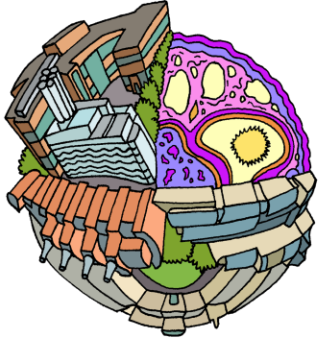
University of BRISTOL



BrisSynBio

biomolecules to biosystems
from understanding to design

Rational & computational design of self-assembling peptide barrels

Woolfson Group from the past decade

Rokas Petrenas, Katherine Albanese,

Elise Naudin, Bram Myelmans,

Fabio Pirro, & Will Dawson

Graham Leggett, Tom Oliver, Nigel Savery, Arne Scott

Dek Woolfson

Chemistry, Biochemistry, & Bristol BioDesign

About today's talk

1. How we design peptide assemblies

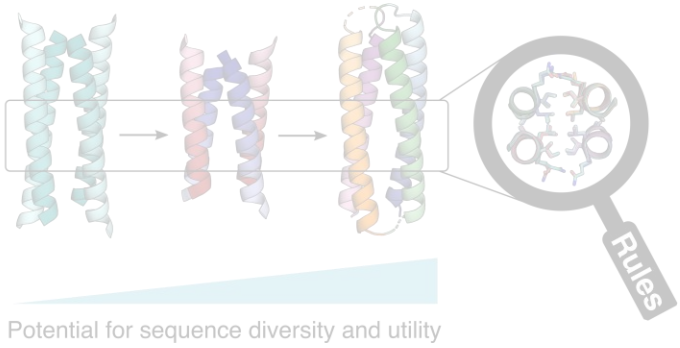
ACS Synth Biol 1, 240-250 (2012)
J Am Chem Soc 135, 5161-5166 (2013)

Science 346, 485-488 (2014)

2. Peptidic molecular flasks

Rokas Petrenas
unpublished work

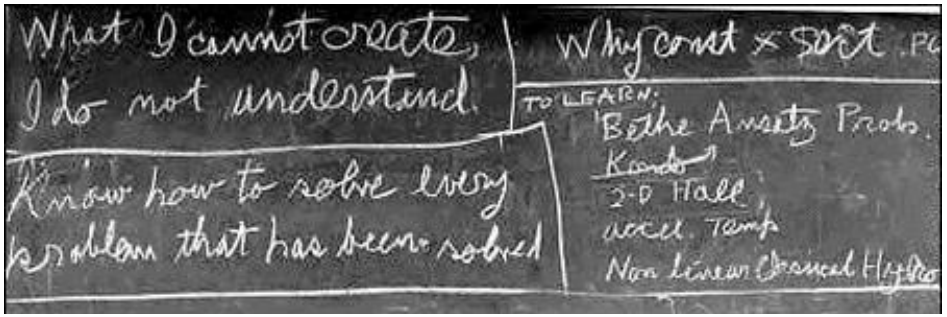
3. From peptides to proteins…



Chem Sci 13, 11330-40 (2022)
& some unpublished work

Why design peptides and proteins?

- **It's still a challenge**



- **Fundamental science**
  - *It's the acid test of our **understanding** of the protein-folding problem; i.e., how does the amino-acid sequence of a protein determine and maintain its 3D structure?*

- **Frontier science**
  - *To design proteins that do not exist in nature; i.e., to explore the dark matter of protein space.*

- **Applied science**
  - *Where possible, translate this to design proteins that address real-world problems & applications.*

- **It's fun**

About today's talk

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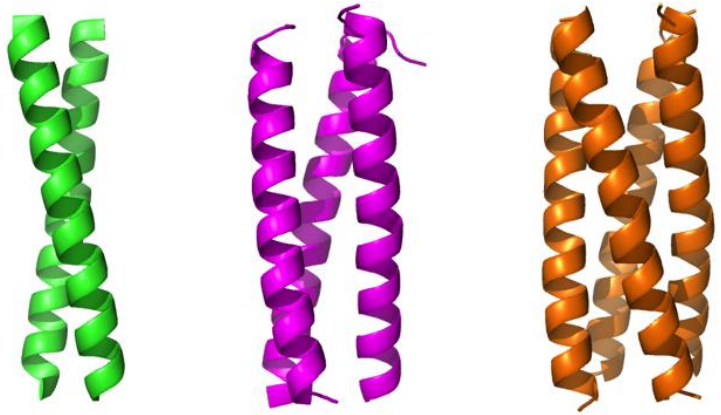

