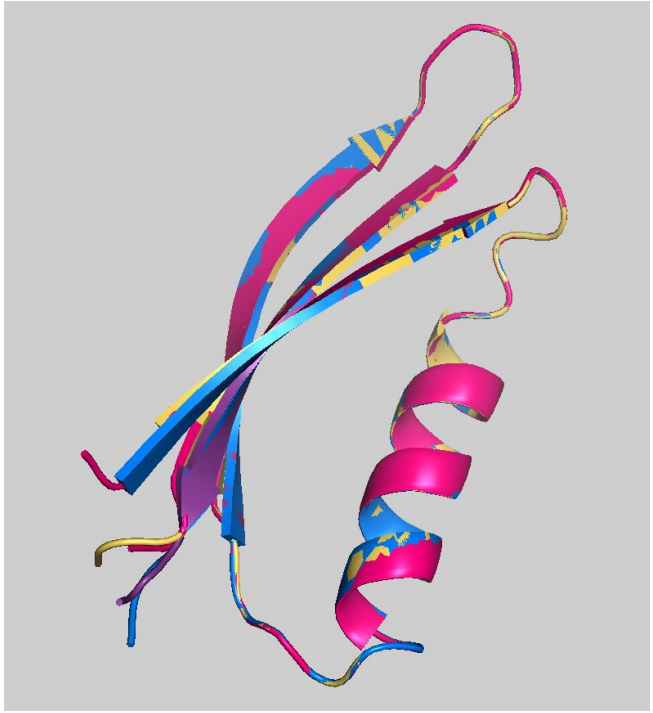
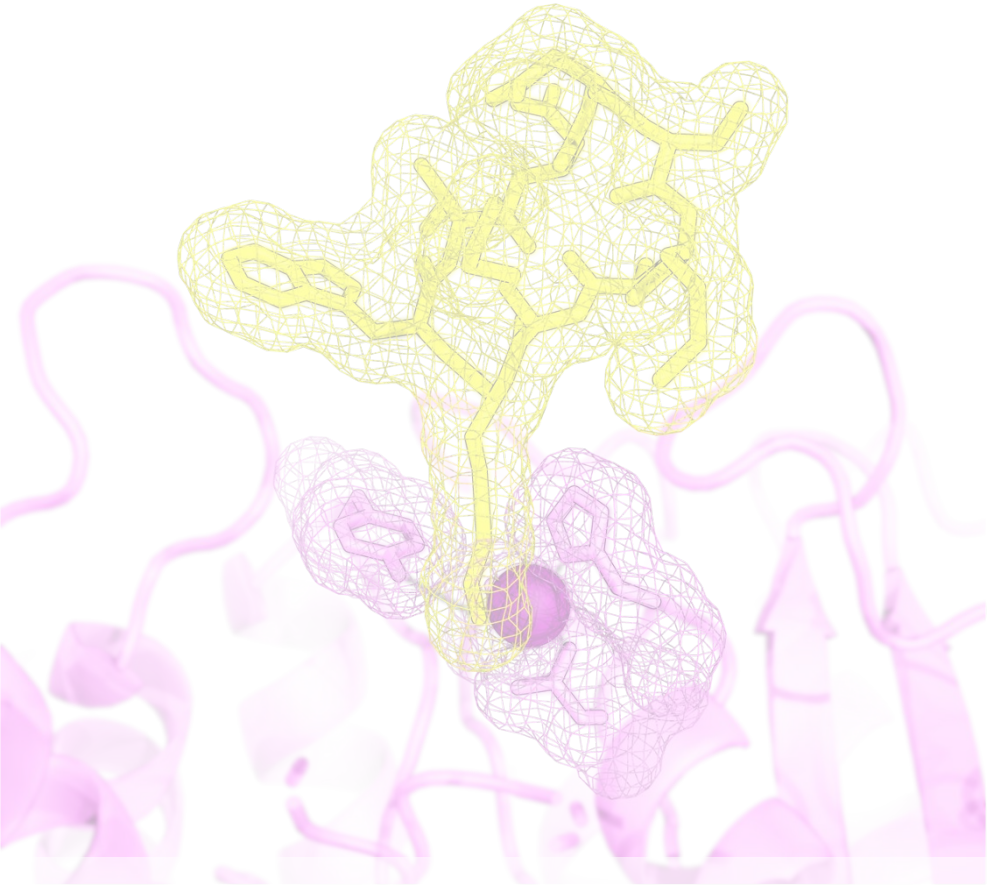
Class core values

1. Be **respect**ful to yourself and others
2. Be **confident** and believe in yourself
3. Always do your **best**
4. Be **cooperative**
5. Be **creative**
6. Have **fun**
7. Be **patient** with yourself while you learn
8. Don’t be shy to **ask “stupid” questions**

The winner of protein design with *Remodeler*:





