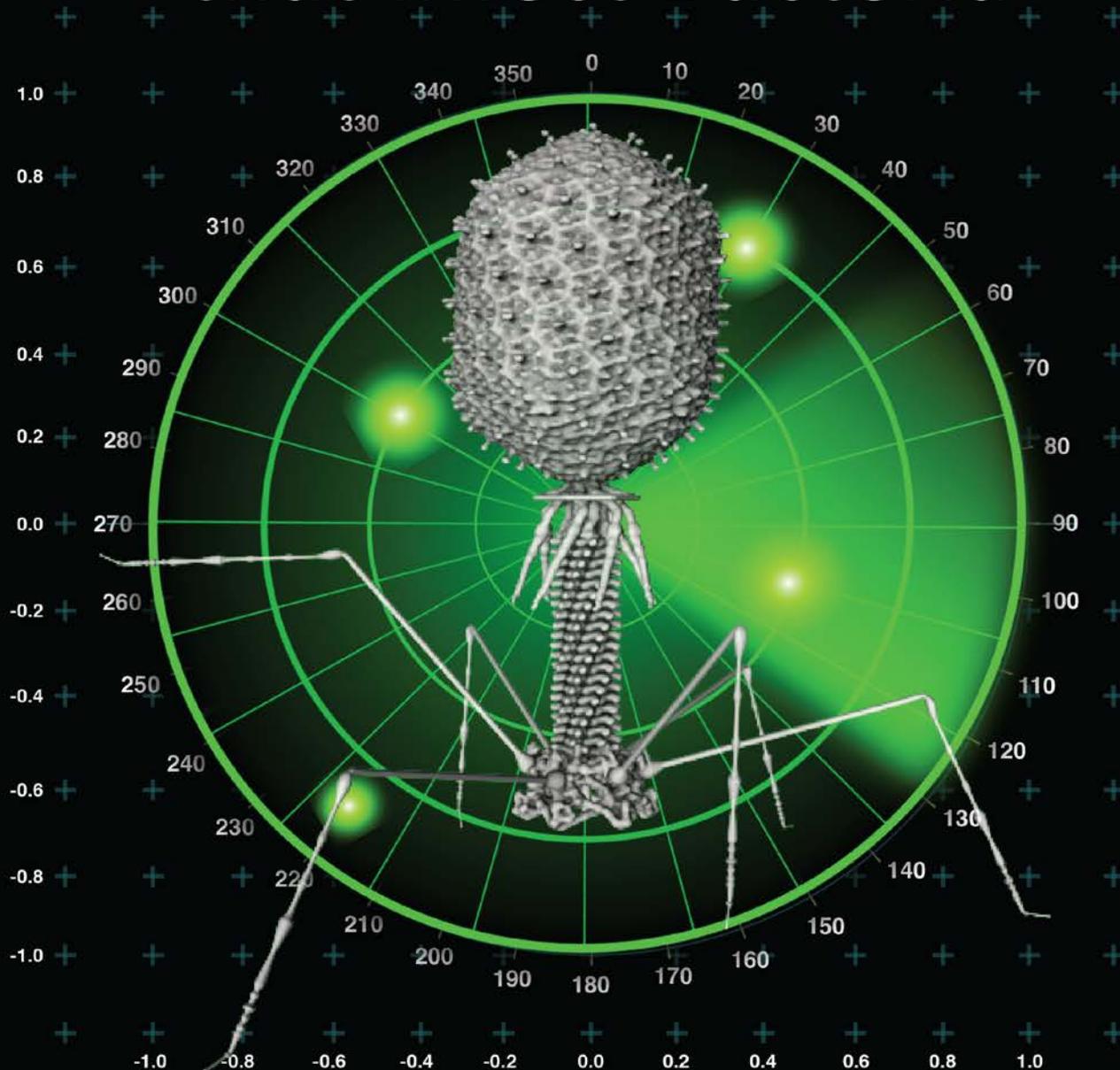
Biomedical  
Technology,  
Bioinformatics,  
Computational  
Biology



Susan Gregurick

Vacancy

# A CRISPR Immune Response to Viruses that Infect Bacteria



# Complex webs of observations and experiments underlie all discoveries

JOURNAL OF BACTERIOLOGY, Dec. 1987, p. 5429-5433  
0021-9193/87/125429-05\$02.00/0  
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Vol. 169, No. 12

## Nucleotide Sequence of the *iap* Gene, Responsible for Alkaline Phosphatase Isozyme Conversion in *Escherichia coli*, and Identification of the Gene Product

YOSHIZUMI ISHINO, HIDEO SHINAGAWA, KOZO MAKINO, MITSUKO AMEMURA, AND ATSUO NAKATA\*

*Department of Experimental Chemotherapy, The Research Institute for Microbial Diseases, Osaka University, 3-1 Yamadaoka, Suita, Osaka 565, Japan*

Received 1 May 1987/Accepted 22 August 1987

# Complex webs of observations and experiments underlie all discoveries

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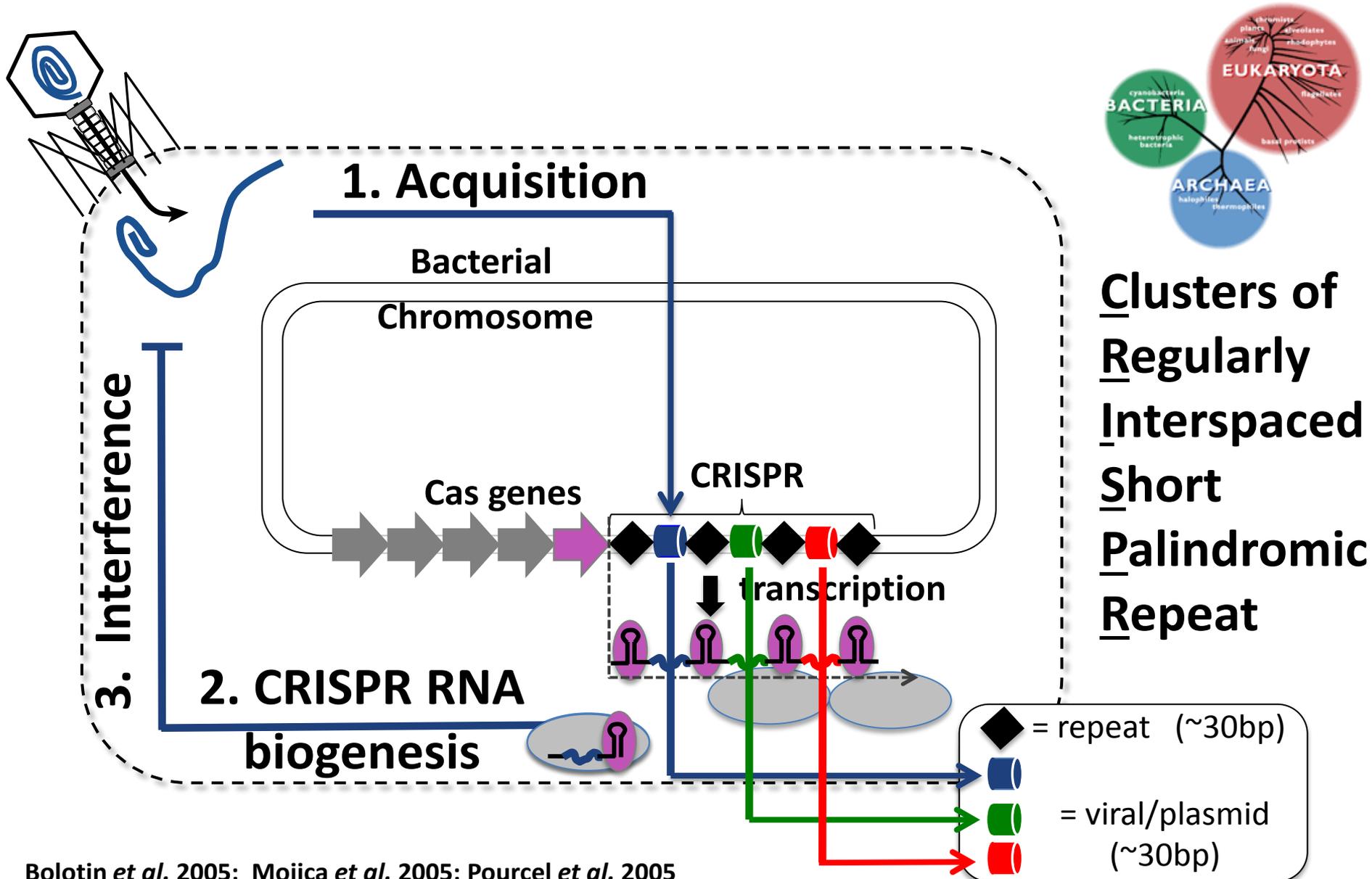
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*Department of Experimental Chemotherapy, The Research Institute for Microbial Diseases, Osaka University, 3-1 Yamadaoka, Suita, Osaka 565, Japan*

