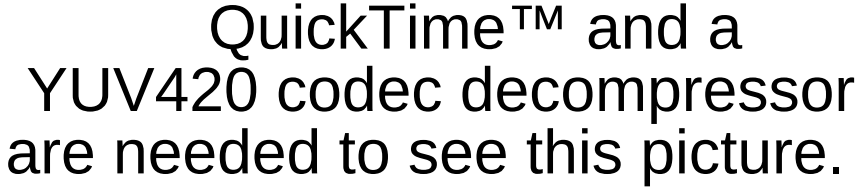
Molecular Design

- Develop accurate computational methods for predicting structures of biological macromolecules and complexes
  - Characterize Nature's energy capture and conversion mechanisms in detail
- Design new world of macromolecules with new functions:
  - Enzymes to catalyze novel chemistry
  - Vaccines for HIV and other diseases
  - Novel endonucleases for gene therapy and fighting malaria
  - Inhibitors of pathogen entry and function
  - New biofuels and carbon fixation pathways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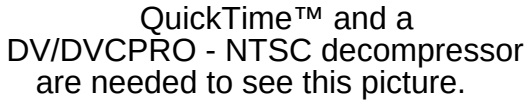
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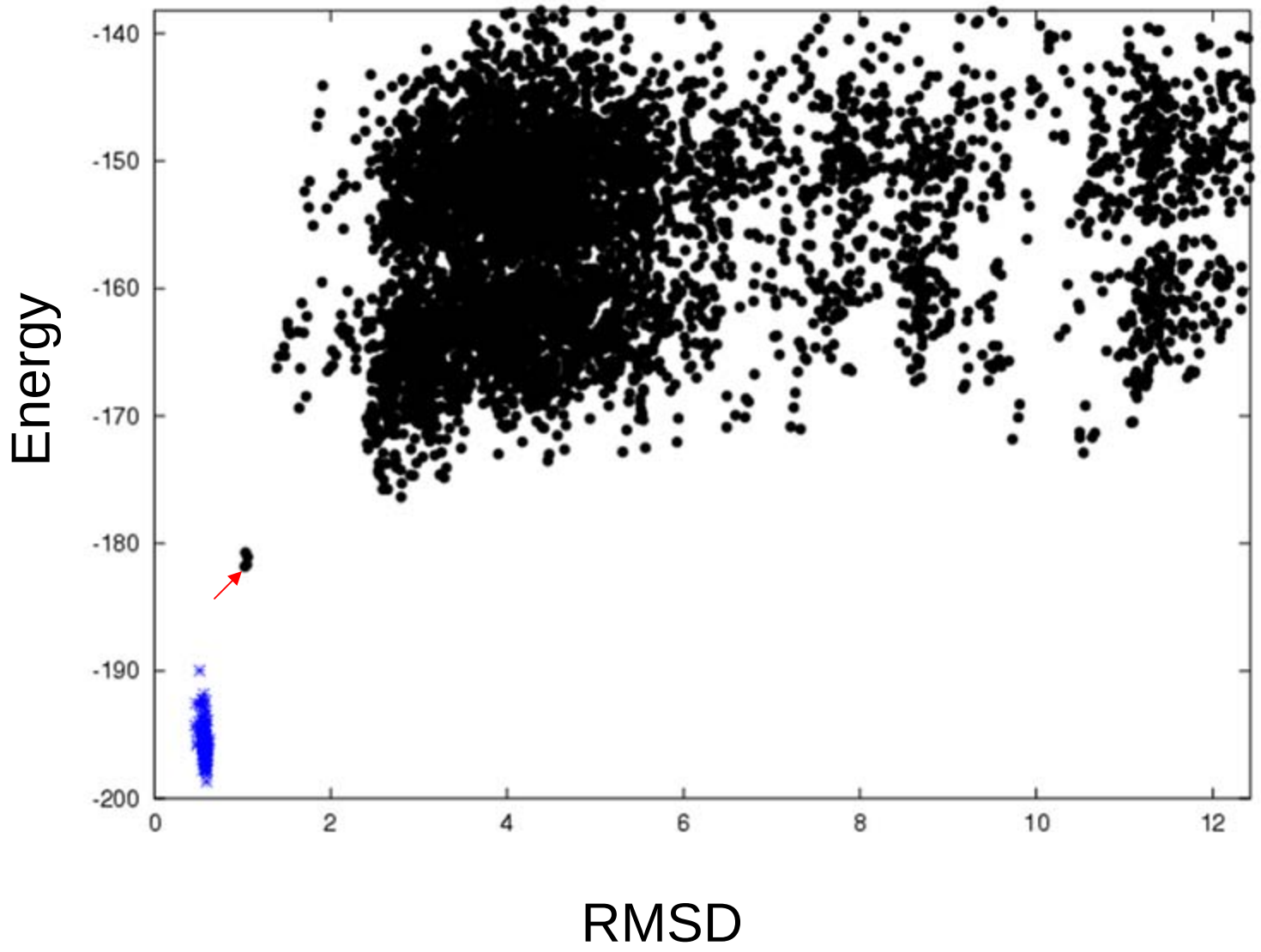
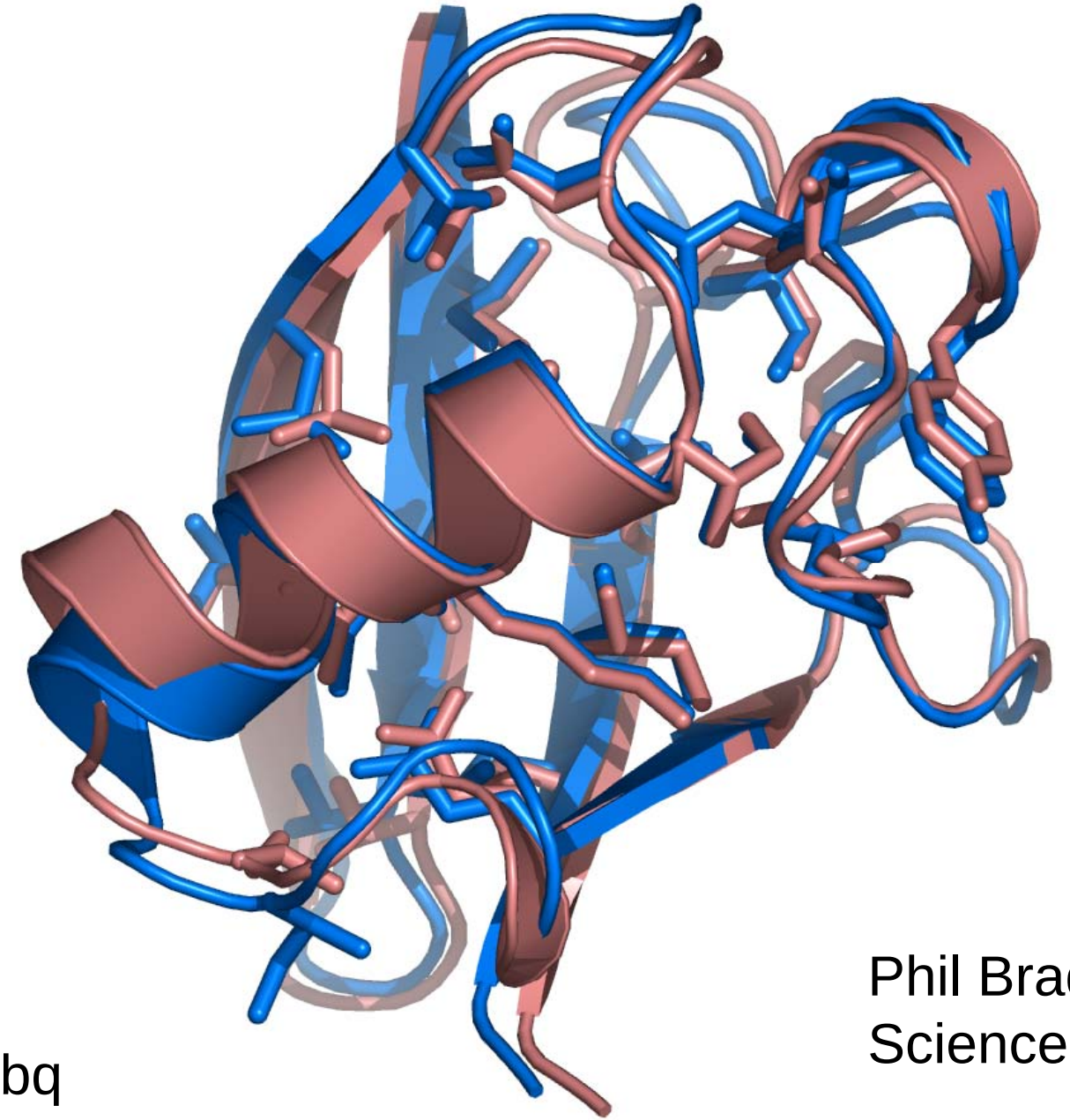
Lowest energy structures sampled on independent trajectories