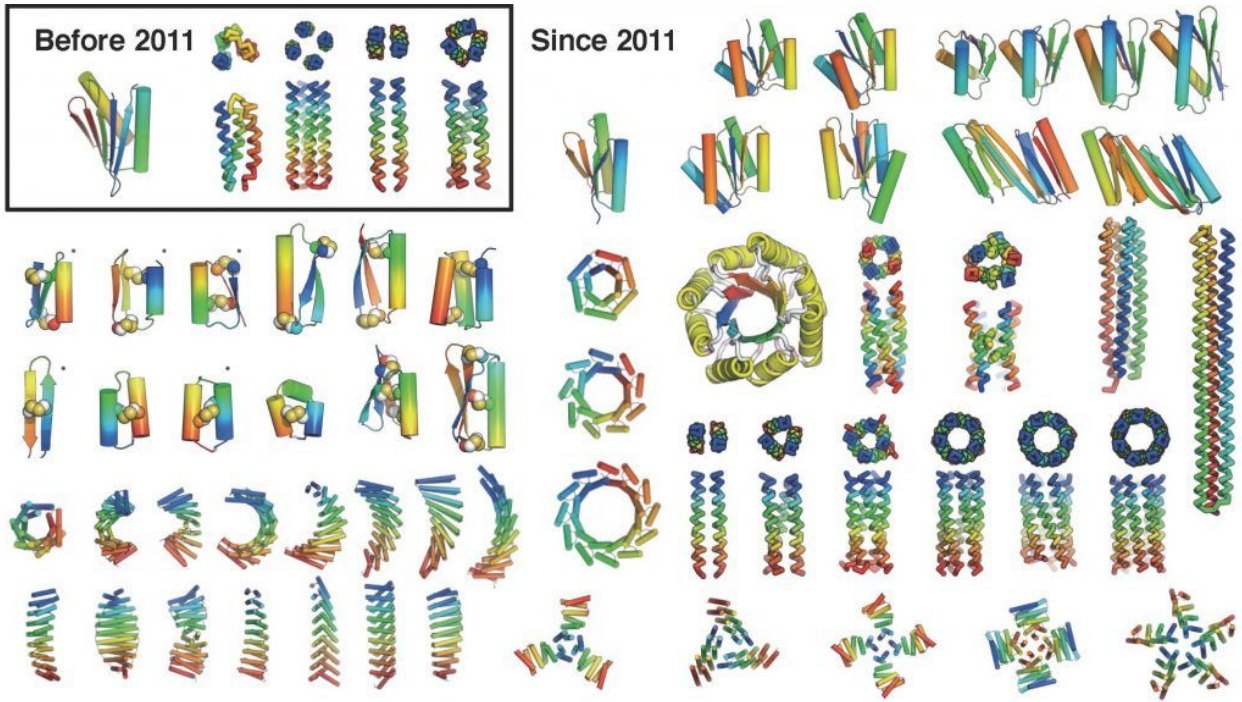
Week 7, Lecture 1

From structure to function

Learning Objectives

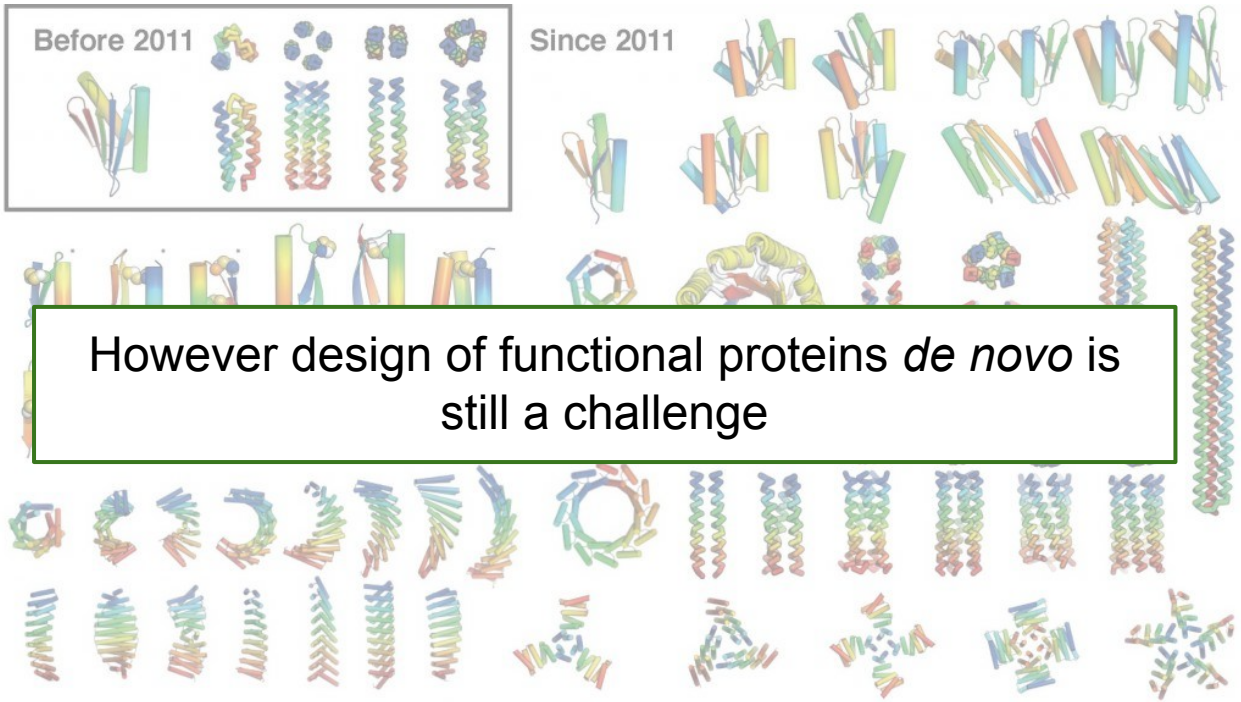
1. Describe main advances in design of function
2. Identify areas of challenge in de novo design of function
3. Identify areas of strength in de novo design of function
4. Critically evaluate literature on de novo design

De novo design of structure has expanded the universe of existing protein shapes



Curated by Ian Haydon from *Nature* 537, 320–327(2016)

De novo design of structure has expanded the universe of existing protein shapes



However design of functional proteins *de novo* is still a challenge

What do we mean by *FUNCTION*?

Examples of functions of interest:

- Enzyme
- Binders
- Assemblies and materials

Challenges of designing functions as a computational problem

Criteria for a *good* computational problem:

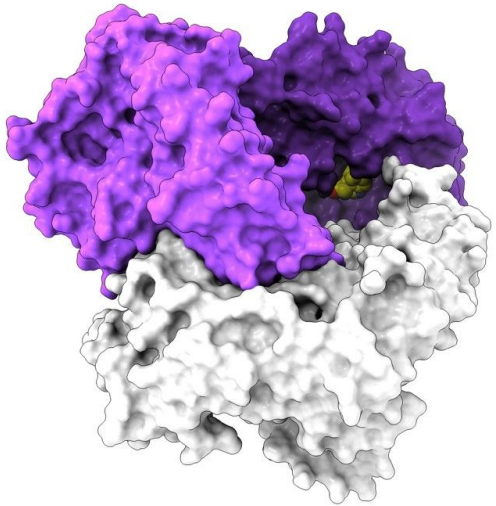
Challenges of designing functions as a computational problem