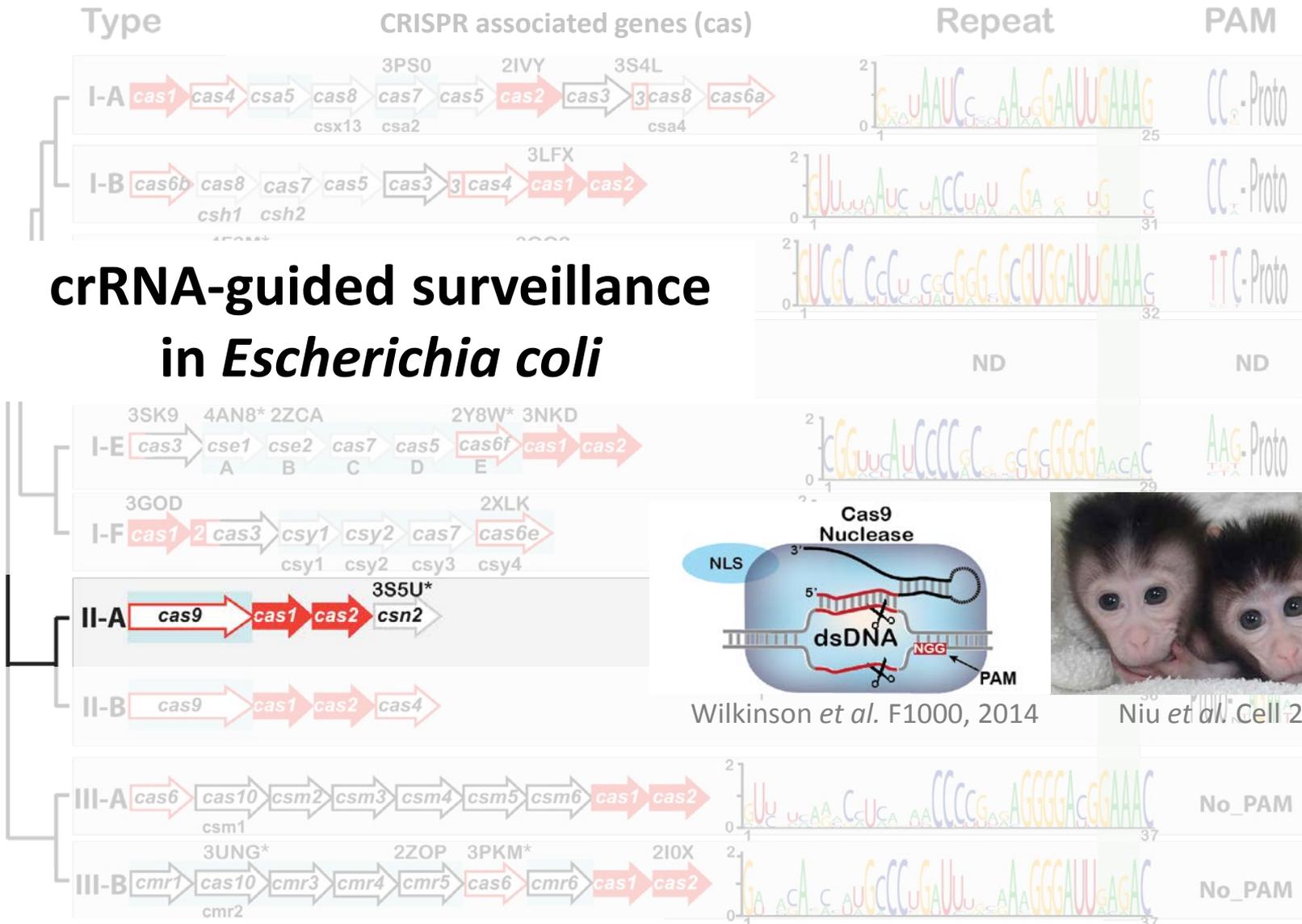
Received 1 May 1987/Accepted 22 August 1987

“An unusual structure was found in the 3’-end flanking region of *iap* (Fig. 5). Five highly homologous sequences of 29 nucleotides were arranged as direct repeats with 32 nucleotides as spacing...So far, no sequence homologous to these has been found elsewhere in procaryotes, and the biological significance of these sequences is not known.”