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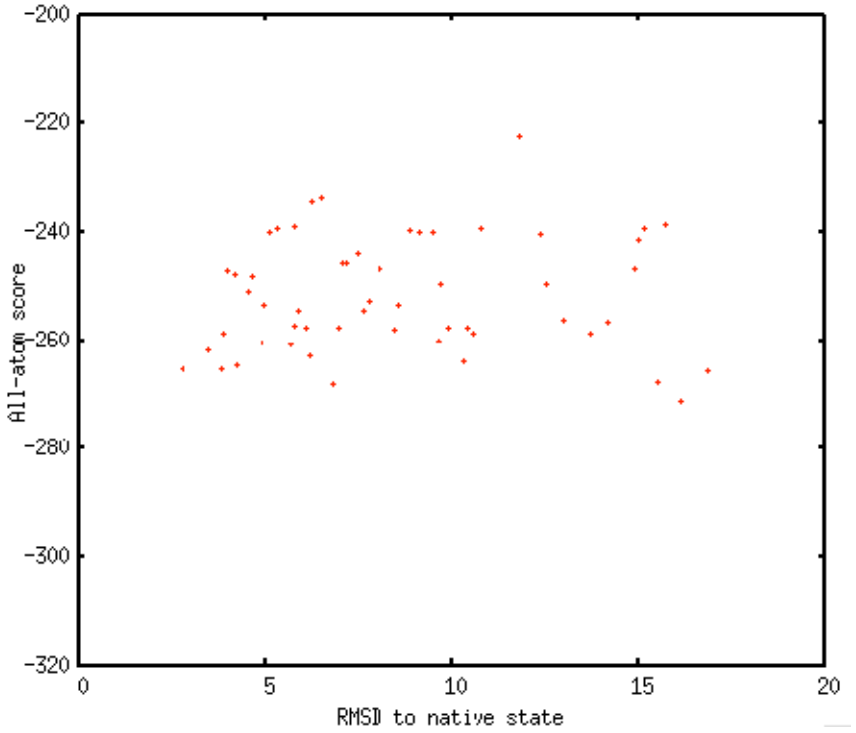
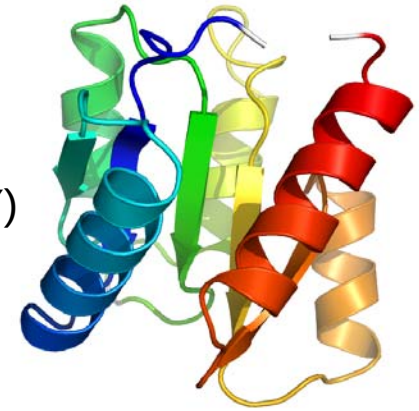
Phil Bradley
Science 2005