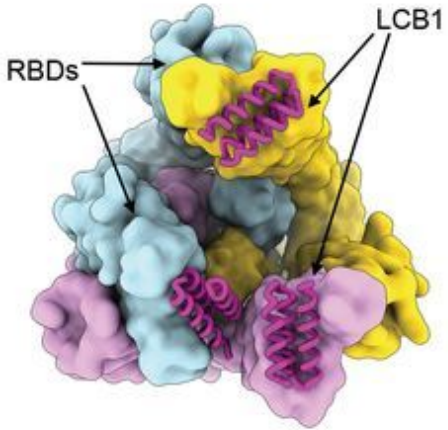
Criteria for a *good* computational problem:

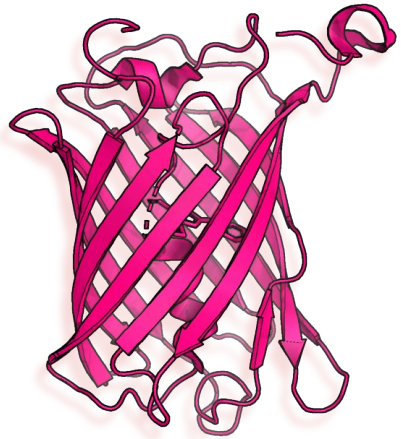
Describable, solvable, tractable, non-trivial, testable

In class activity:

It’s all about asking the right question







Images from: C&EN

Science **2020** 370(6515)

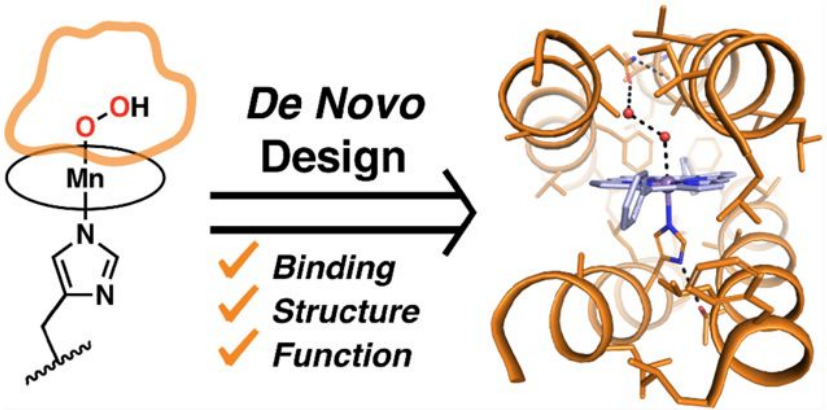
PDB ID: 6YLM

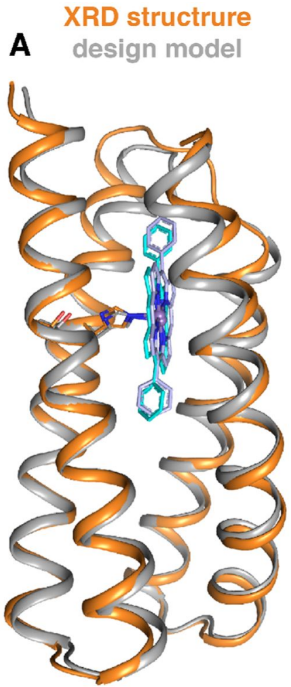
De novo designed proteins can be used as scaffolds for incorporating new functions

De novo designed proteins can be used as scaffolds for incorporating new functions

New enzyme:

incorporating Mn-porphyrin into helical bundles



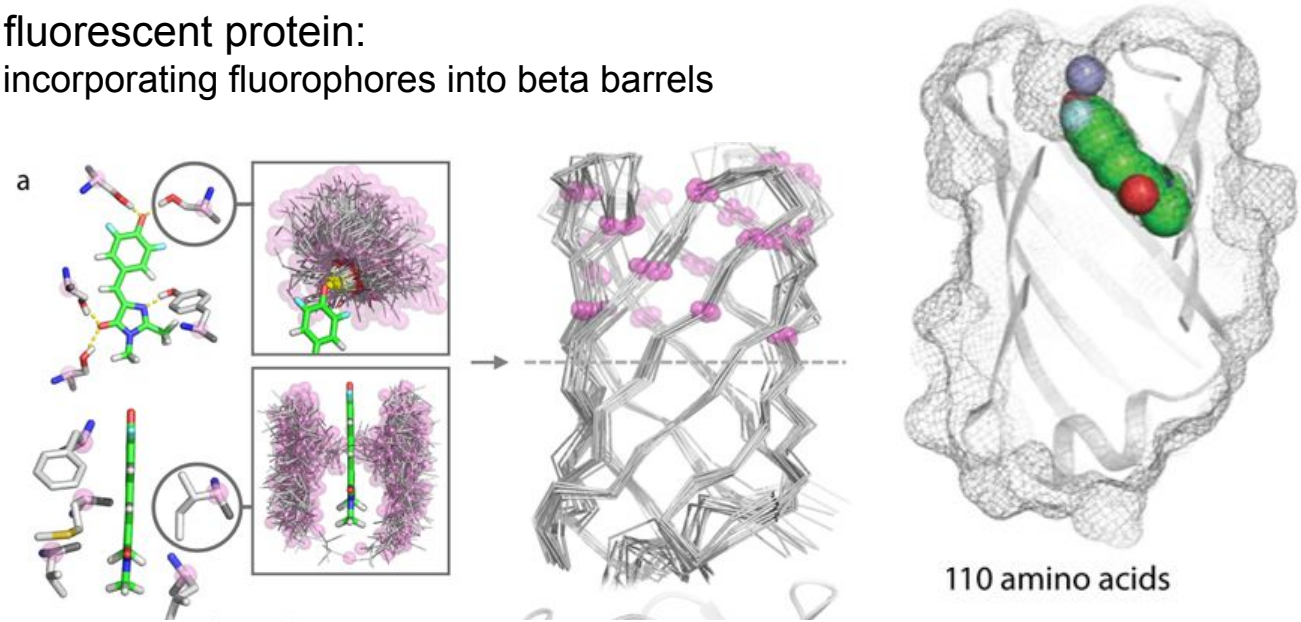


J Am Chem Soc. 2021 Jan 13; 143(1): 252–259

De novo designed proteins can be used as scaffolds for incorporating new functions