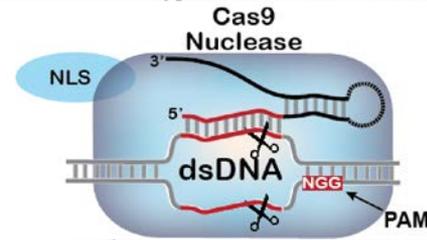
# CRISPR-associated Adaptive Immunity



# Diversity of CRISPR-mediated Immune Systems



## crRNA-guided surveillance in *Escherichia coli*



Wilkinson et al. F1000, 2014



Niu et al. Cell 2014

# Two new investigators solve a big problem: the structure of the CRISPR CASCADE Complex



**Blake Wiedenheft**  
**Montana State University**



**Scott Bailey**  
**Johns Hopkins University**

# Two new investigators solve a big problem: the structure of the CRISPR CASCADE Complex



**Blake Wiedenheft**  
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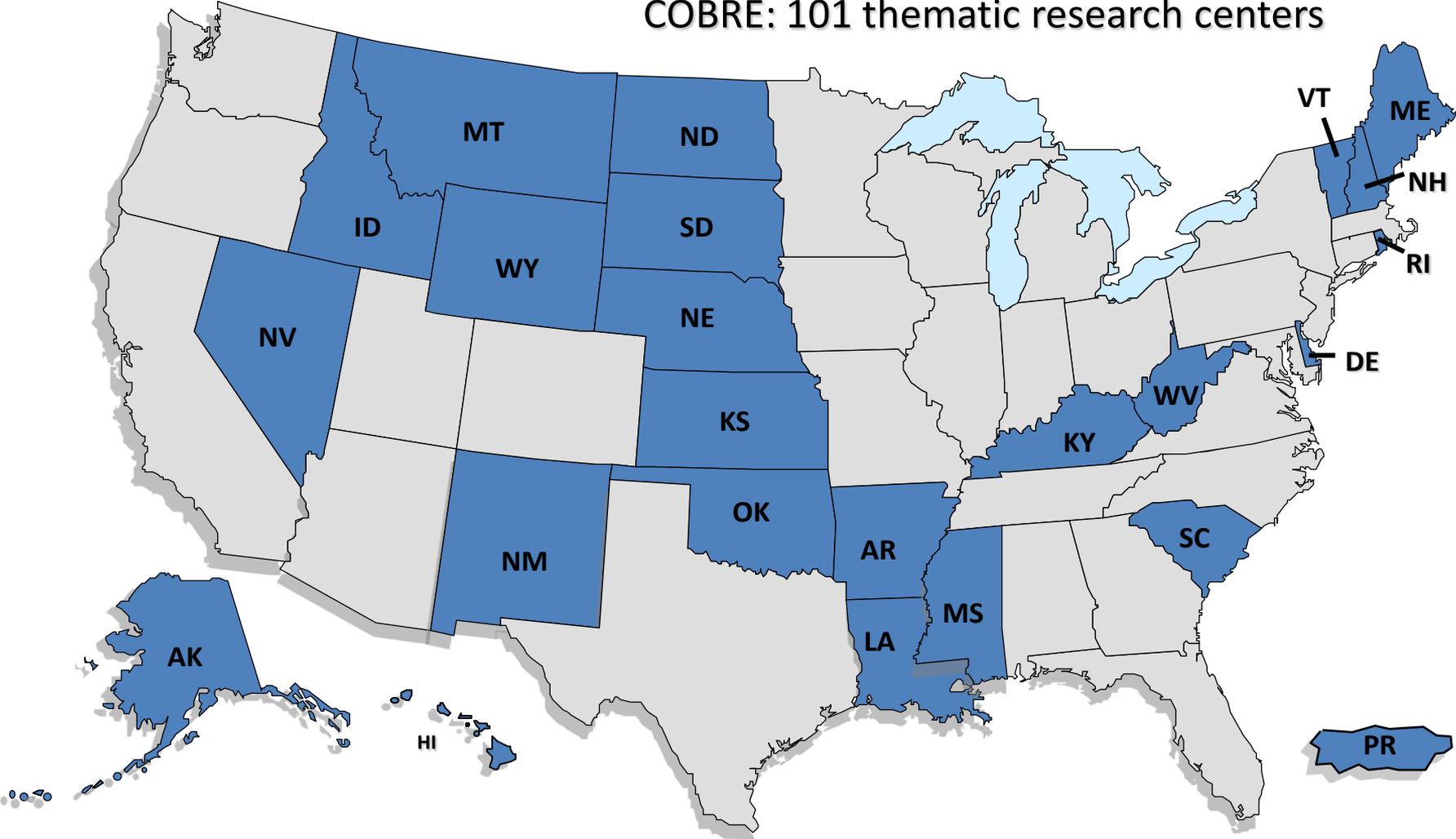


**Scott Bailey**  
Johns Hopkins University

*“Us little fishes have to stick together so  
we don’t get eaten by the big fishes.”*

# IDeA Centers of Biomedical Research Excellence: Developing Young Investigators

INBRE: 24 statewide networks  
COBRE: 101 thematic research centers



# The Wiedenheft Lab

[home](#)

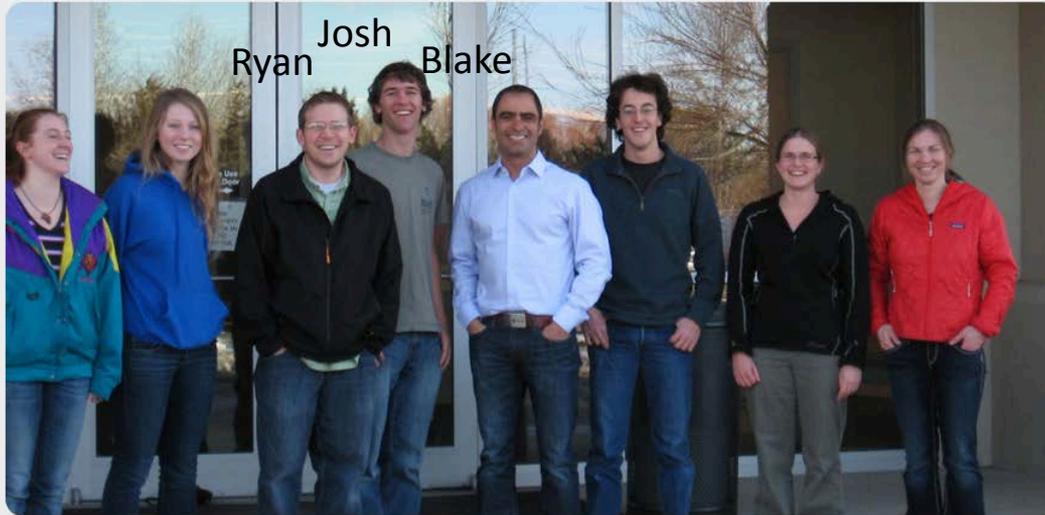
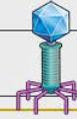
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[people](#)

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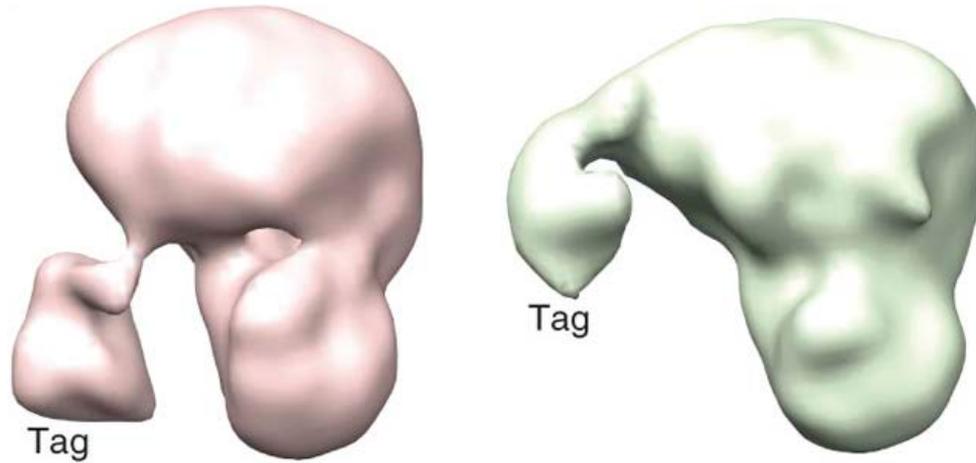
## Support from the COBRE:

- Allowed him to return to his native Montana to do research
- Allowed him to recruit key personnel
  - postdoctoral fellow Ryan Jackson: published 4 papers in 2 years; recently awarded NRSA fellowship (F32 GM108436)
- Allowed him to incorporate undergraduates into research
  - Joshua Carter (Mechanical Engineering/Microbiology double major): co-authored 2 papers; awarded HHMI research fellowship