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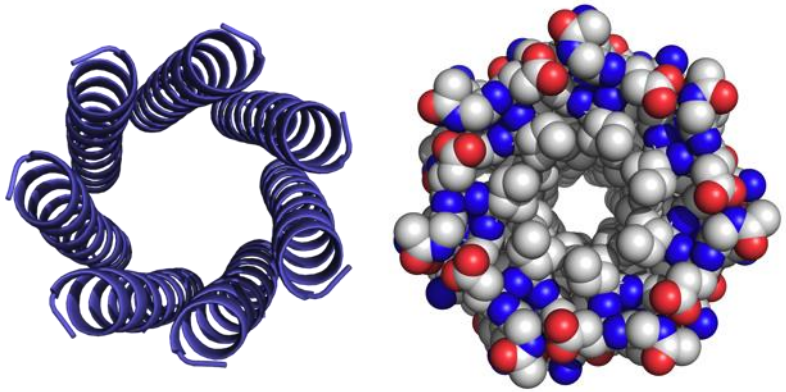

Science 346, 485-488 (2014)

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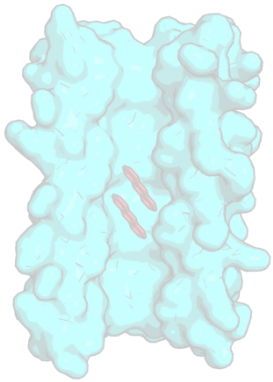
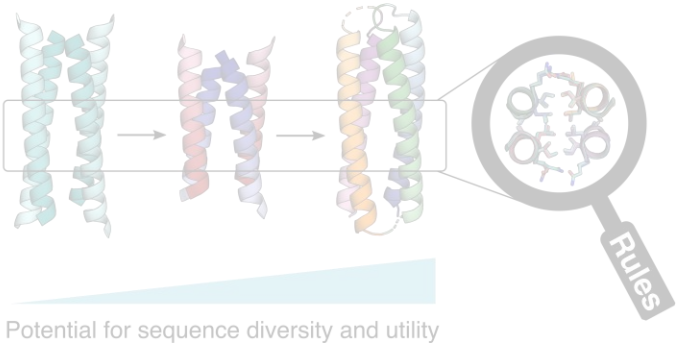