New fluorescent protein:

incorporating fluorophores into beta barrels

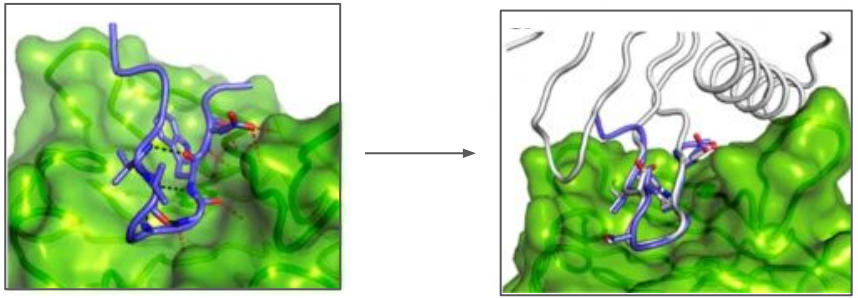


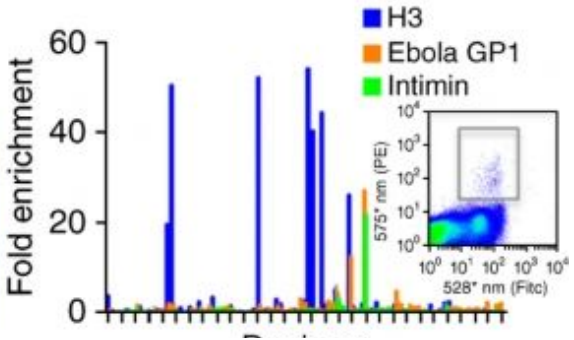
Nature. **2018** Sep; 561(7724): 485–491

De novo designed proteins can be used as scaffolds for incorporating new functions

New binders:

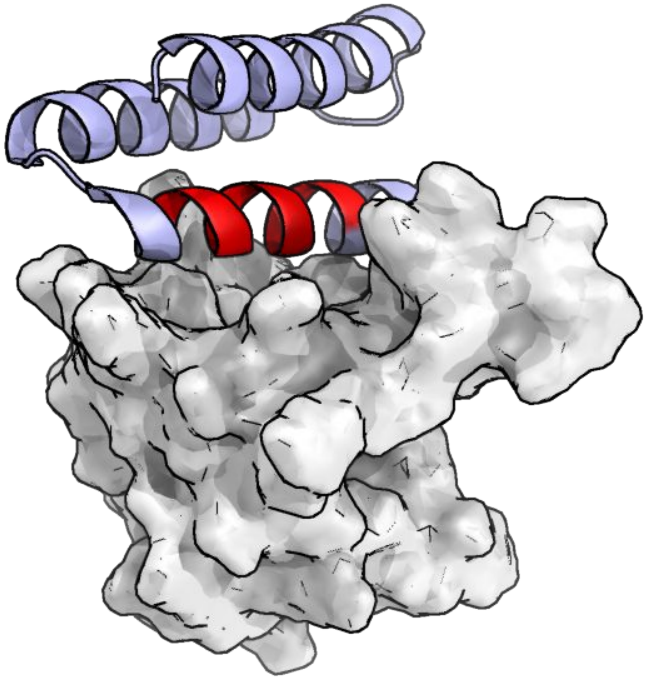
incorporating binding motifs into designed scaffolds





In class activity:

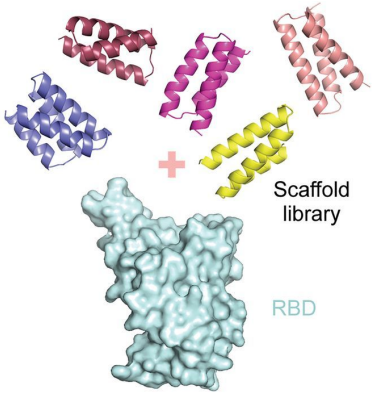
Motif Grafting

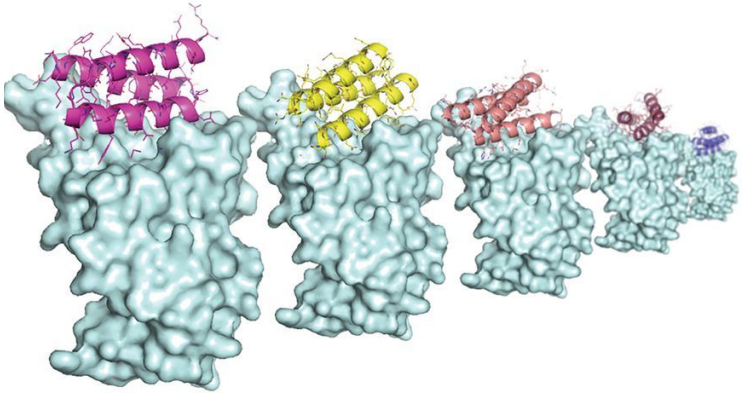


De novo designed proteins can be used as scaffolds for incorporating new functions

New binders:

