

Molecular Mechanisms of Antibiotic Action on the Ribosome

PI: Alexander Mankin (UIC)

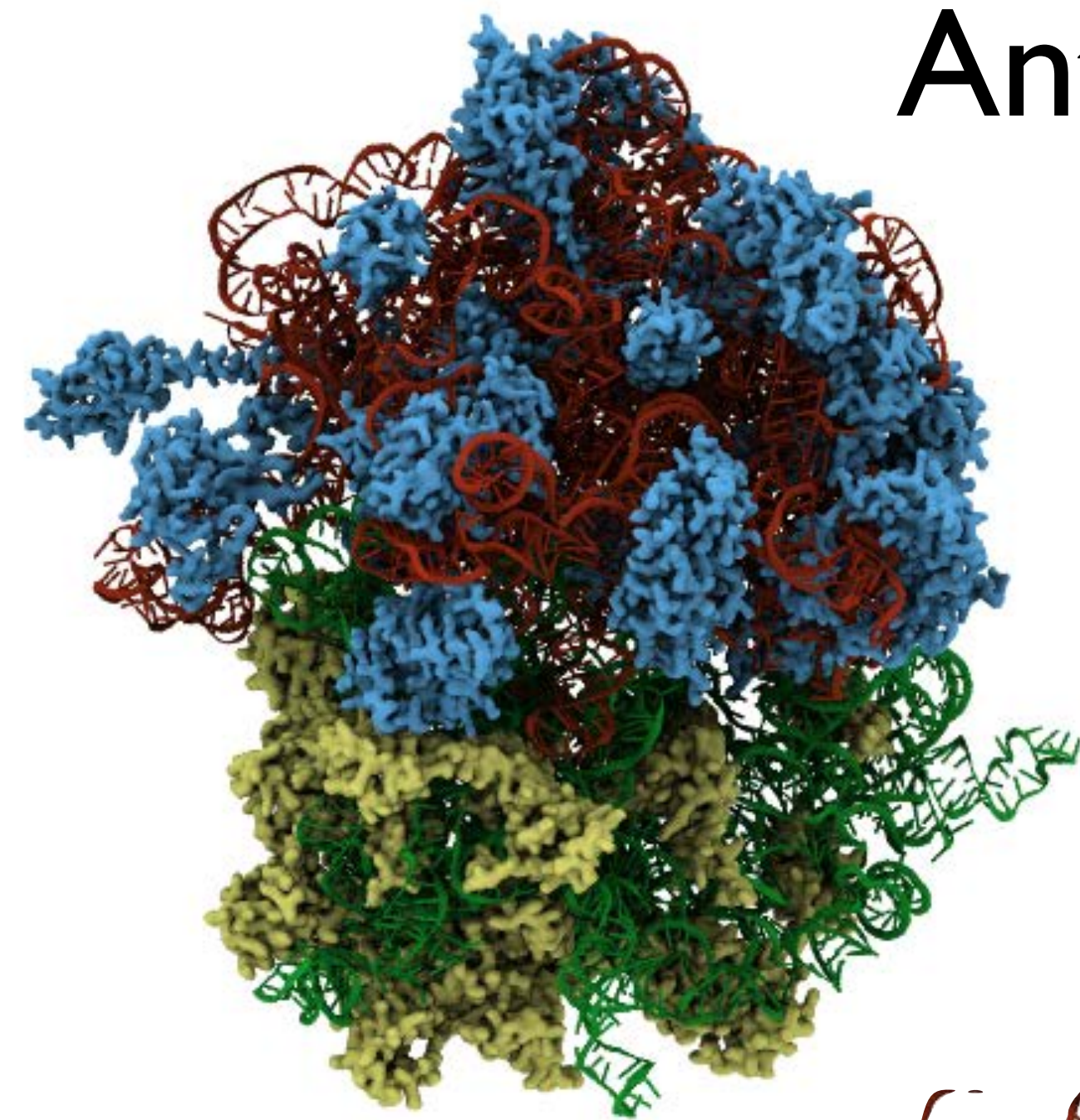
co-PI: Klaus Schulten (UIUC)

Presenter: Bo Liu (UIUC)

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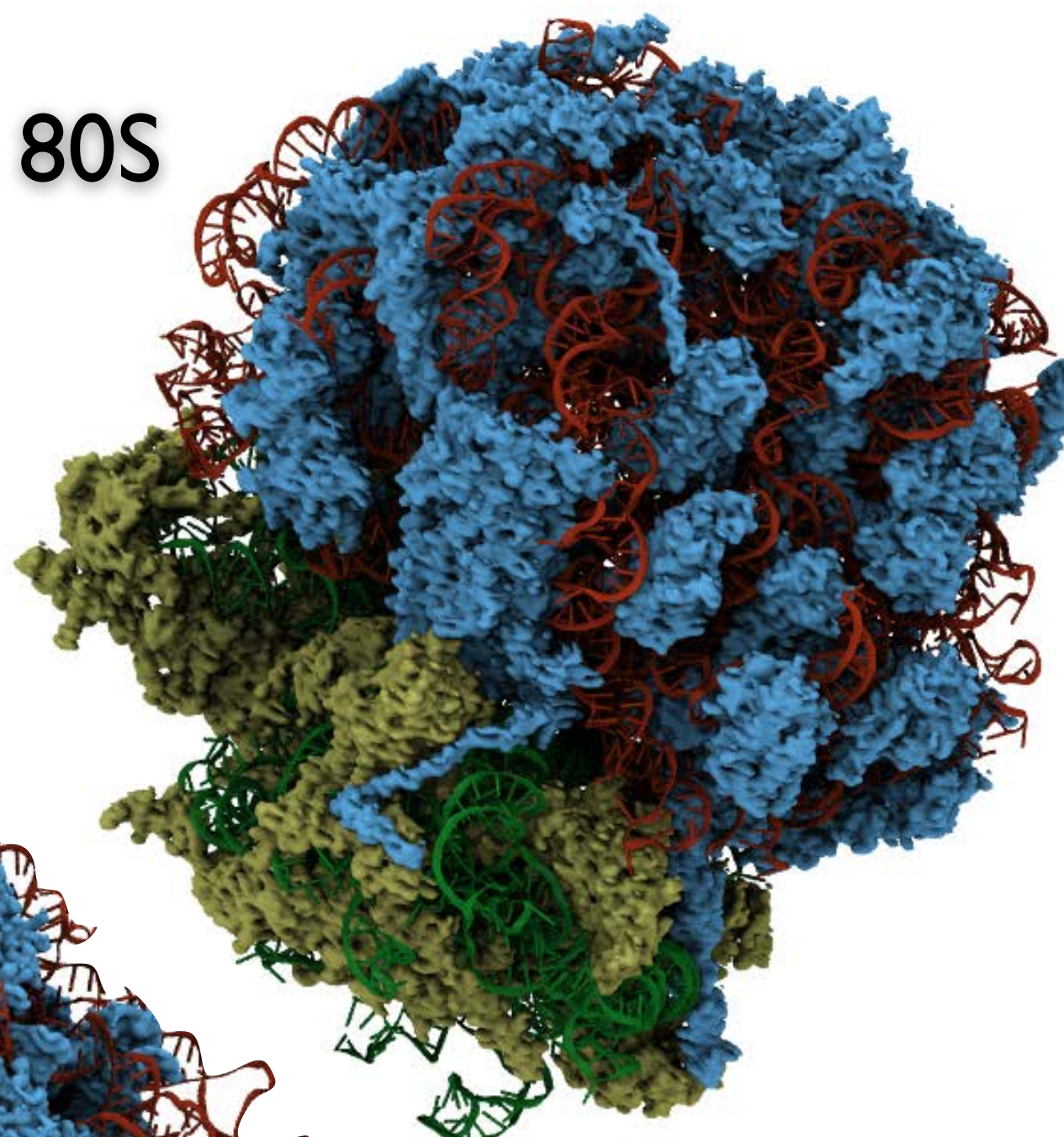
Allocation granted by the Great Lakes Consortium for Petascale Computation