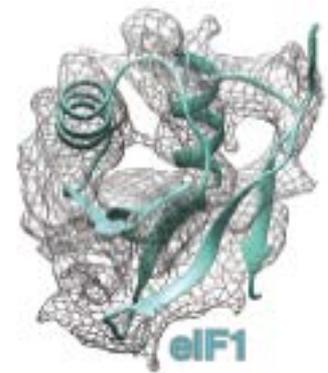
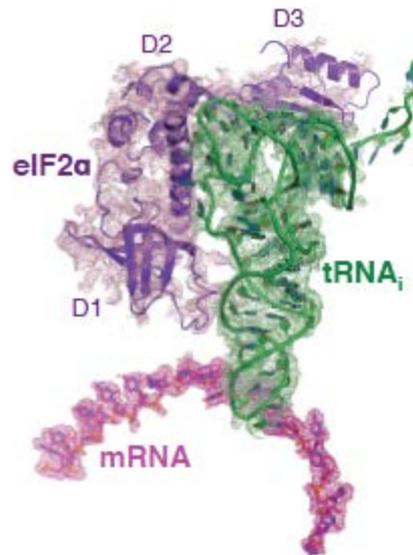
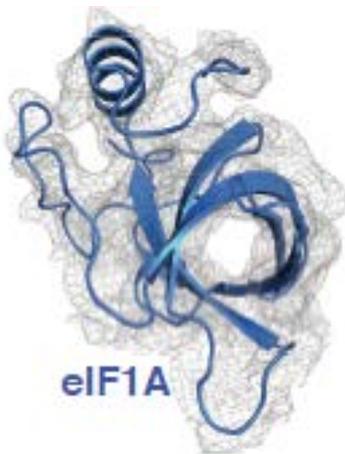
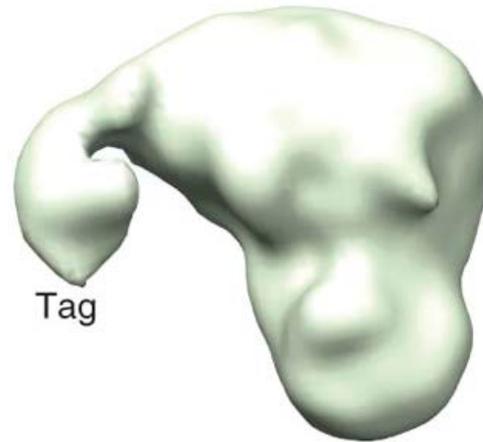
# A Dynamic Model for RNA-guided Detection of DNA



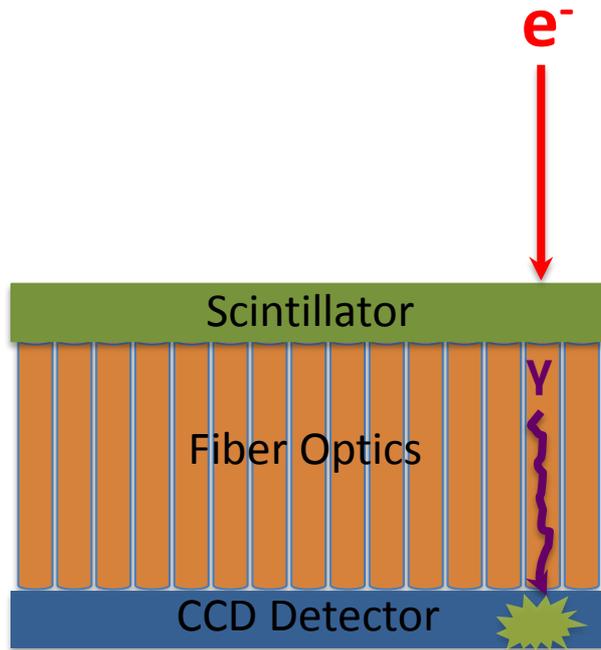
# Cryo-electron microscopy moves from blobology to atomic resolution



# Cryo-electron microscopy moves from blobology to atomic resolution

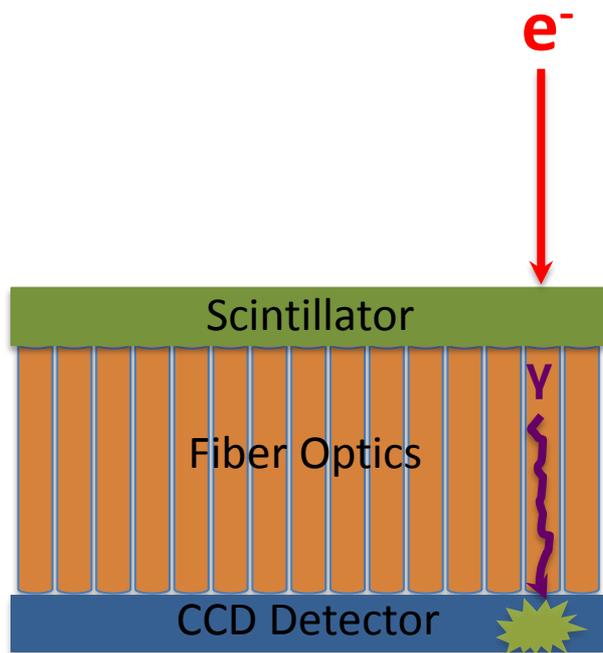


# Direct Electron Detectors: A major advance in cryo-electron microscopy imported from astrophysics

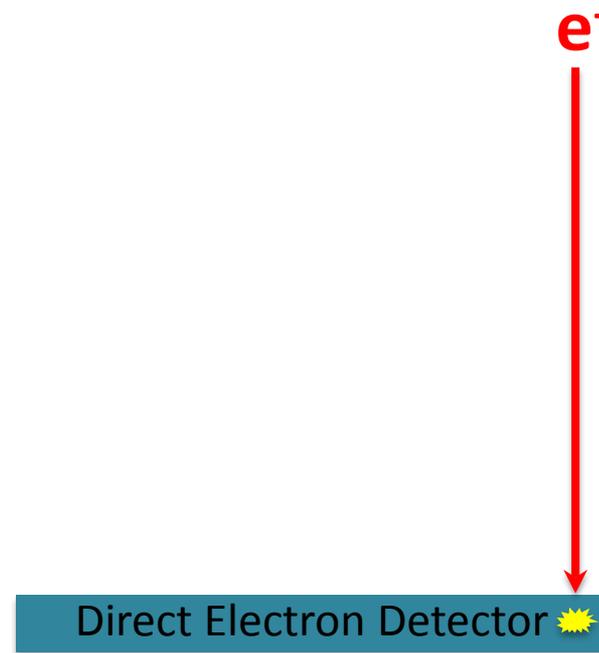


**Transfer of electrons into photons results in signal loss and blurring**

# Direct Electron Detectors: A major advance in cryo-electron microscopy imported from astrophysics



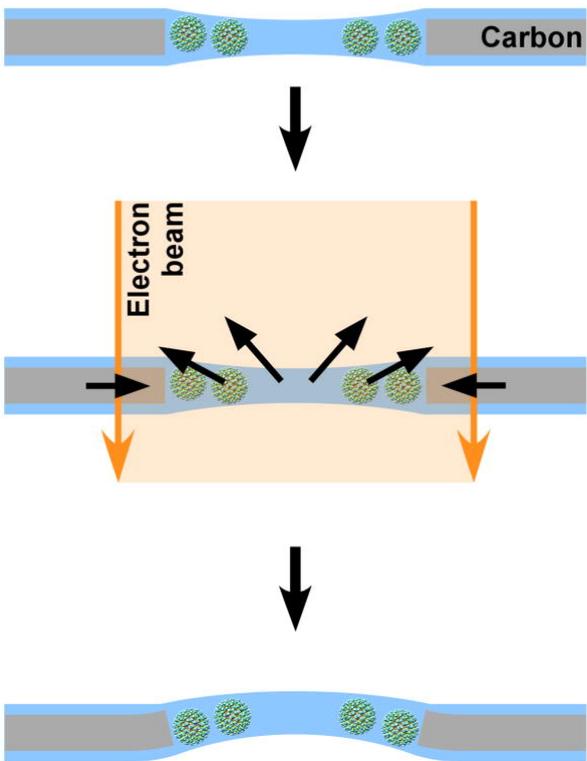
**Transfer of electrons into photons results in signal loss and blurring**