Docking scaffolds onto de novo placed hotspot residues



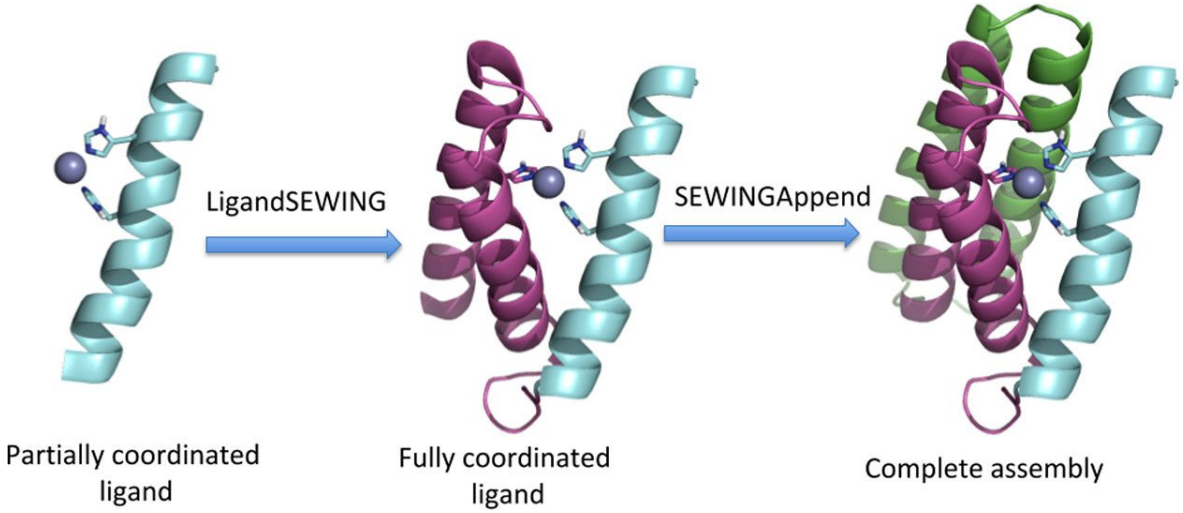


New functional proteins can be designed by assembling fragments from natural proteins

New functional proteins can be designed by assembling fragments from natural proteins

New enzymes/small molecule binders:

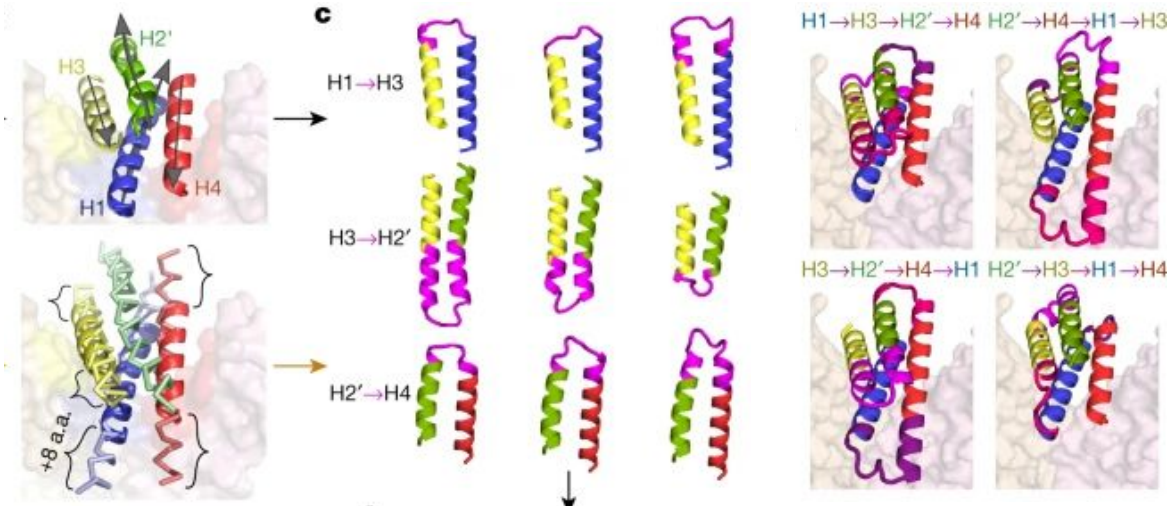
Assembling structures around a known motif



New functional proteins can be designed by assembling fragments from natural proteins

New binders:

Assembling idealized secondary structures around a known motif



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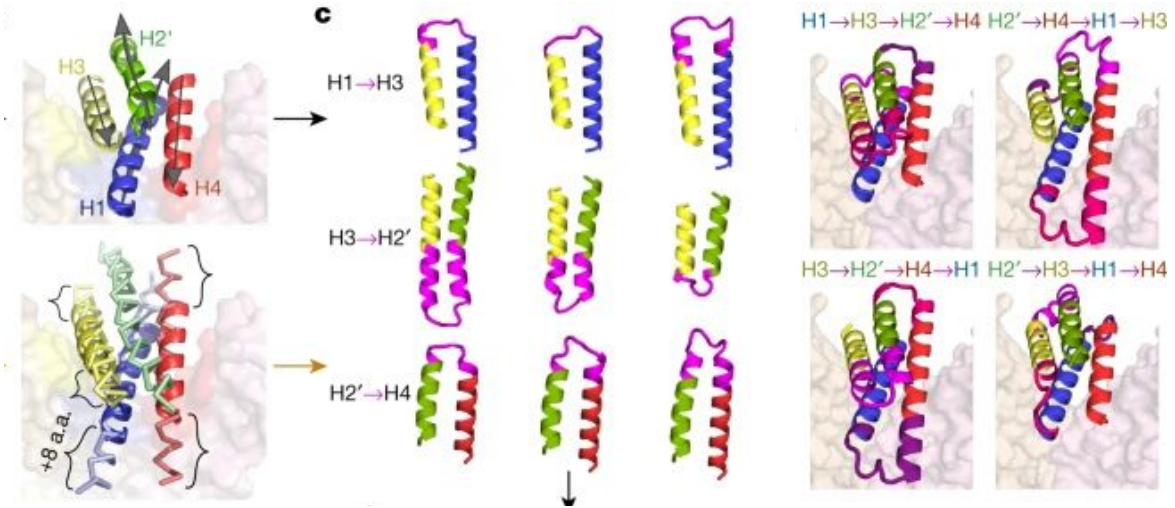
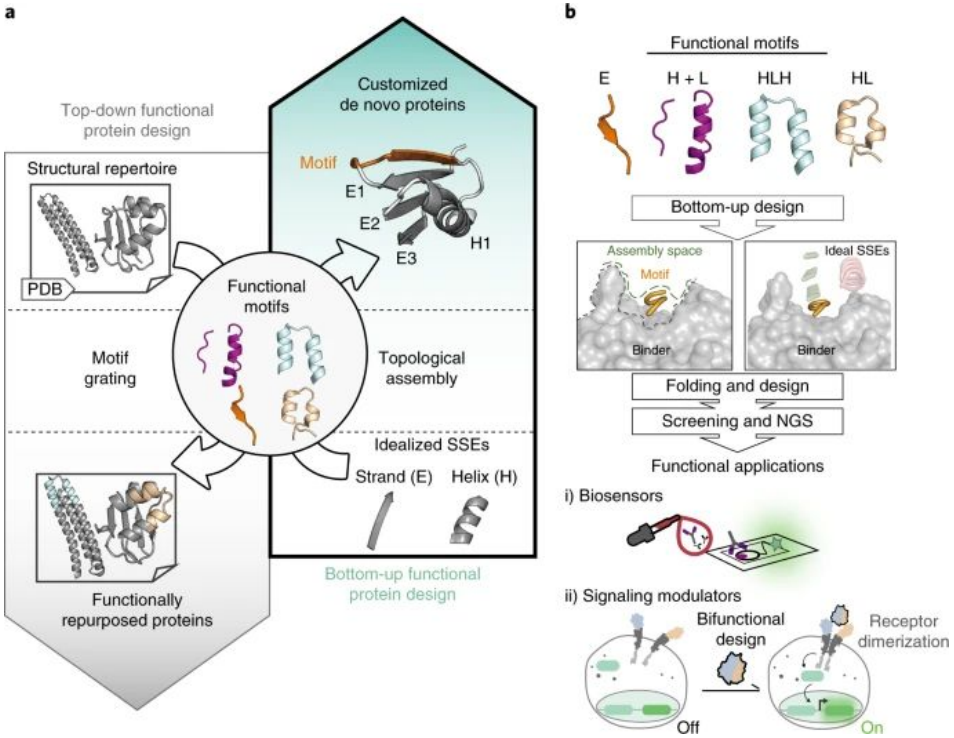