Antibiotics-ribosome simulations on Blue Waters

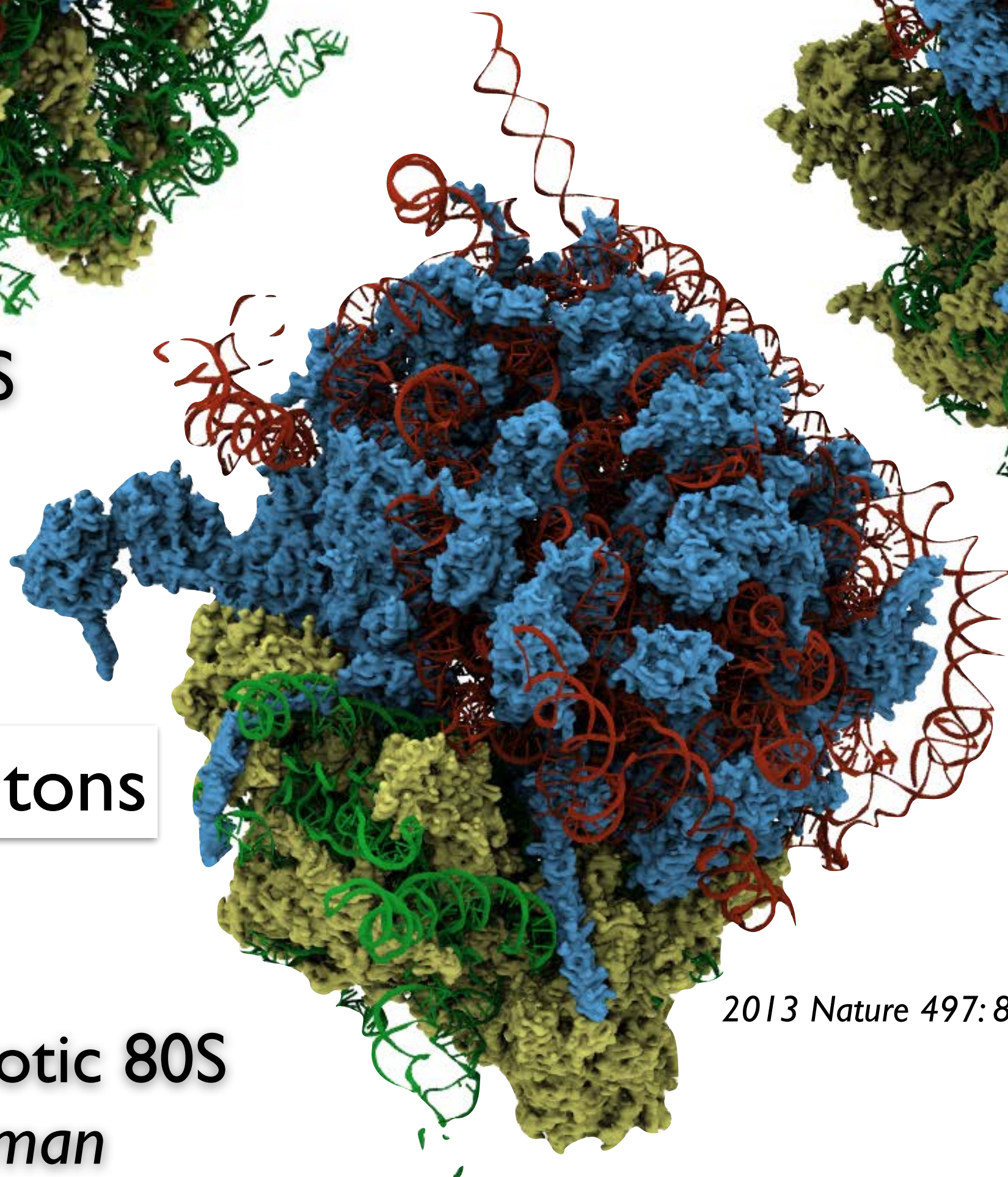


bacterial 70S
E. coli.