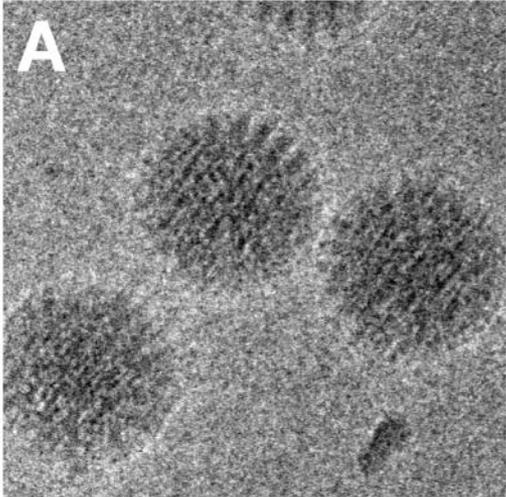
**Direct Electron Detectors eliminate these problems**

**Far fewer images are needed and atomic resolution is now possible!**

# Problem: Particles move when high-energy electron beams hit them, blurring the images

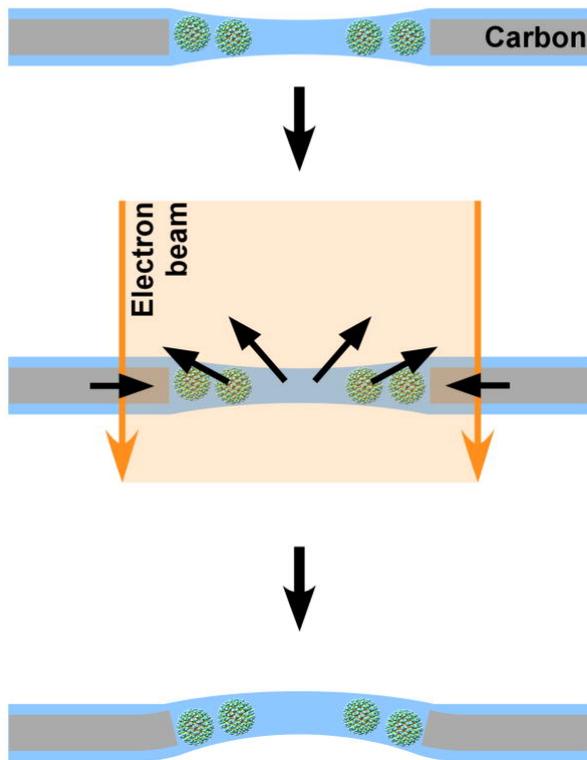


Niko Grigorieff

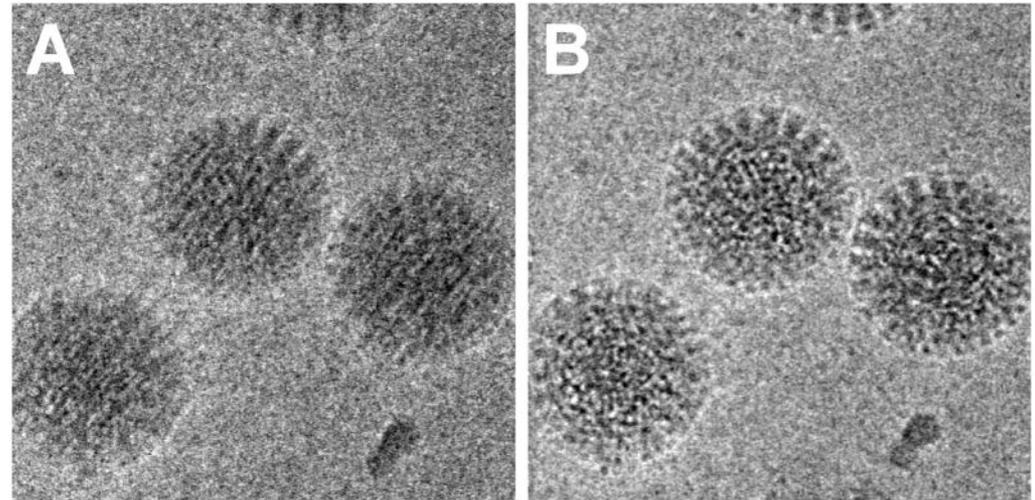


Blurry Rotavirus

# Problem: Particles move when high-energy electron beams hit them, blurring the images



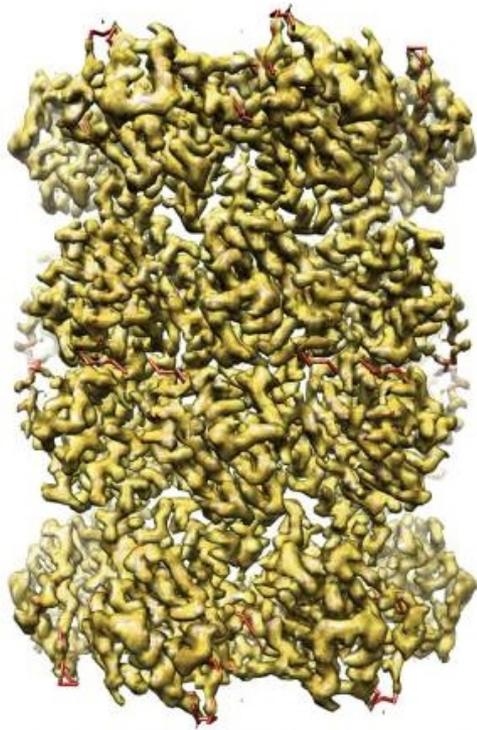
Niko Grigorieff



Blurry Rotavirus

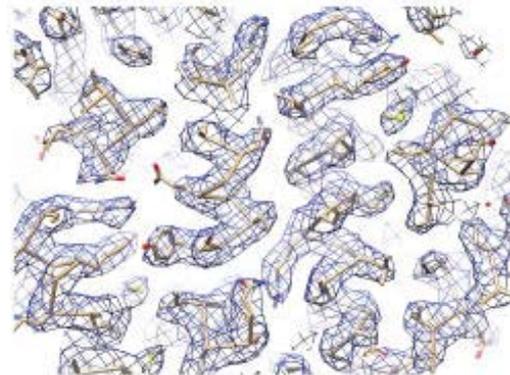
**Solution: Take movies and correct for movement**