neoleukin™ THERAPEUTICS

New functional proteins can be designed by assembling fragments from natural proteins

New sensors:

Building ideal scaffold around known motifs

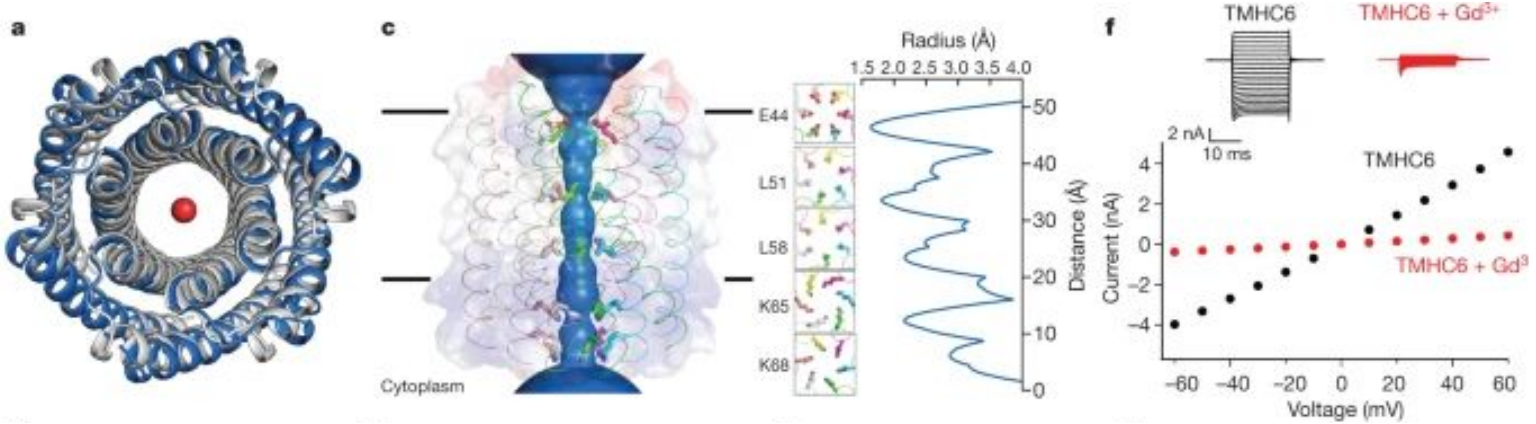


Functions that do not require movement can be engineered using de novo design

Functions that do not require movement can be engineered using de novo design

Ion channels

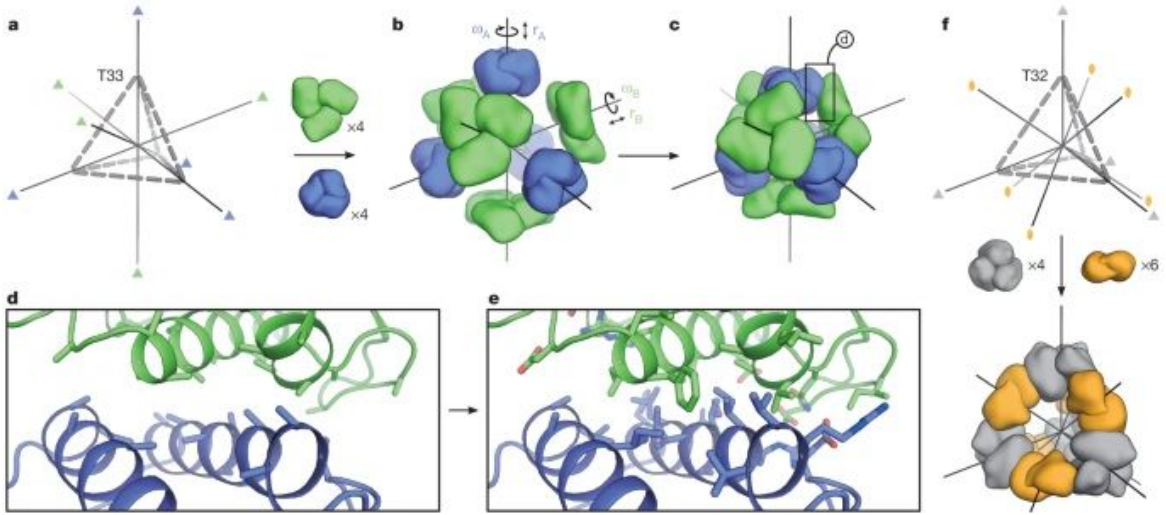
Design of membranous helical bundles with given diameters