Extensive conformational sampling with Rosetta@Home



Native (CheY)



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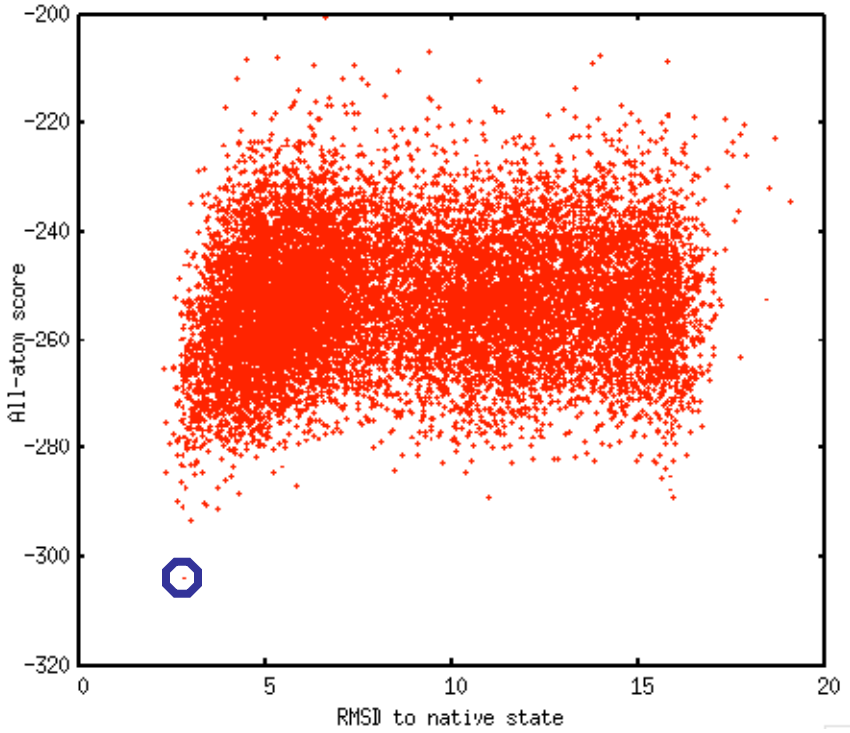
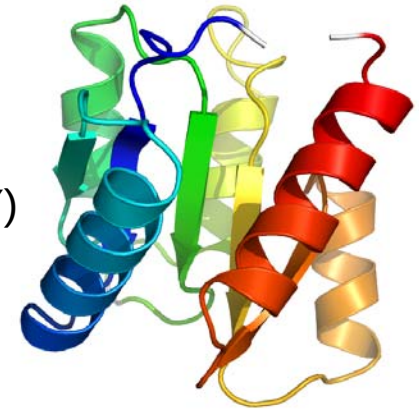


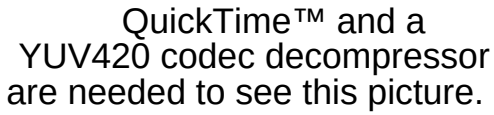
Native (CheY)