# Yifan Cheng and David Agard showed the same approach can be used for non-symmetric particles



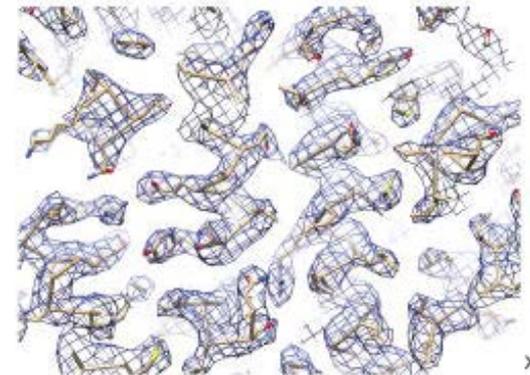
**Proteasome  
at 3.4 Å  
resolution**

**EM**



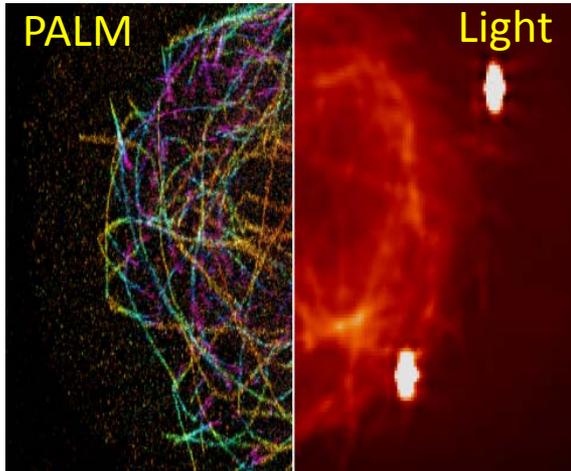
EM

**X-ray**

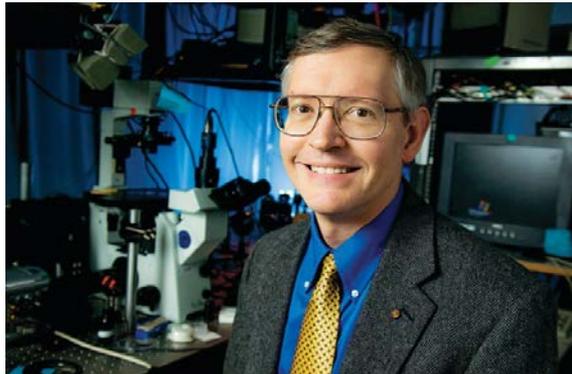


Xray

# 2014 Nobel Prize in Chemistry: Super-Resolution Fluorescence Microscopy



**Microtubules in a fruit fly cell**

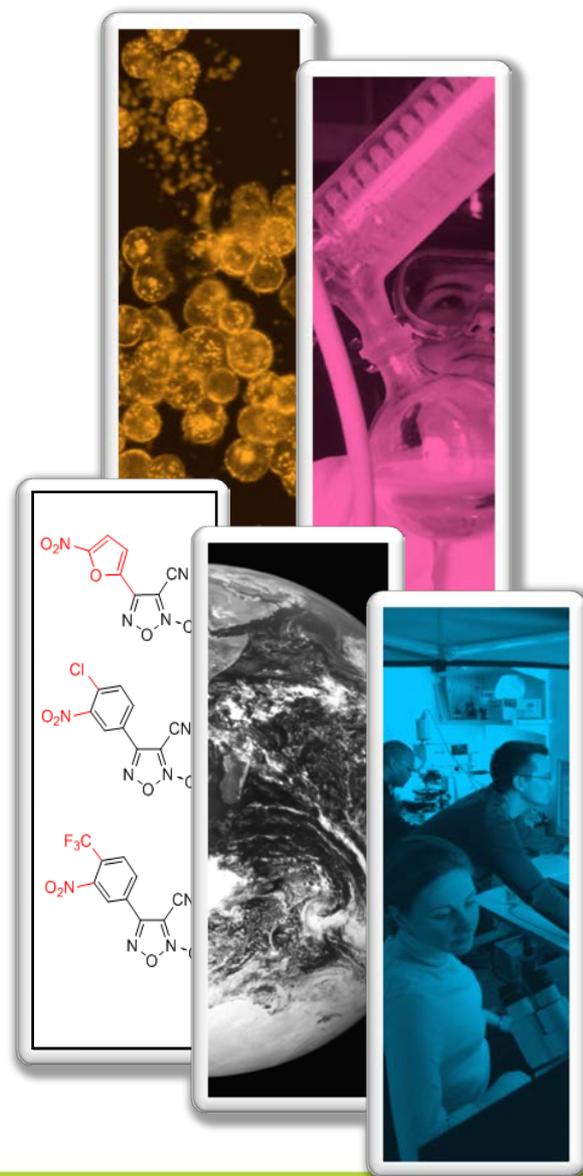


**W.E. Moerner, Stanford University**

## **Nobel Recipients: Eric Betzig, Stefan Hell and W.E. Moerner**

- Imaging at the nanometer scale, well below the diffraction limit of conventional microscopy
- Moerner: the first to detect single fluorescent molecules and to discover that fluorescent proteins can be turned on and off at will – “photoactivation”
- Photoactivation forms basis for PALM (photoactivated localization microscopy) and STORM (stochastic optical reconstruction microscopy)
- Leader in adapting super-resolution fluorescence microscopy to biological systems

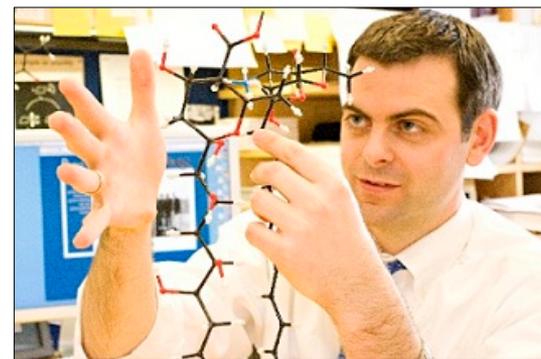
- Molecules from nature, genetically encoded for bioactivity, were once the source of all drugs
- Today natural products still account for over 50% of all drugs and remain the inspiration for many more
- Advances in the field of organic chemistry provide the ability to construct molecules nature never imagined, now providing new drugs and biological tools



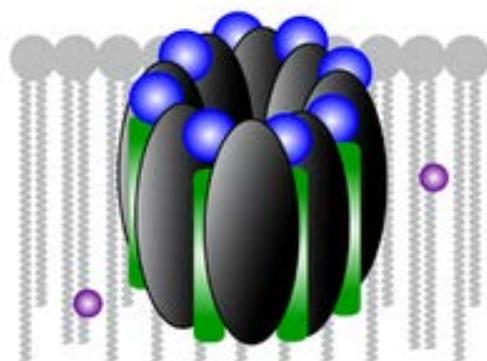


# Amphotericin is a sterol sponge

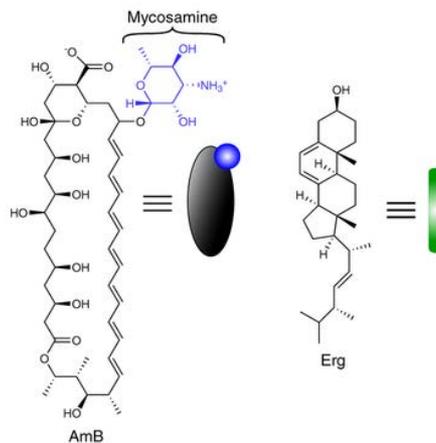
- New chemical methods for synthesizing molecules of greater complexity to probe biological function
- Revelations of how Amphotericin behaves, both in eliminating fungal infections and inducing debilitating side-effects