Functions that do not require movement can be engineered using de novo design

Protein cages

Safe assembling cages built from native/de novo scaffolds

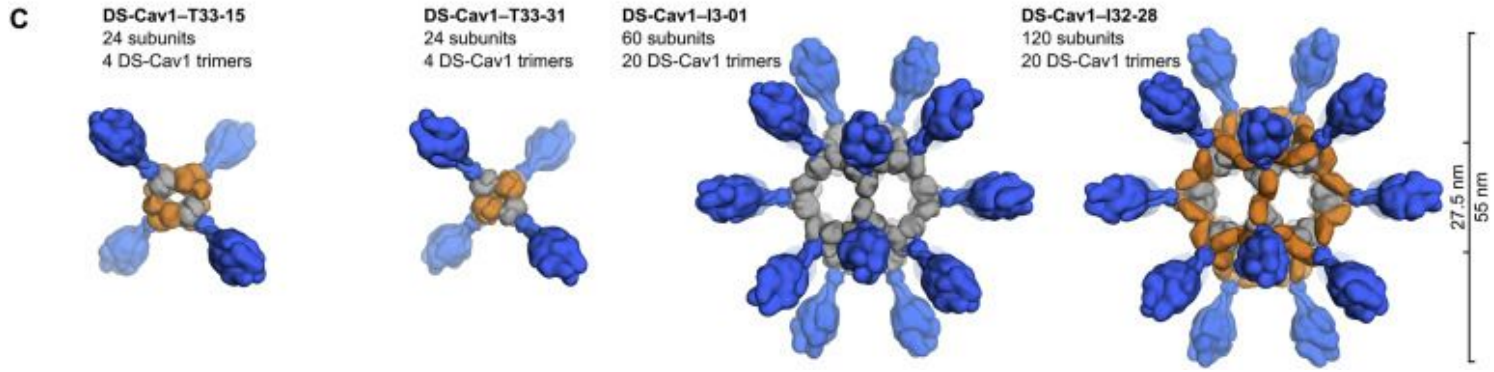


Nature 510, 103–108(**2014**)

Functions that do not require movement can be engineered using de novo design

Protein cages

Can be used for antigen representation and vaccine generation



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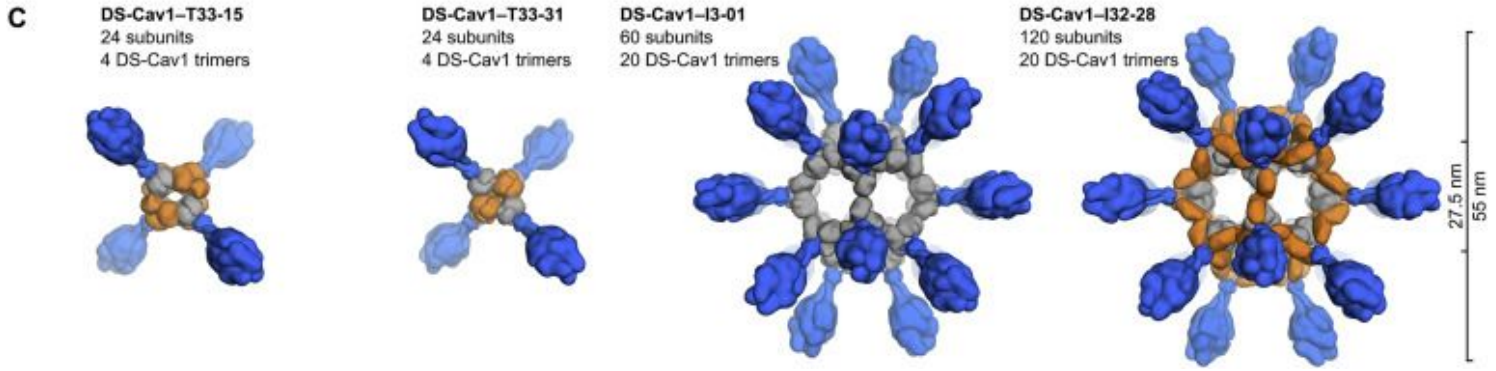
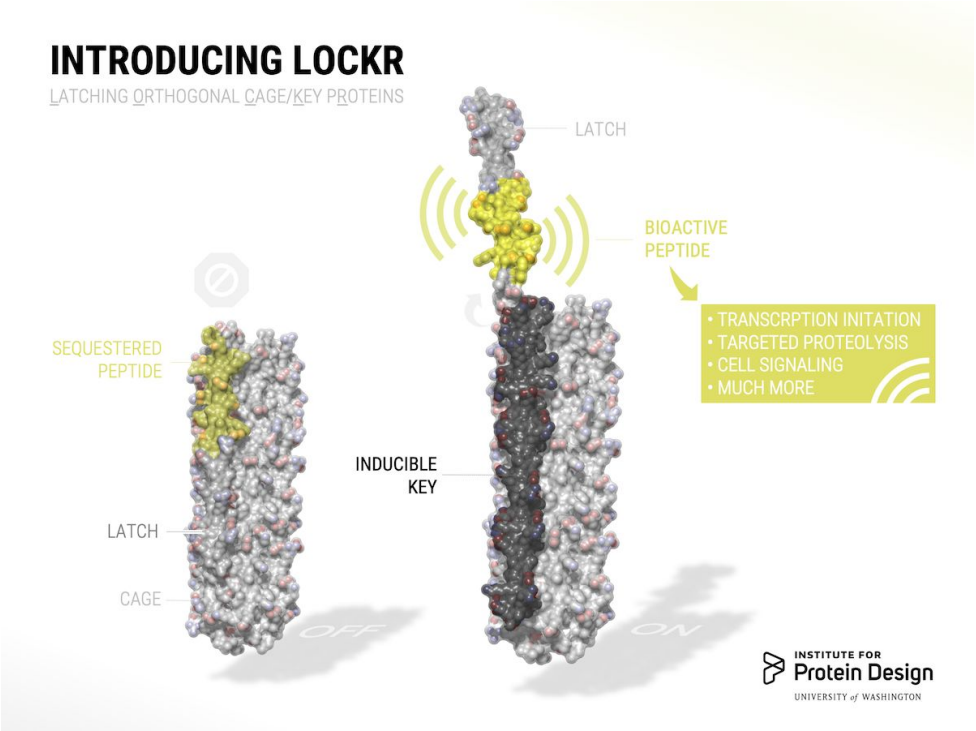