Rokas Petrenas
unpublished work

3. From peptides to proteins…



Chem Sci 13, 11330-40 (2022)
& some unpublished work

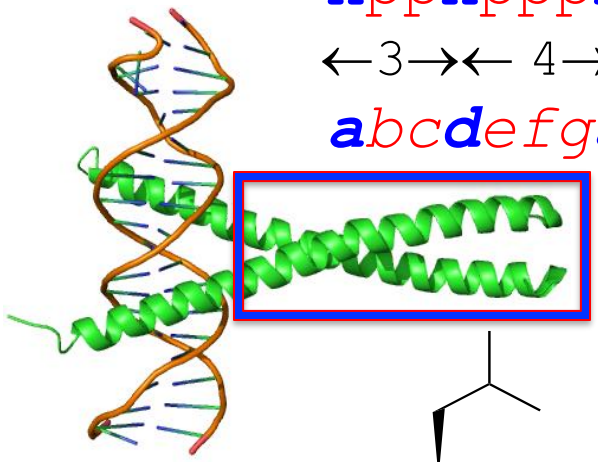
How we design peptide assemblies

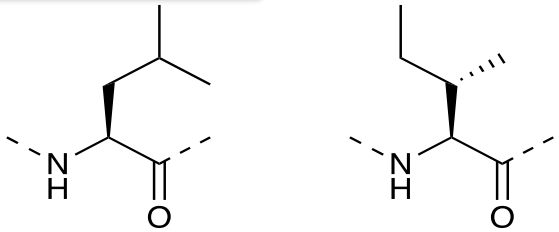
1. Rationally

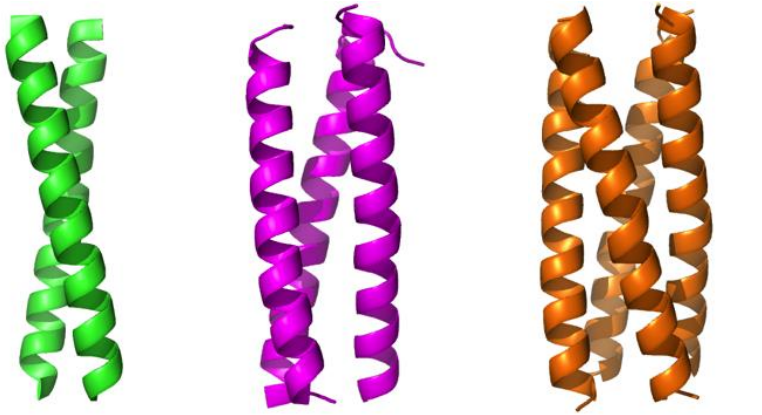
hpp**h**ppp**h**pp**h**ppp**h**

←3→← 4→←3→← 4→

abc***d***efg***a***bc***d***efg***a***



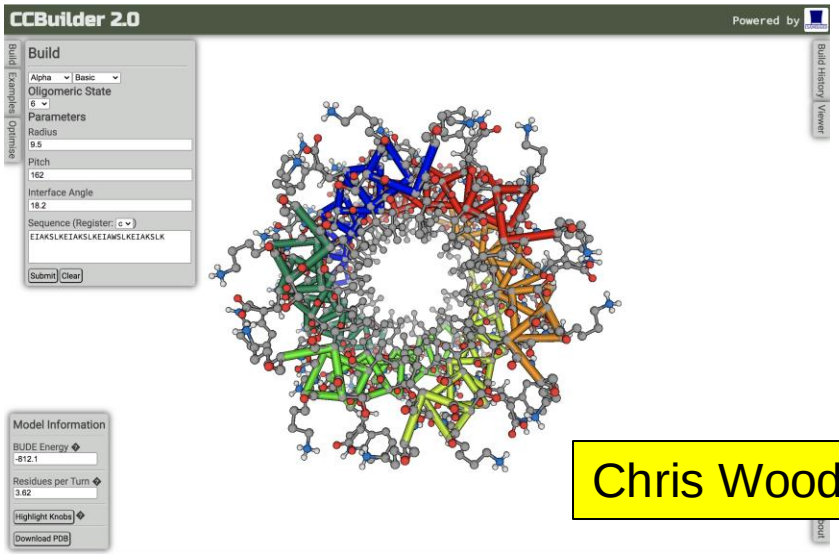




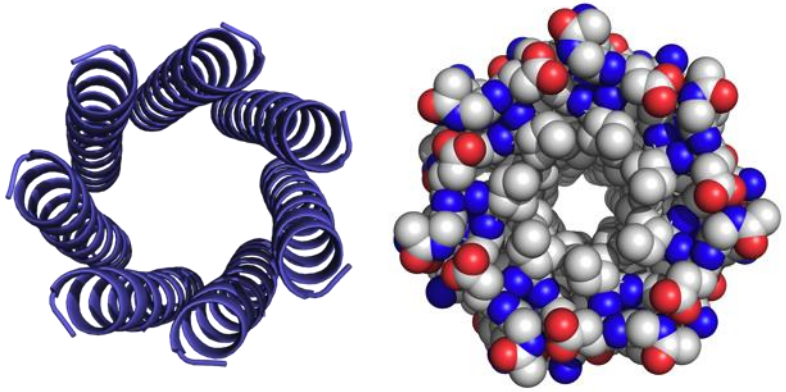
ACS Synth Biol 1, 240-250 (2012)

J Am Chem Soc 135, 5161-5166 (2013)