**Martin D. Burke, M.D. Ph.D**  
*University of Illinois at Urbana-Champaign*

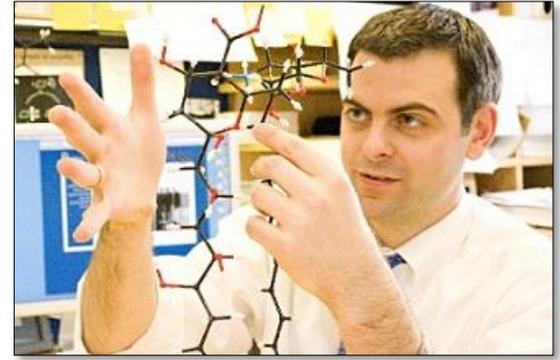


Ion channel model

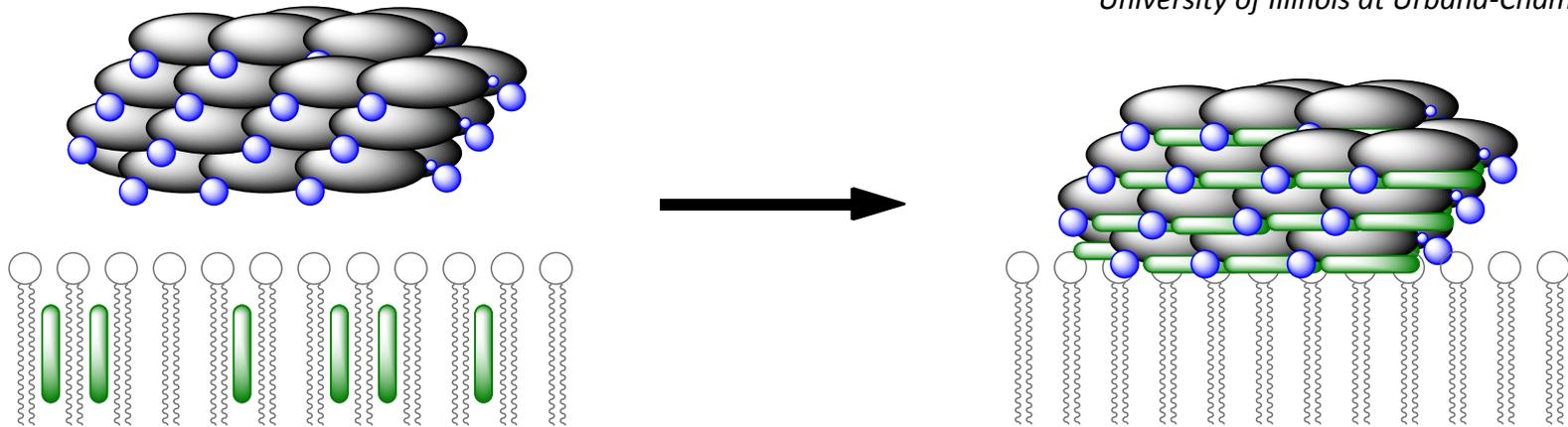


# Amphotericin is a sterol sponge

- New chemical methods for synthesizing molecules of greater complexity to probe biological function
- Revelations of how Amphotericin behaves, both in eliminating fungal infections and inducing debilitating side-effects



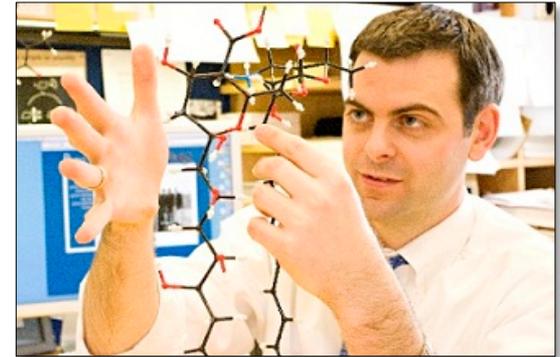
**Martin D. Burke, M.D. Ph.D**  
University of Illinois at Urbana-Champaign



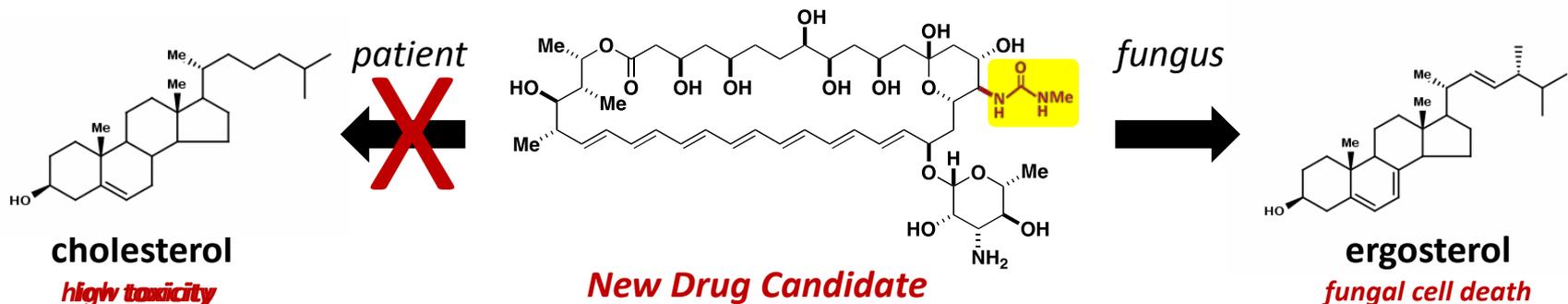
***New finding:*** Amphotericin exists primarily in the form of large, greasy aggregates that kill fungi by extracting ergosterol - their version of cholesterol - from membranes. But it also sucks cholesterol out of human cell membranes, which is why it is toxic.

# Amphotericin is a sterol sponge

- New chemical methods for synthesizing molecules of greater complexity to probe biological function
- Revelations of how Amphotericin behaves, both in eliminating fungal infections and producing debilitating side-effects
- Selective new molecule with preferential binding of **ergosterol** (*vital for fungal cell survival*) over **cholesterol** (*critical for human health*).
- **Tested in small animals and soon headed into clinical testing for treatment of fungal infections without Amphotericin's toxicity**



**Martin D. Burke, M.D. Ph.D**  
University of Illinois at Urbana-Champaign



# Aimee Shen at the University of Vermont is elucidating the fundamental mechanisms of bacterial development in order to find weak links in *C. difficile's* armor