Lowest energy Rosetta structure

Architect of [Rosetta@home](): David Kim

Protein Design


QuickTime™ and a
YUV420 codec decompressor
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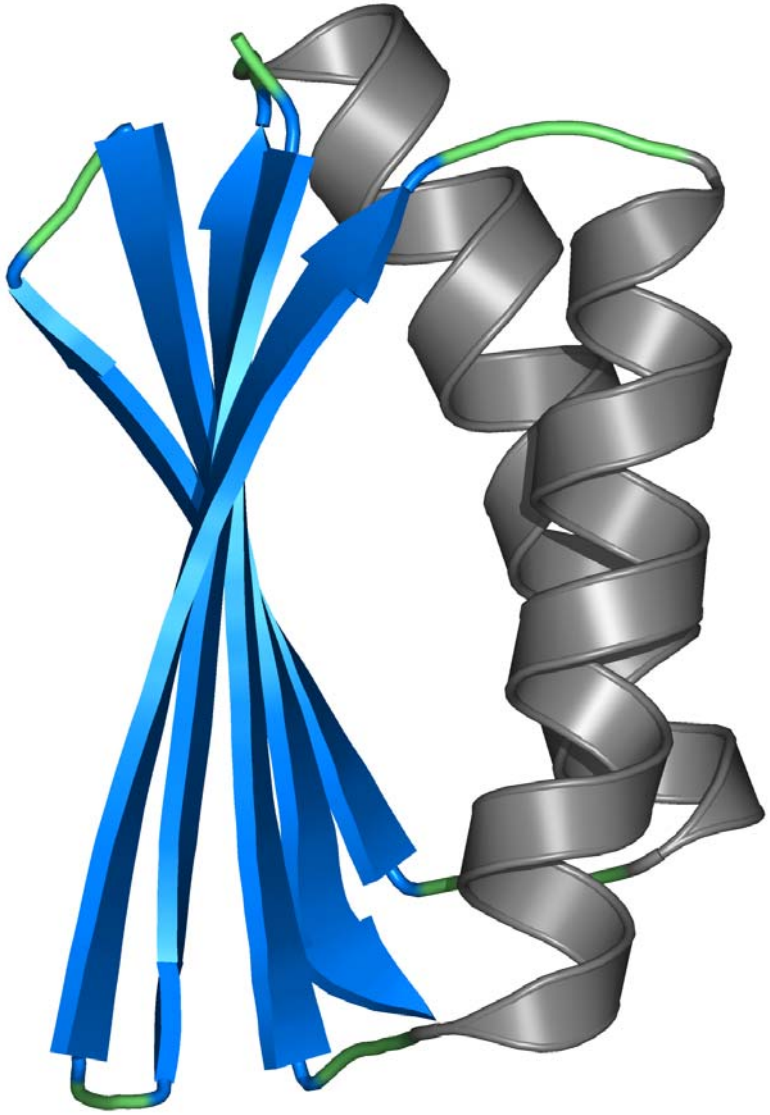
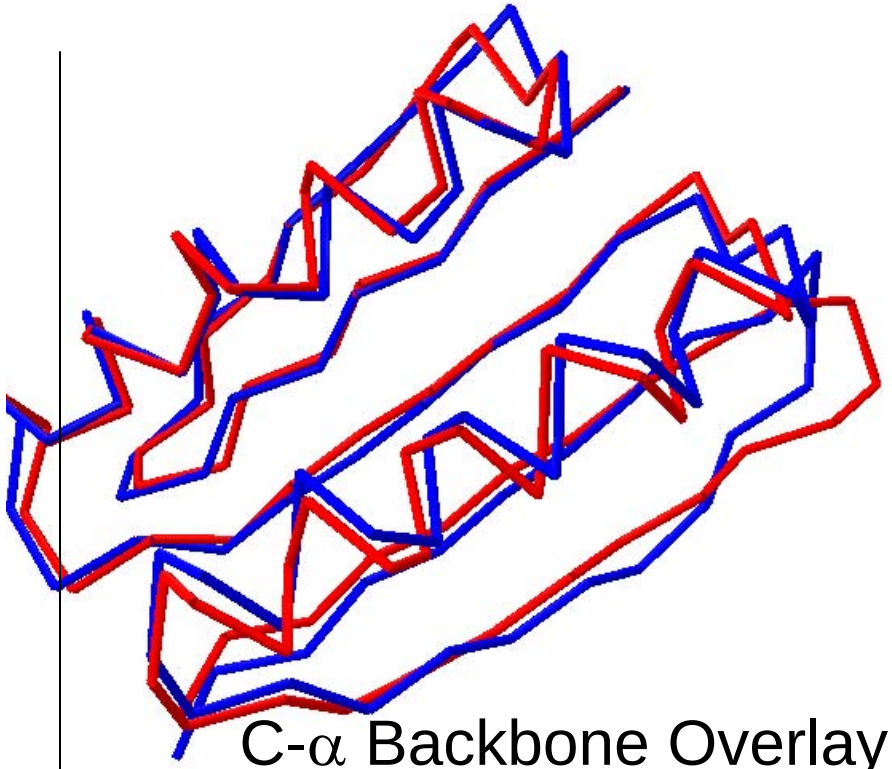
Top7 X-ray structure has correct topology. Backbone RMSD to design only 1.2Å