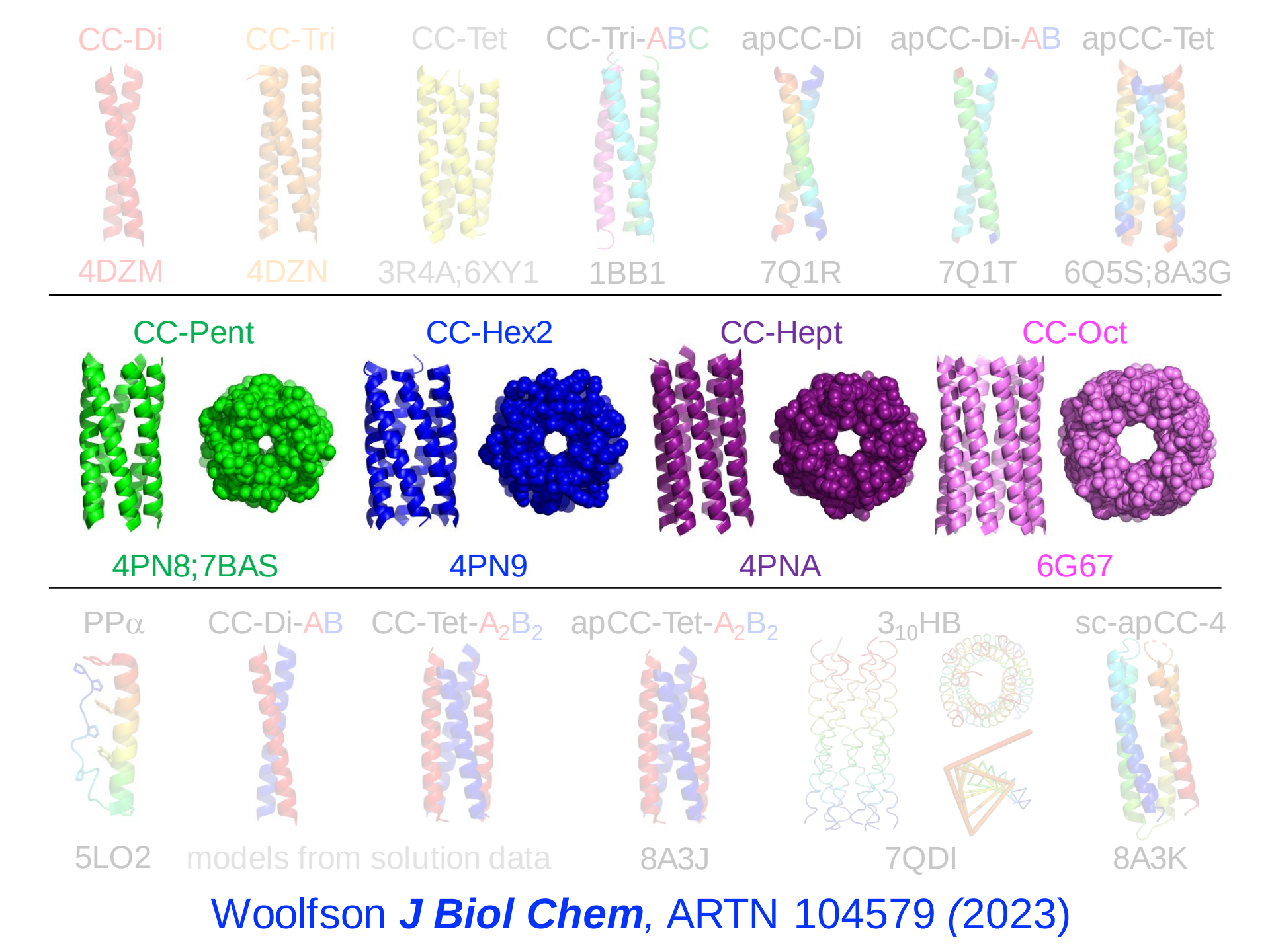
2. Computationally



coiledcoils.chm.bris.ac.uk/ccbuilder2/builder



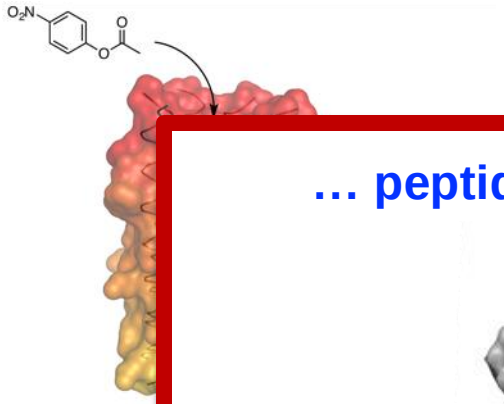
Science 346, 485-488 (2014)



Woolfson ***J Biol Chem***, ARTN 104579 (2023)