eukaryotic 80S
yeast



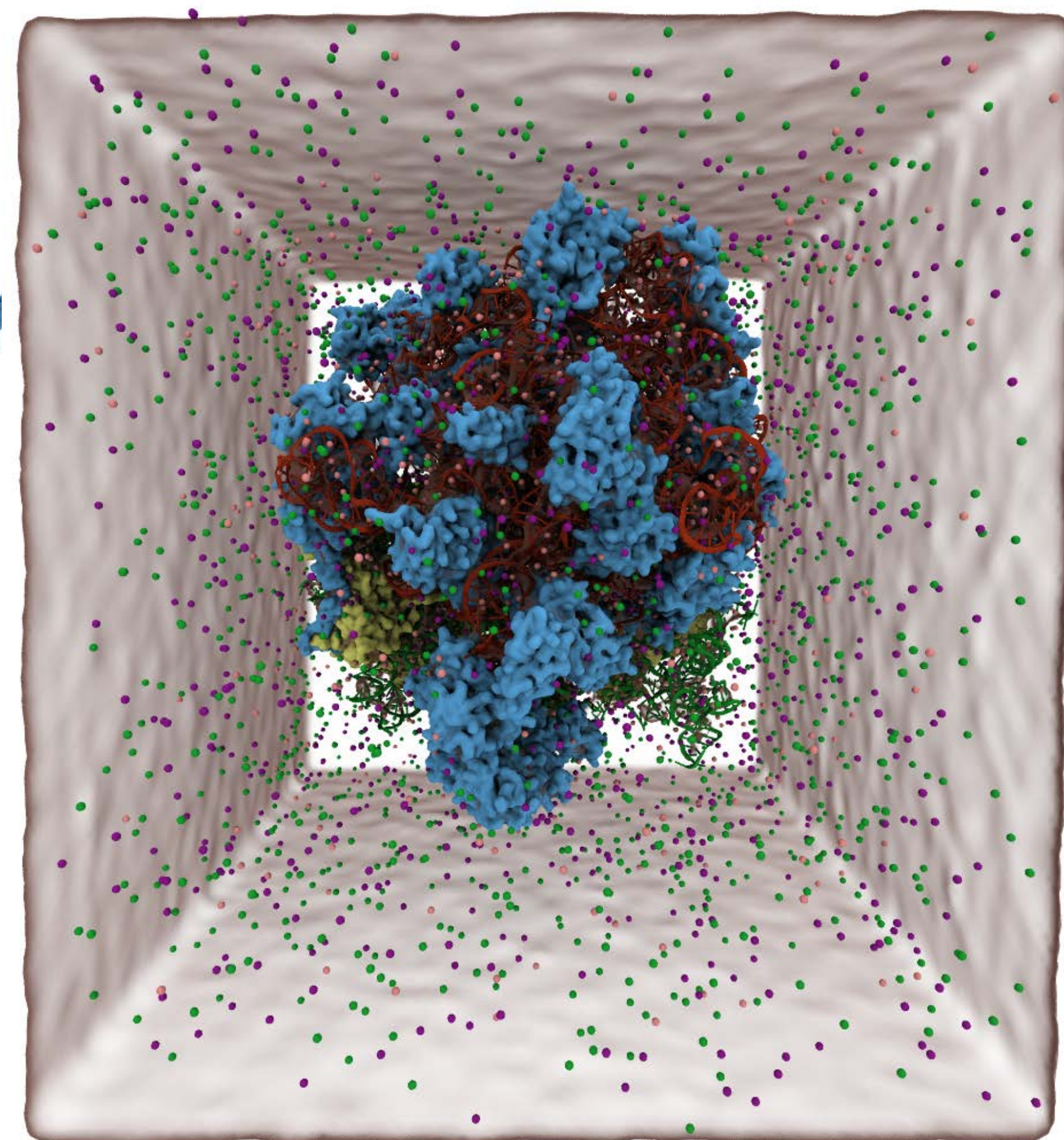
2011 *Science*
334: 1524-1529



2013 *Nature* 497: 80-85

eukaryotic 80S
human

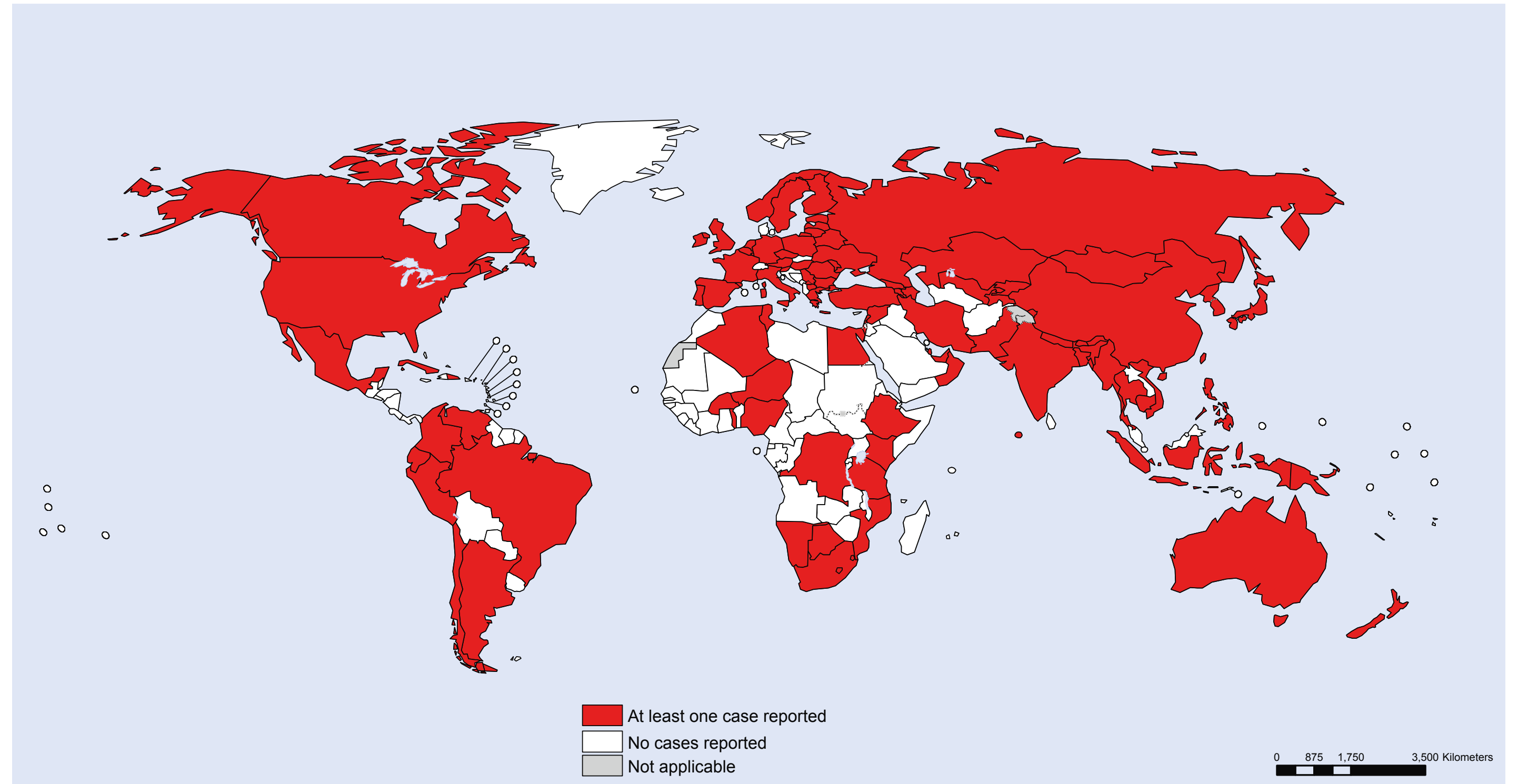
2.5~3.0M daltons



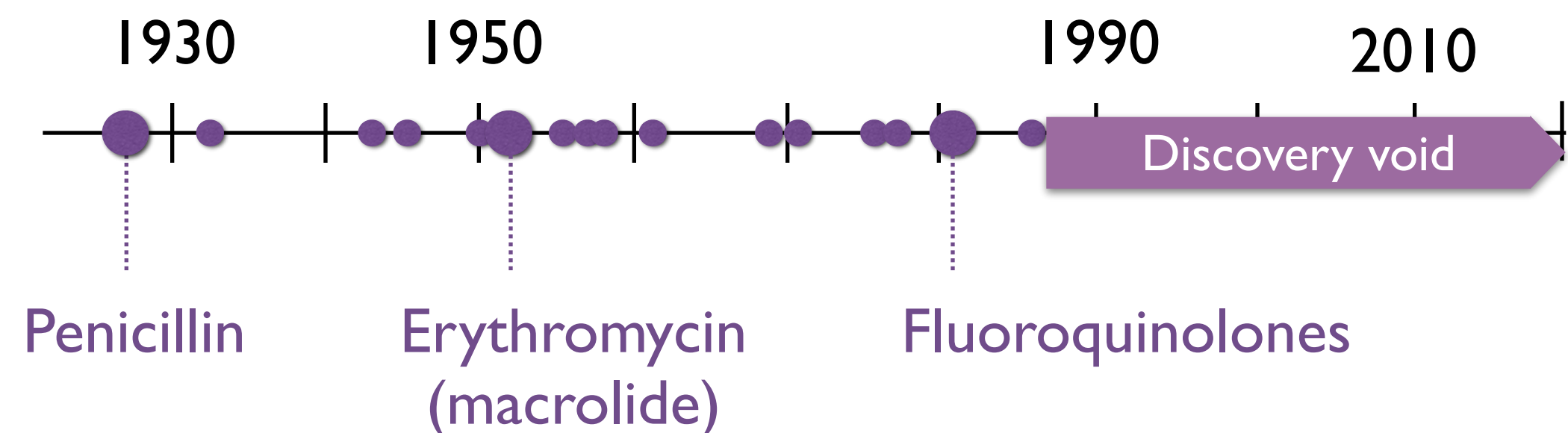
up to 5.0M atoms, microsecond
MD simulations on Blue Waters

The global crisis of antibiotic drug resistance

“A post-antibiotic era - in which common infections and minor injuries can kill”



multi-drug resistance by 2012 (TB case)