Movement can be achieved by destabilizing the interactions between protein domains

Movement can be achieved by destabilizing the interactions between protein domains

Biological switches

Key-LOCKR system



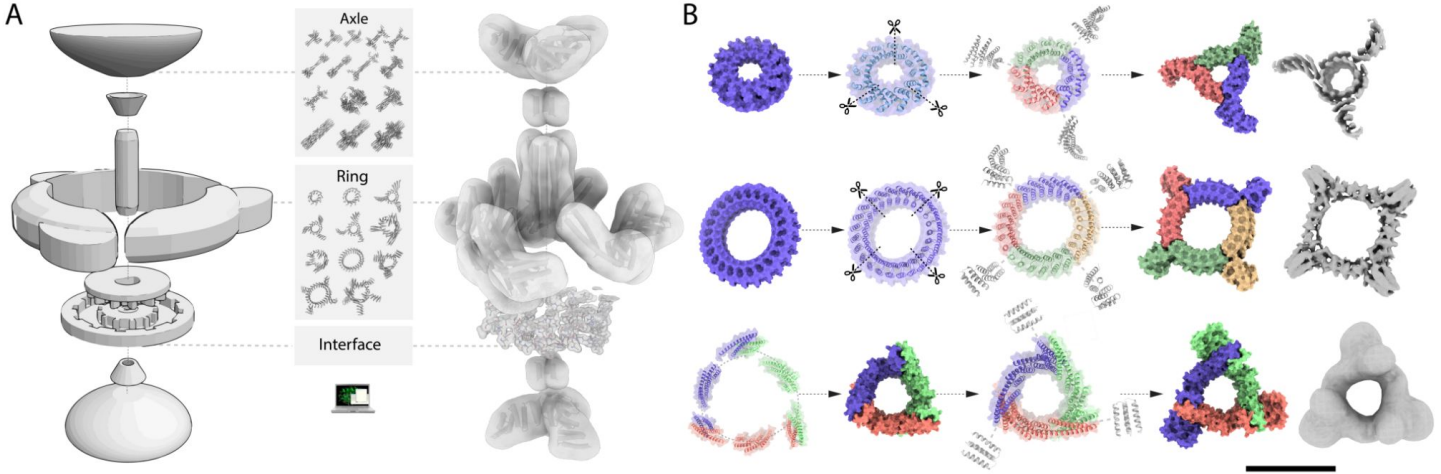
Nature 572, 205–210(2019)

Image from Institute for Protein Design

Movement can be achieved by destabilizing the interactions between protein domains

Rotating molecules

Design of rotating molecules



Courbet et al, bioRxiv

How will you design movement into the system?

For the next lecture:

1. Submit updated specific aims page

2. Post-class assignment
   The one from W6L2 due next lecture

Next lecture:

The protein structure prediction challenge

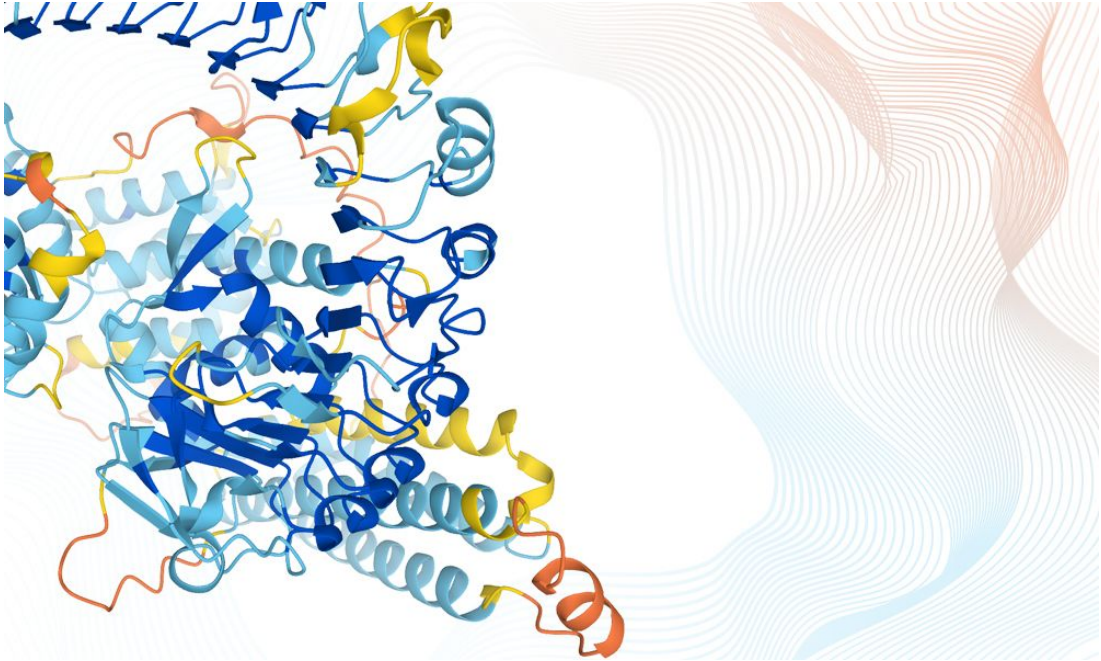


Image from EMBL