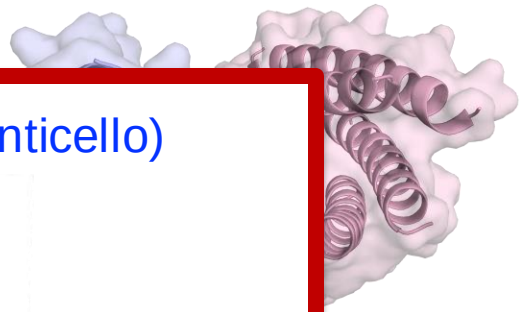
Functions we've added to αHBs …

… catalysis



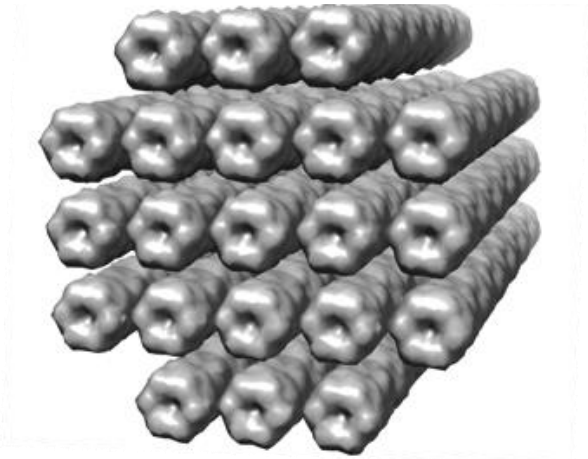
Nature Chemi

… inducible structural switches



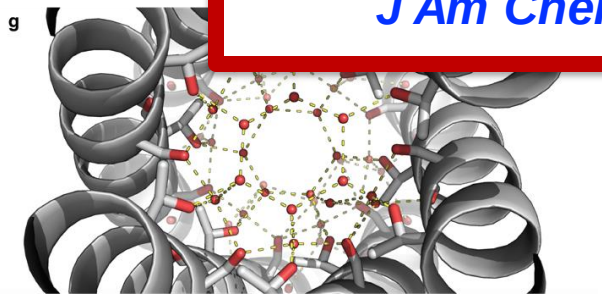
TN 1530 (2021)

… peptide nanotubes (after Conticello)



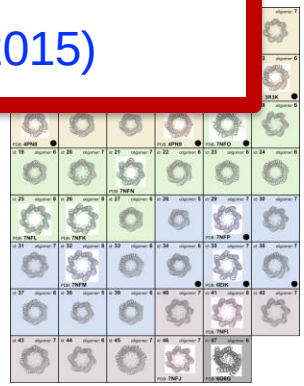
J Am Chem Soc 137, 10554-62 (2015)

… membrane-s



Nature Chemistry 13, 643-50 (2021)

ased biosensor



Nature Commun 14, ARTN 383 (2023)

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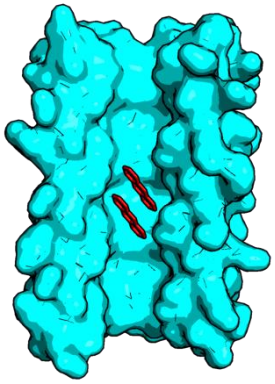
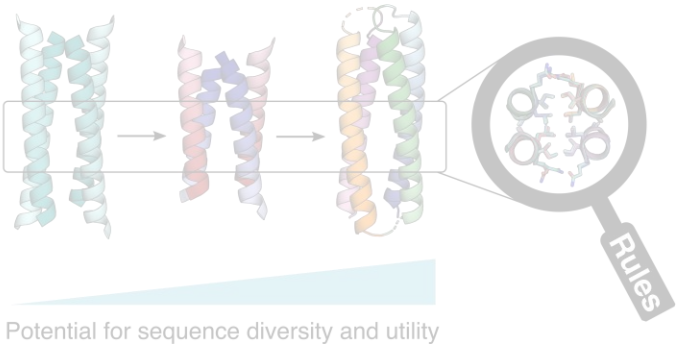