Aimee Shen



R00 GM092934  
R01 GM108684  
COBRE P20 GM103496

# CLOSTRIDIUM DIFFICILE



**250,000**

INFECTIONS PER YEAR



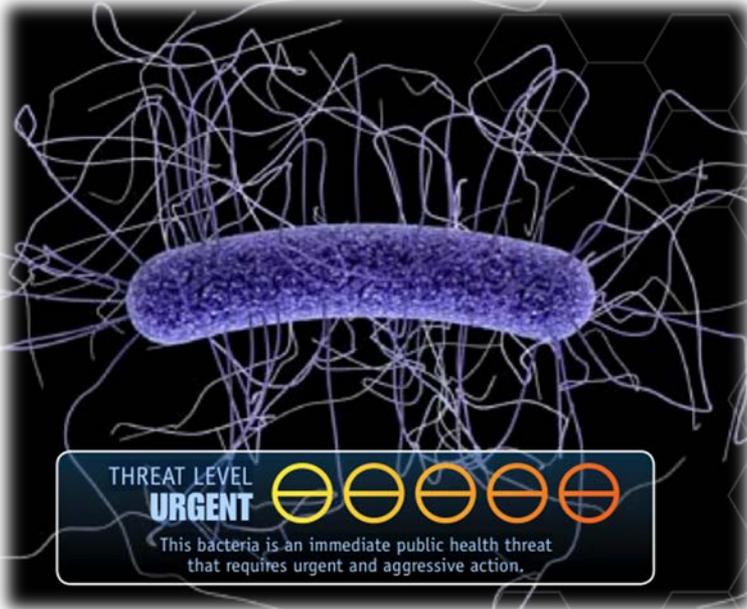
**14,000**

DEATHS



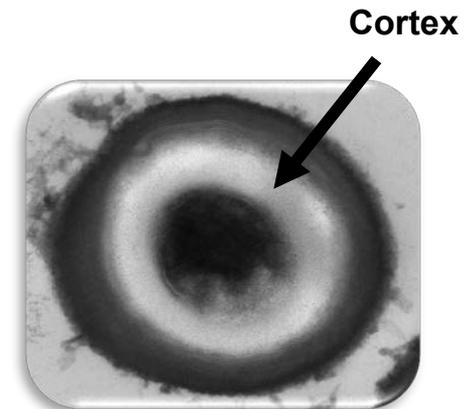
**\$1,000,000,000**

IN EXCESS MEDICAL COSTS PER YEAR

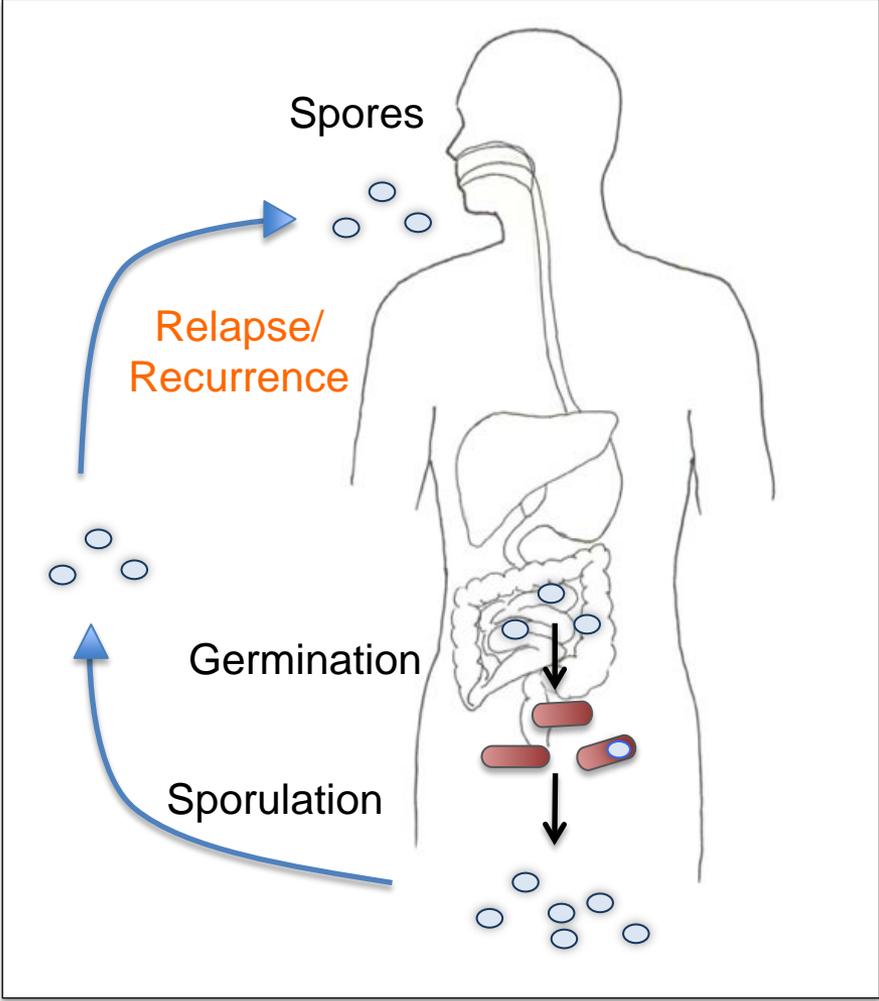


- Antibiotic resistant, spore-forming obligate anaerobe
- Spores are essential for disease transmission and recurrence

Germination



*C. difficile* spore





# Areas of Clinical Interest

**Anesthesiology**

**Burn**

**Peri-operative injury and pain**

**Sepsis**

**Trauma**

**Wound healing**

# Areas of Clinical Interest

**Anesthesiology**

**Burn**

**Peri-operative injury and pain**

**Sepsis**

**Trauma**

**Wound healing**

# Protocolized Care for Early Septic Shock: ProCESS



**Derek Angus  
Donald Yealy  
John Kellum  
Amber Barnato  
Et al.**

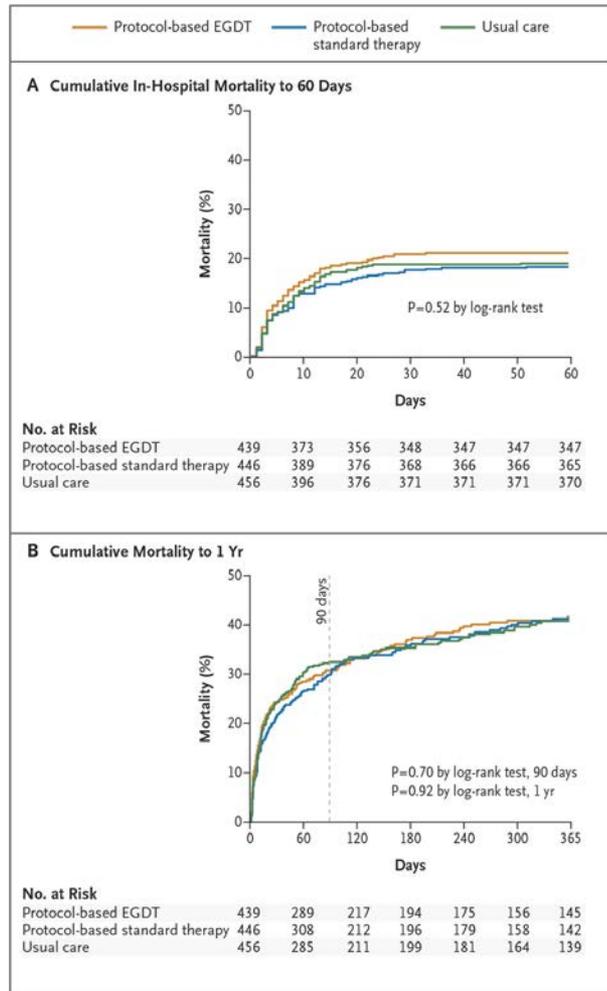
**31 E.D.s**

**1341 patients**

# ProCESS Design

- Inclusion Criteria
  - 18 years of age, suspected infection, two or more SIRS criteria, refractory hypotension
- Treatment Arms
  - Early Goal Directed Therapy, Protocolized Standard Care, Usual Care
- Primary Outcome Measure
  - Hospital Mortality
- Secondary Outcome Measures
  - Changes in markers of inflammation, oxidative stress, cellular hypoxia, coagulation/thrombosis

# ProCESS Results



No significant differences in 60-day or 1-year mortality, or the need for organ support.

No significant mortality or morbidity advantage from protocol-based resuscitation over bedside care that was provided according to the treating physician's judgment.

**No significant benefit from the mandated use of central venous catheterization and central hemodynamic monitoring in all patients.**



National Institute of  
General Medical Sciences



# Questions or Comments?