Most antibiotic drugs are bacterial protein synthesis inhibitors

the macrolide drugs

Erythromycin

- longest service time
- widely-prescribed
- drug-resistance



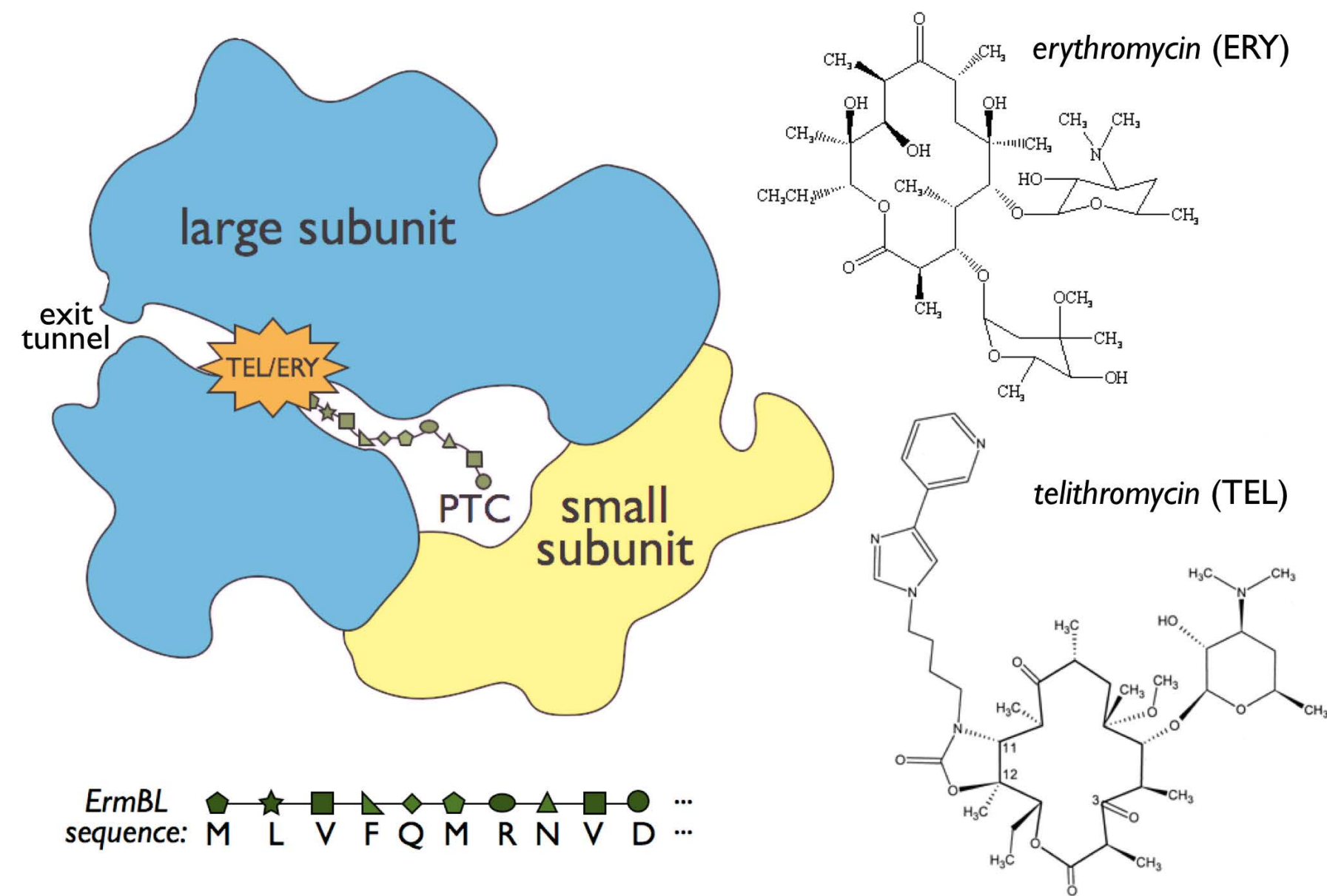
Telithromycin

- newest generation macrolide
- more effective
- no drug-resistance, yet.

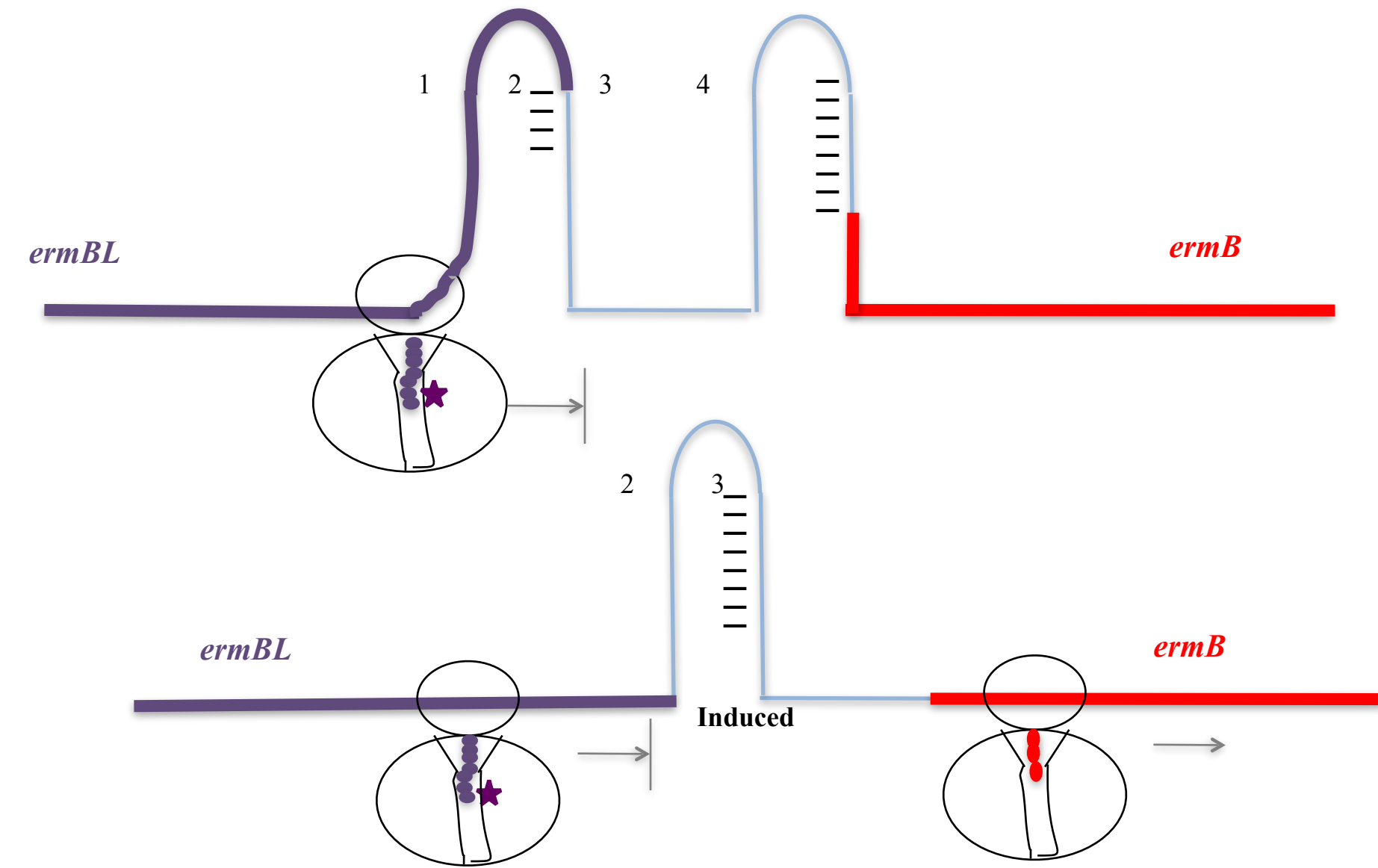
Macrolides (antimicrobial spectrum wider than penicillin) treat infections by Gram-positive bacteria, such as respiratory tract and soft-tissue infections

Mechanisms of antibiotic action on the ribosome

the macrolide myth



ERY/TEL inhibit ribosomal translation



certain stalling sequences lead to drug resistance

suggested mechanisms of antibiotic action

- nascent protein has to be present to stall translation?
- macolide acts on ribosome directly (disables ribosome)?!