C-α Backbone Overlay

Red : X-ray structure

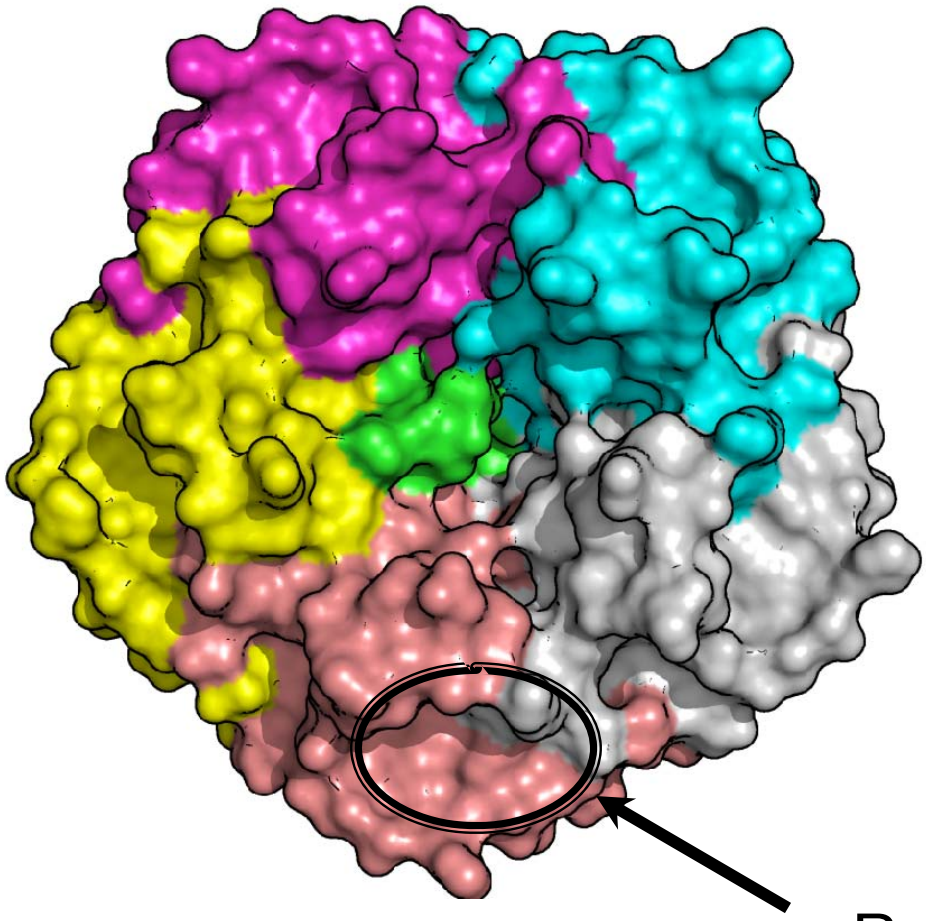
Blue : Design model

Brian Kuhlman, Gautam Dantas; Science 302 1364-8

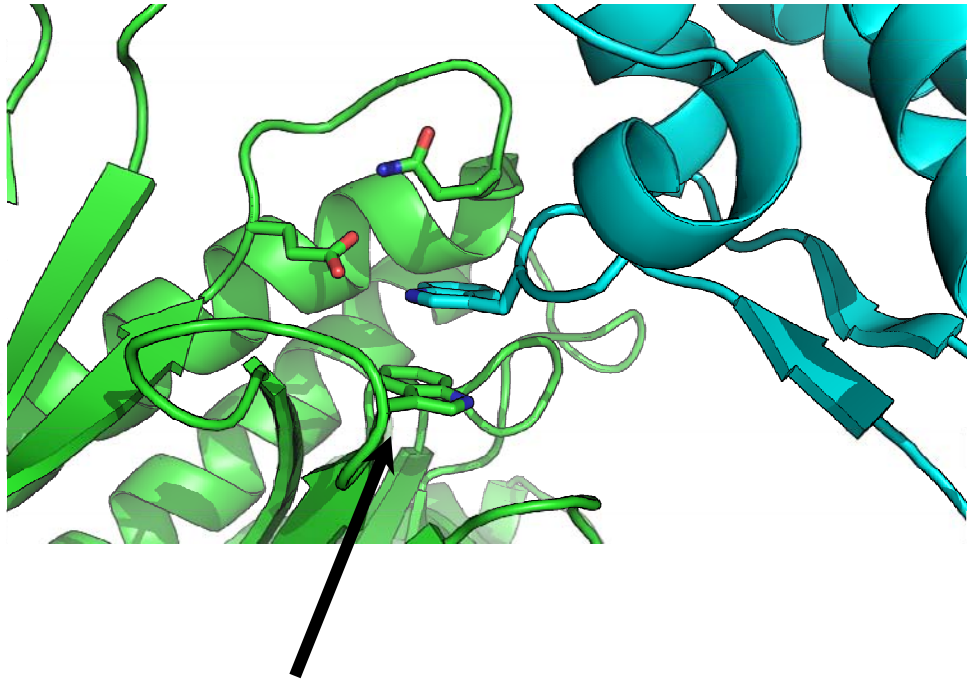
Design of new protein functions

- Design of new protein-protein interactions
- Design of new DNA cutting enzymes
- Design of enzymes catalyzing novel chemical reactions
- Design of HIV vaccine