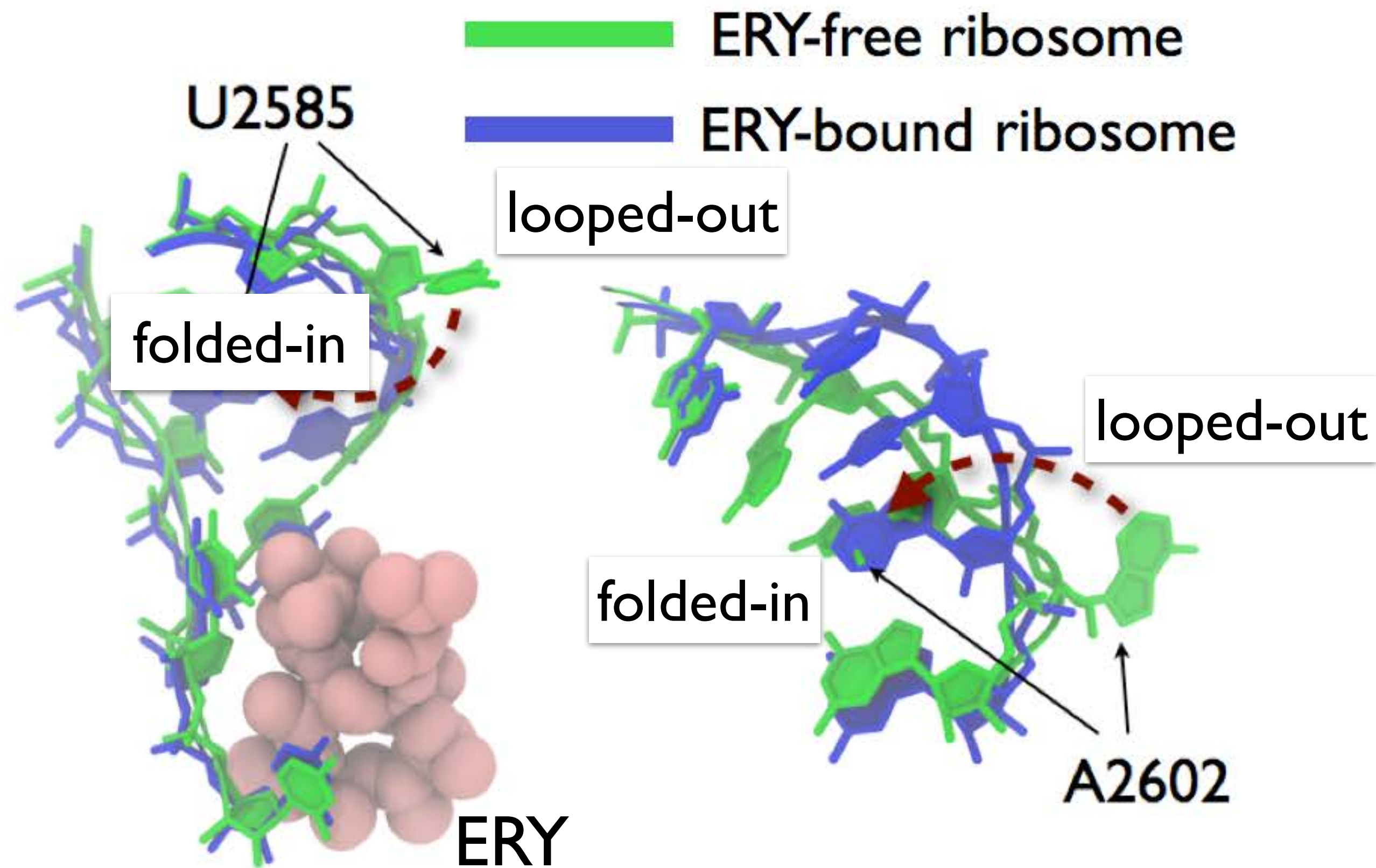
1975 PNAS 72: 2649-2652
 1982 Anti.Ag. Chem. 21: 810-818
 2001 Nature 413: 814-821
 2002 Mol. Cell 10: 117-128

2003 J. Mol. Biol. 330: 1005-1014
 2006 J. Bio. Chem. 281: 6742-6750
 2008 Mol. Cell 30: 190-202

Question 1:

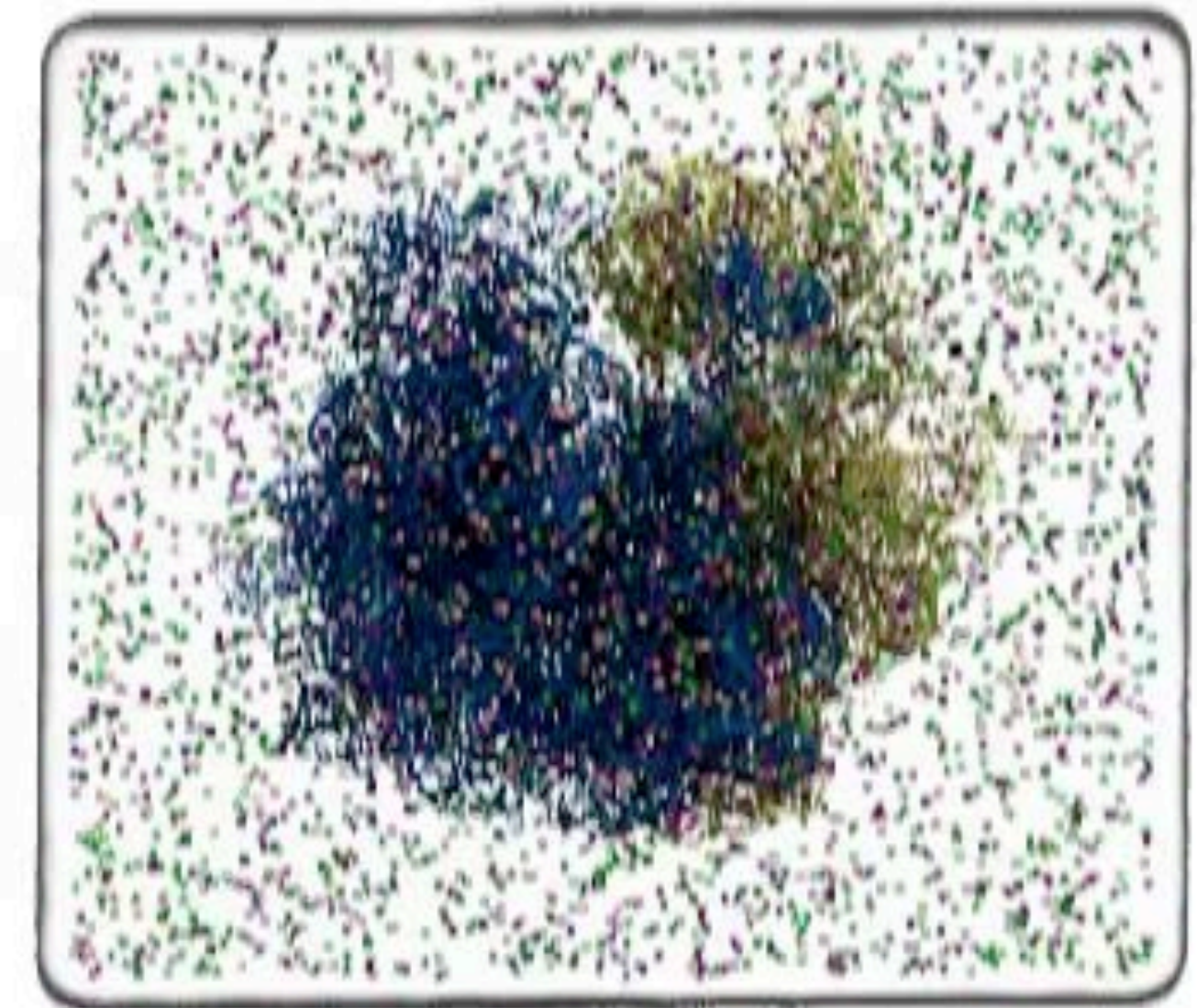
Does macrolide act on the bacterial ribosome without the presence of a nascent protein ?

Macrolide antibiotics allosterically predispose the ribosome *revealed by joint efforts of biochemical experiments and BW simulations*



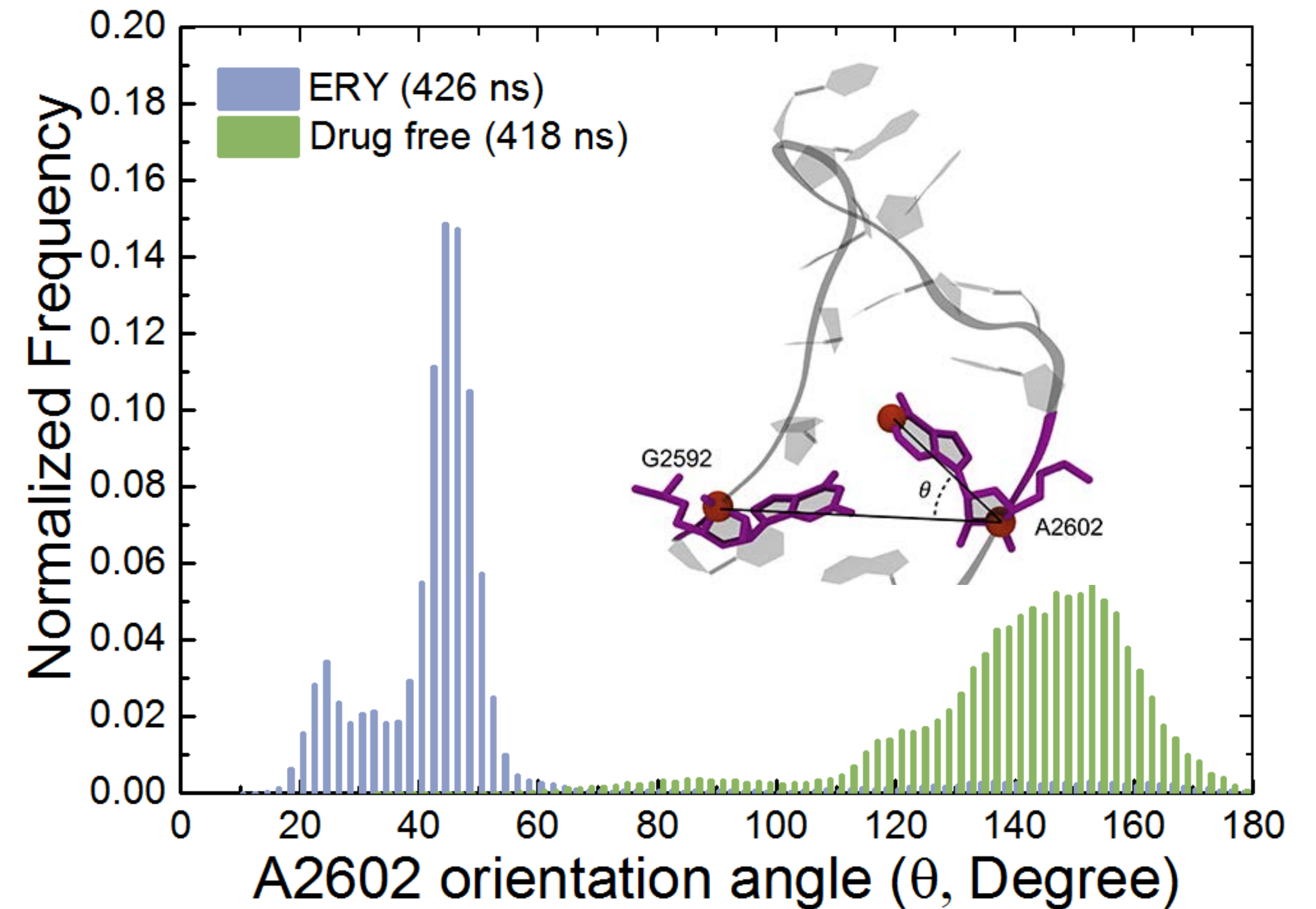
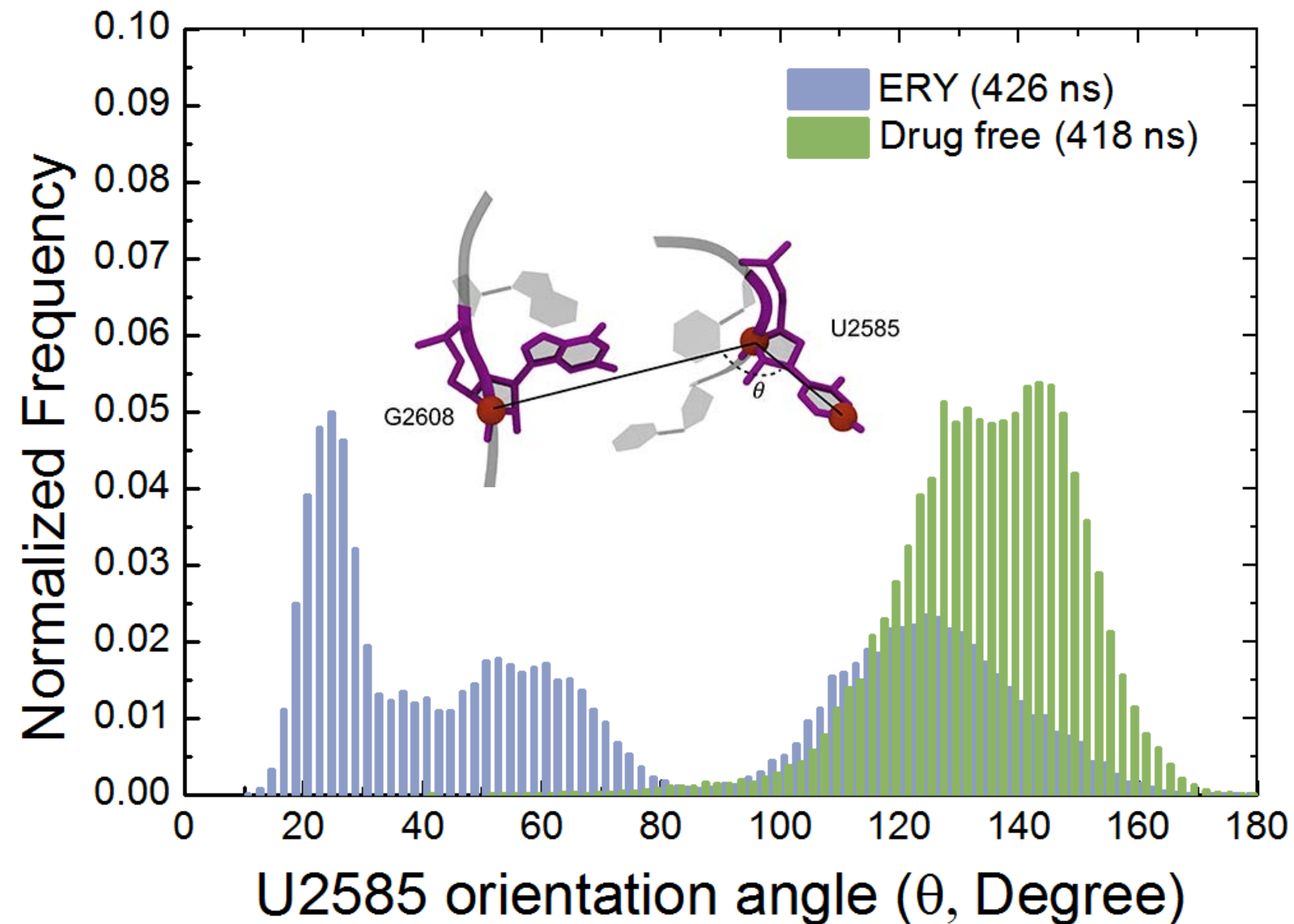
ERY can predispose an empty ribosome.