Design of a cholera toxin binder



Cholera toxin Designed binder



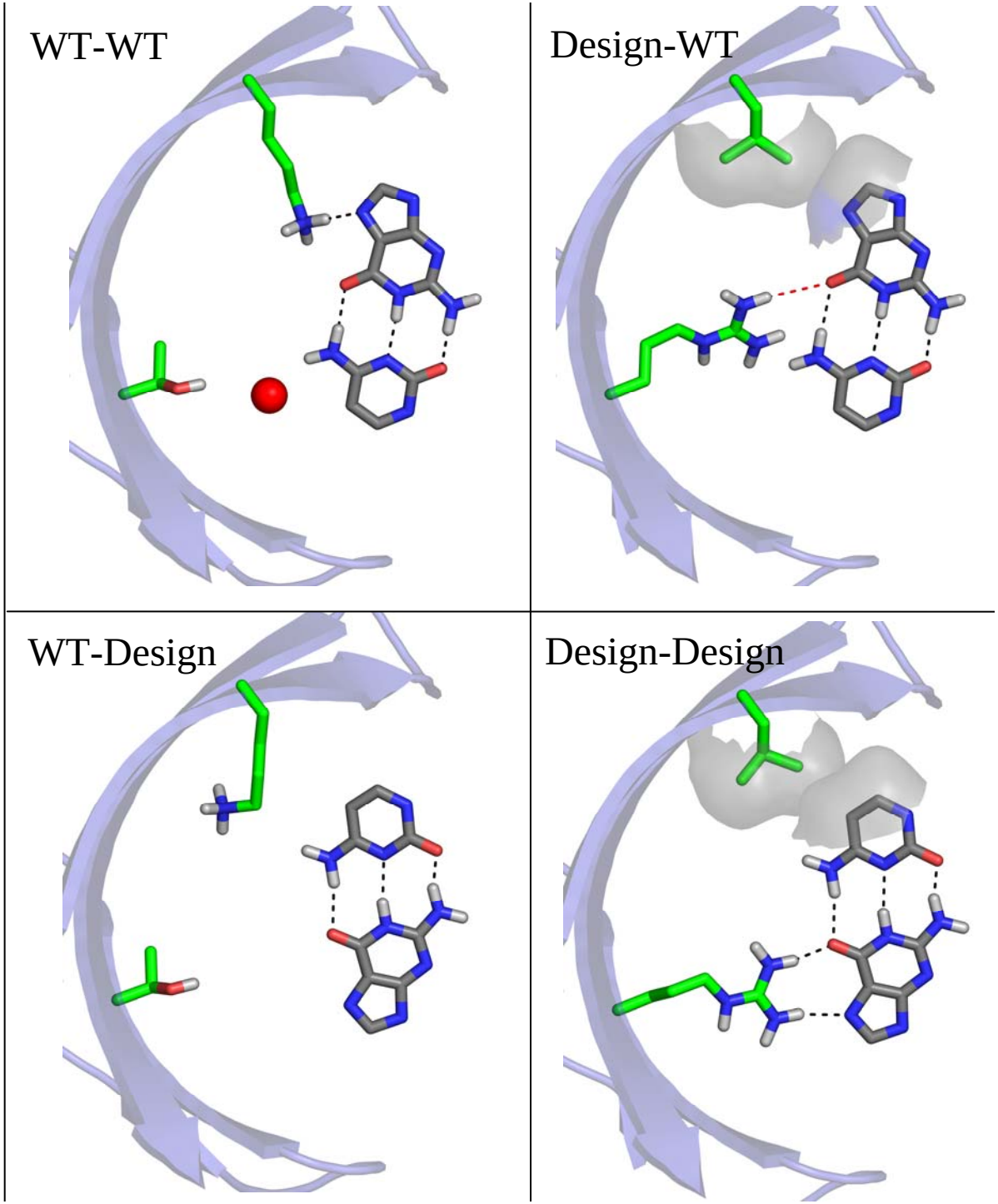
Receptor-binding pocket

Design proteins which cut DNA specifically within single genes in a genome

- Gene Therapy: Correct mutations in human genes responsible for disease
- Destroy mosquito genes needed by malaria parasite

Redesign of endonuclease DNA cleavage specificity

Justin Ashworth,
Jim Havranek
Nature 2006



Goal: Create enzymes which catalyze reactions not catalyzed by naturally occurring enzymes

- Wide range of important and useful applications (synthetic chemistry, biofuels, medicine, diagnostics, etc.)
- Test of our understanding of how naturally occurring enzymes work
- Grand challenge for computational protein design
- Success! (March 7 Science, Nature May 8)

Design of Novel Enzymes

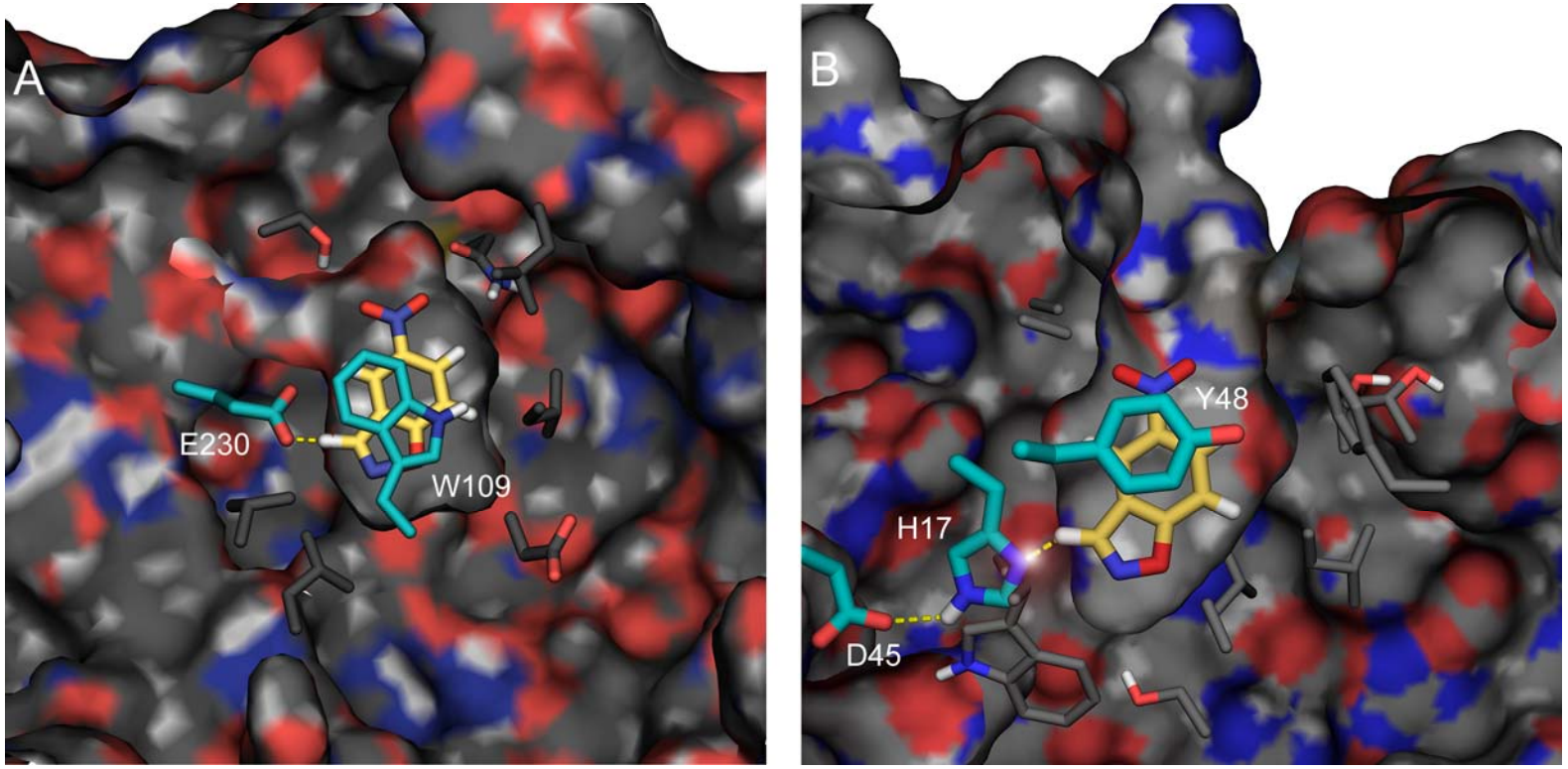
I. Compute reaction transition state

II. Design ideal active site around transition state
  - Position sidechain functional groups in positions optimal for catalysis
  - Maximize transition state binding affinity
  - Ensure steric compatibility with substrate and product