1991 PNAS 88(9):3725-3728
1997 J. Mol. Biol. 266:40-50
2010 Jin et al. PNAS Early edition



2014 PNAS, minor revision submitted
Collaborators: the Schulten lab (UIUC)

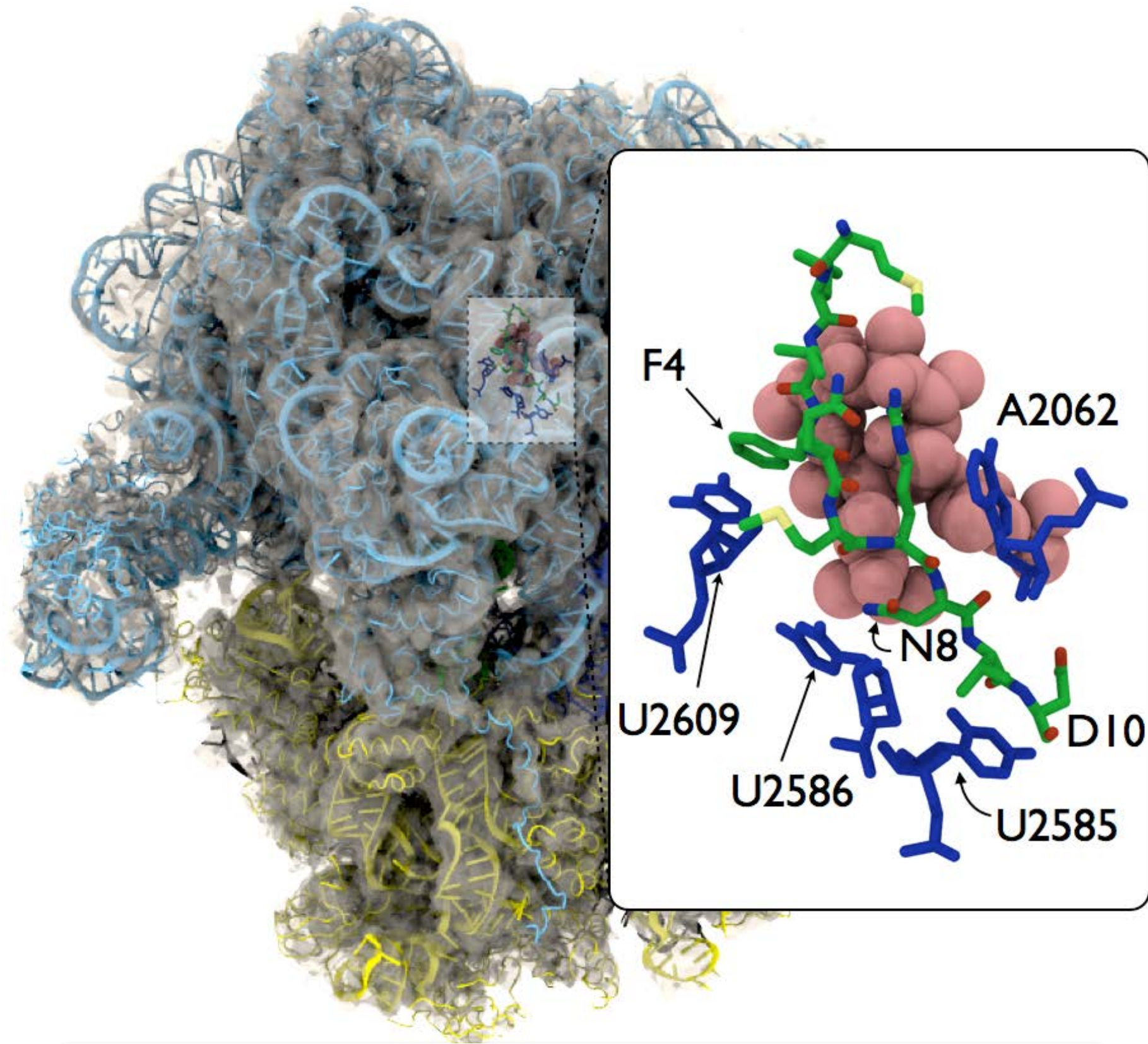
Macrolide antibiotics allosterically predispose the ribosome *revealed by joint efforts of biochemical experiments and BW simulations*



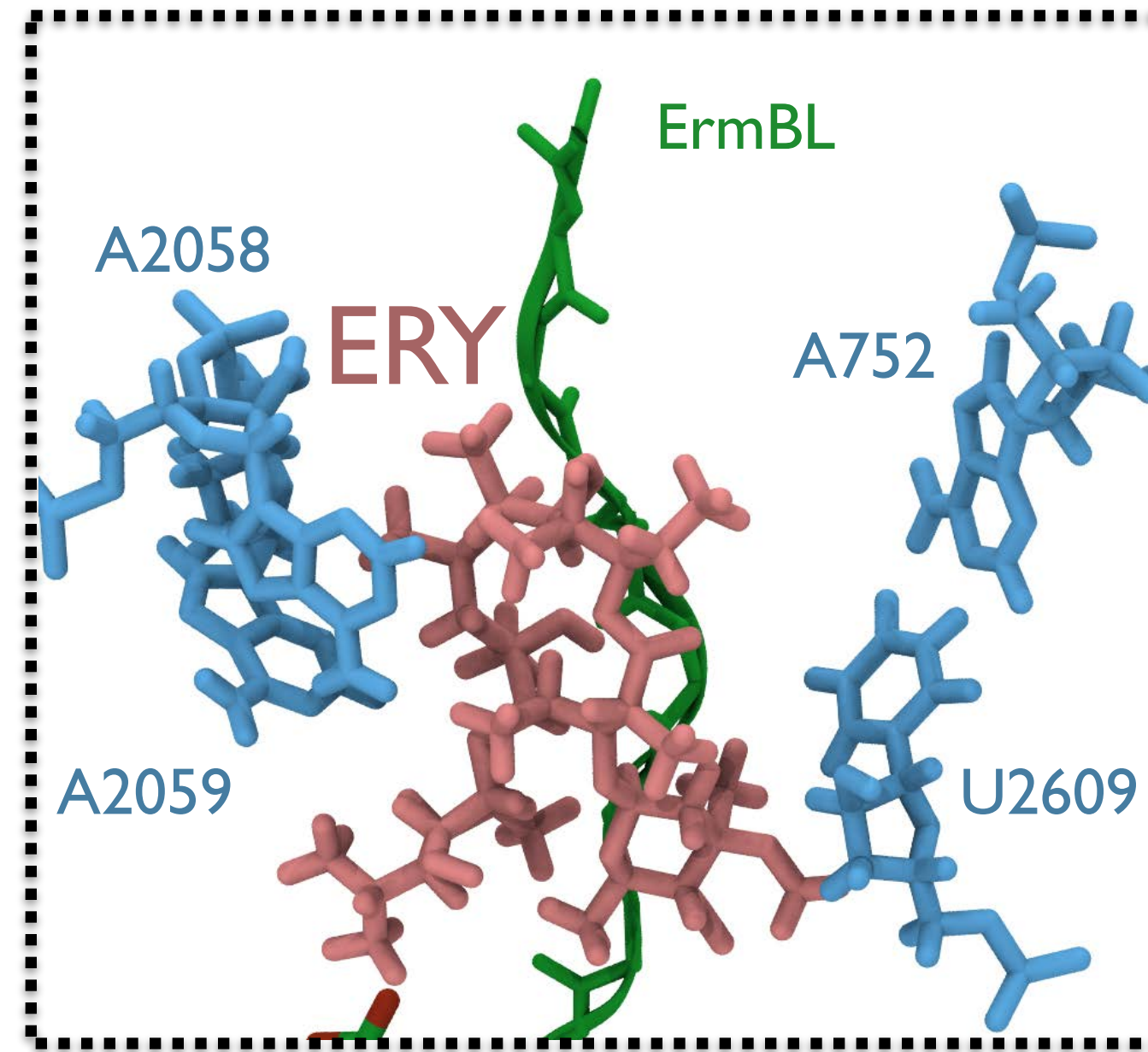
Question 2:

What is the role of nascent proteins in regulating antibiotic action?

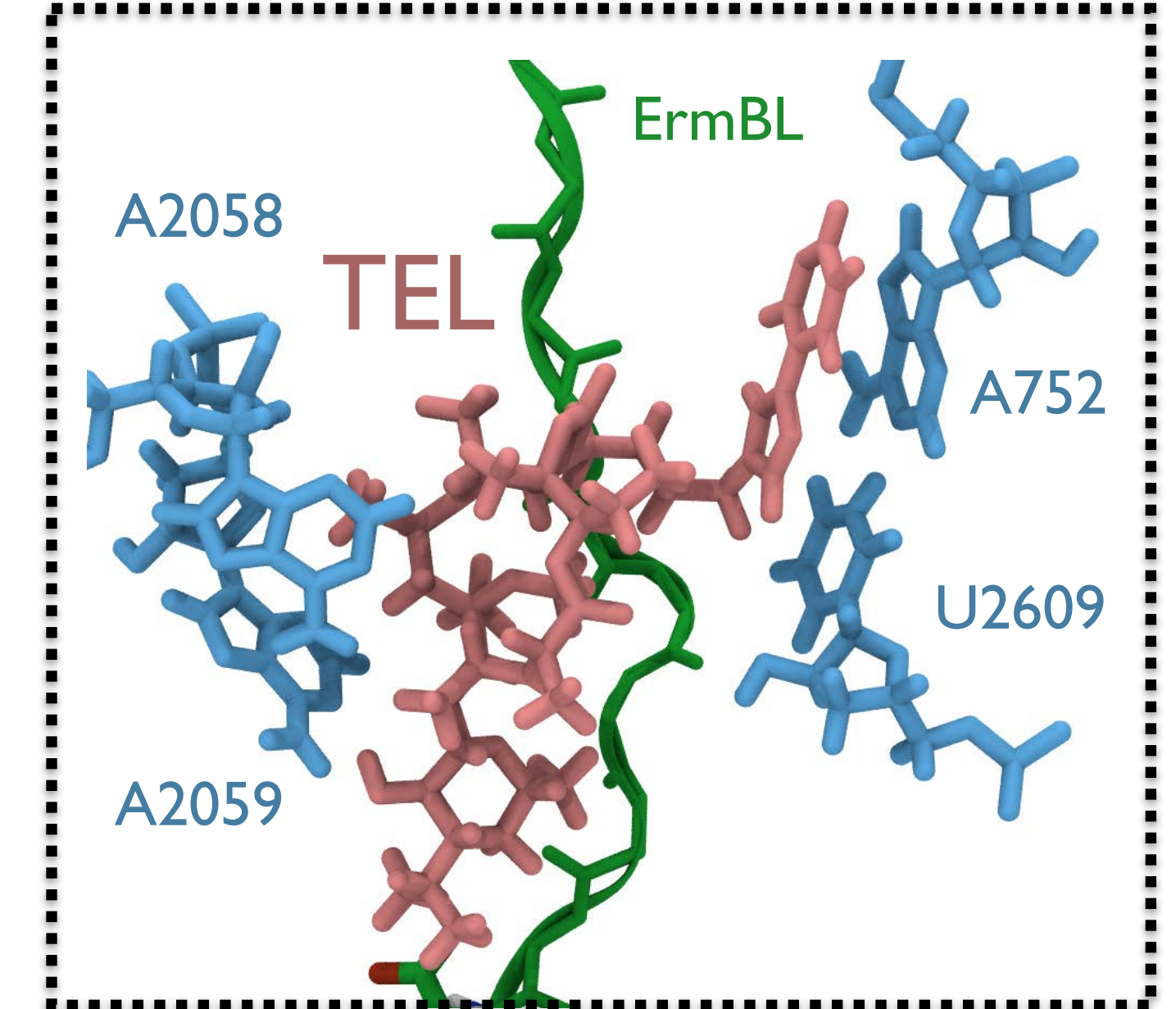
Nascent protein mediated ribosome stalling with antibiotics



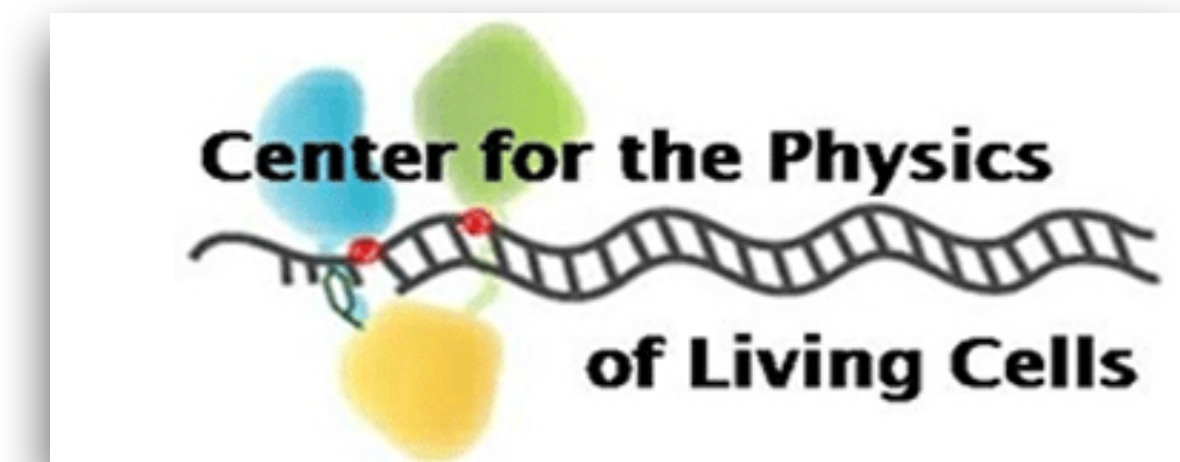
an atomic structure solved by the molecular dynamics flexible fitting (MDFF) method



macrolide binding site



Acknowledgement



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