III. Design protein containing ideal active site

Alex Zanghellini, Daniela Roethlisberger, Lin Jiang,
Eric Althoff

Examples of designed enzymes



Daniela Roethlisberger, Andrew Wollacott

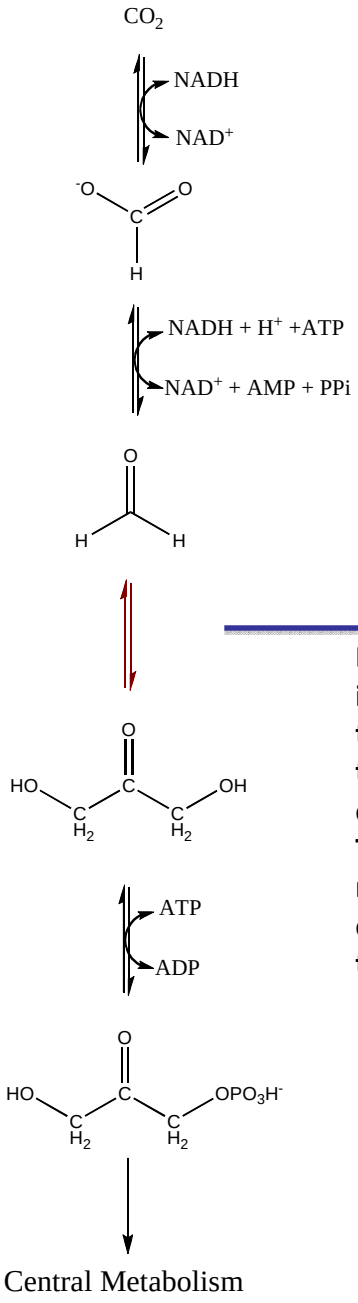
Successes thus far

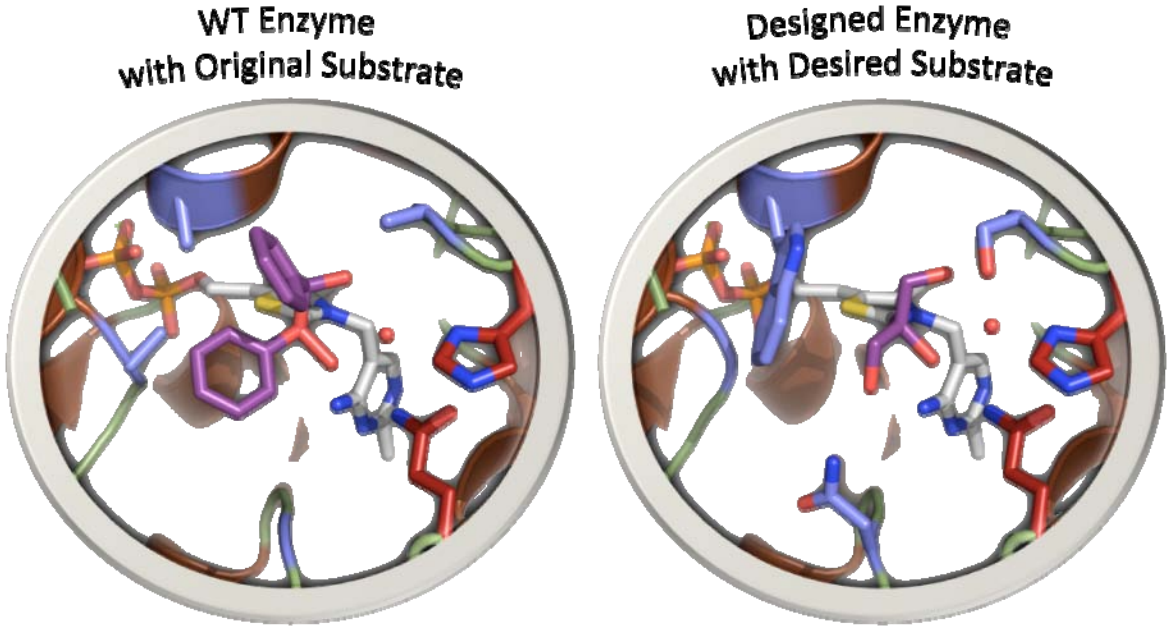
- General acid-base catalysis: Kemp elimination
- Covalent catalysis: novel aldol and Michael condensation catalysts
- Bimolecular reactions: Diels Alder
- Polar transition state stabilization: ester hydrolysis

Applications of computational enzyme design to 21st century energy challenges

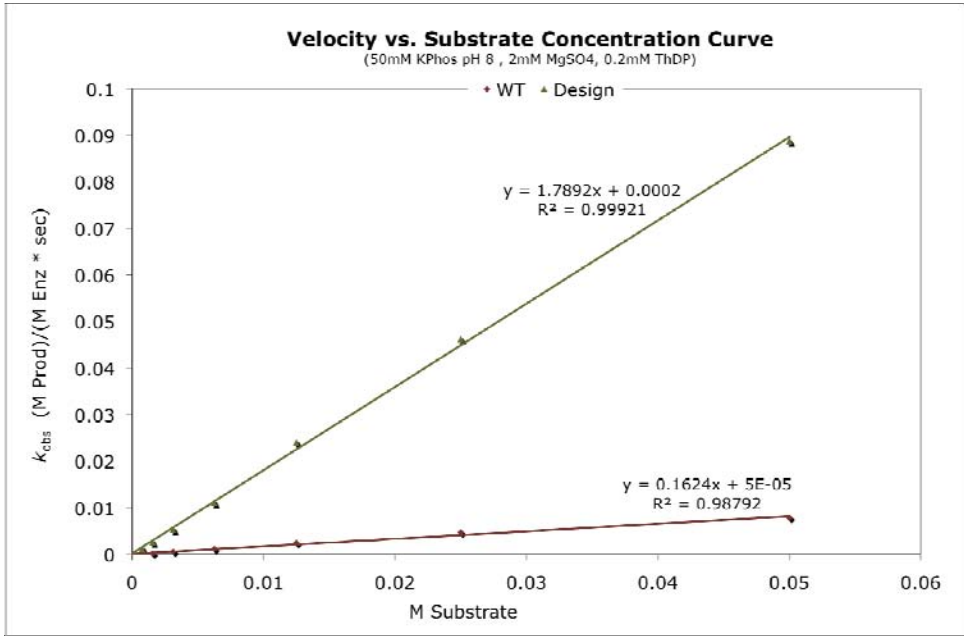
- Streamlined CO2 fixation pathway!
- New direct route for light-driven reduction of protons to molecular hydrogen through direct coupling of photosystem I to hydrogenases
- New pathways to novel biofuels (Bio Architecture Lab)

Engineering an Enzyme to Create a New Biosynthetic Pathway for CO_2 Utilization





Enzymes have been isolated for all of the transformations except for this one. Therefore we have redesigned an enzyme to catalyze this step.



Justin Siegal

Mary Lidstrom

Rosetta@home puts people's computers to work to solve problems; how to enlist their brains as well?

Turn the public into molecular designers through multiplayer online computer game!

Solve critcial problems in global health, energy and educate at same time!

Adrien Treuille, Seth Cooper, Zoran Popovic, David Salesin