Rokas Petrenas
unpublished work

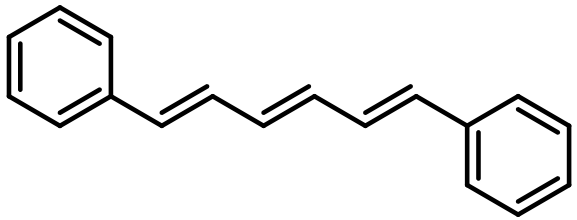
3. From peptides to proteins…

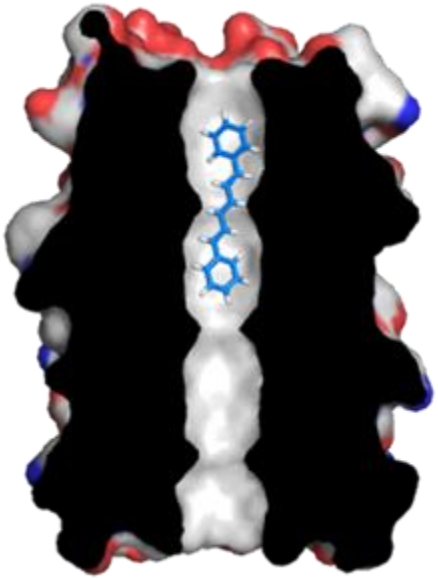


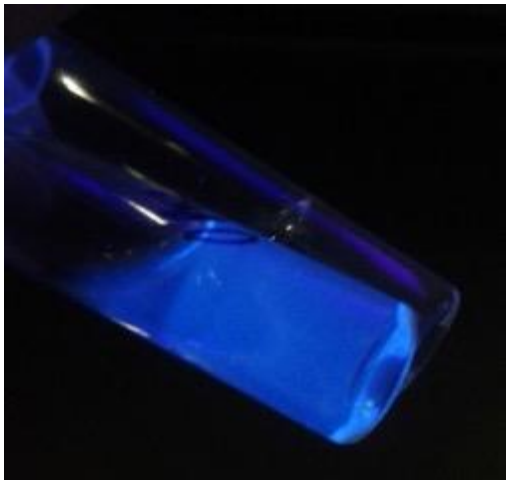
Chem Sci 13, 11330-40 (2022)
& some unpublished work

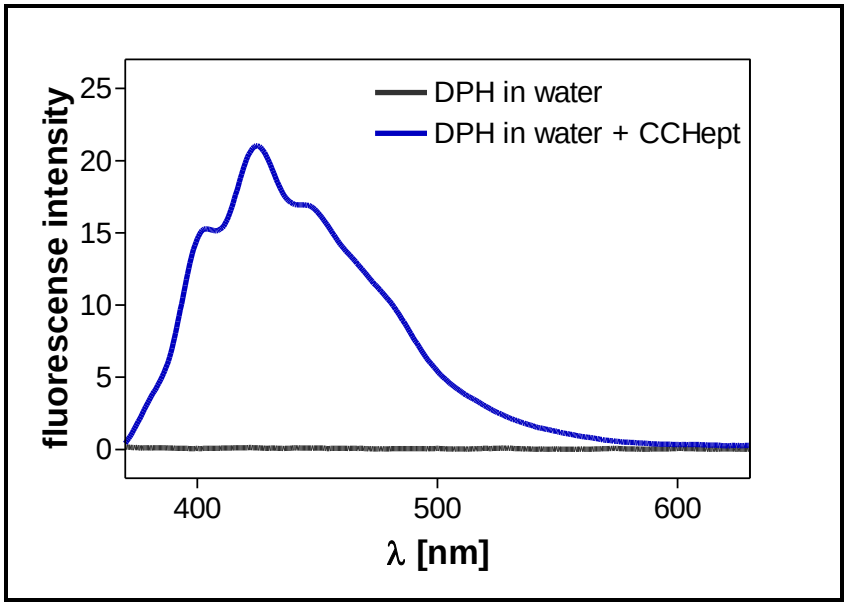
Organic dyes bind peptide barrels

1,6-Diphenylhexatriene (DPH)

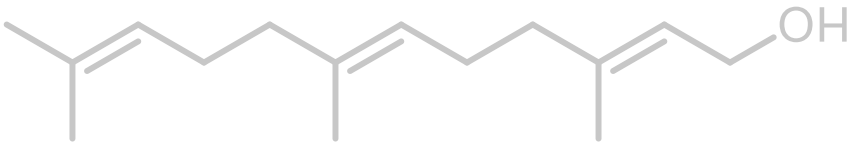


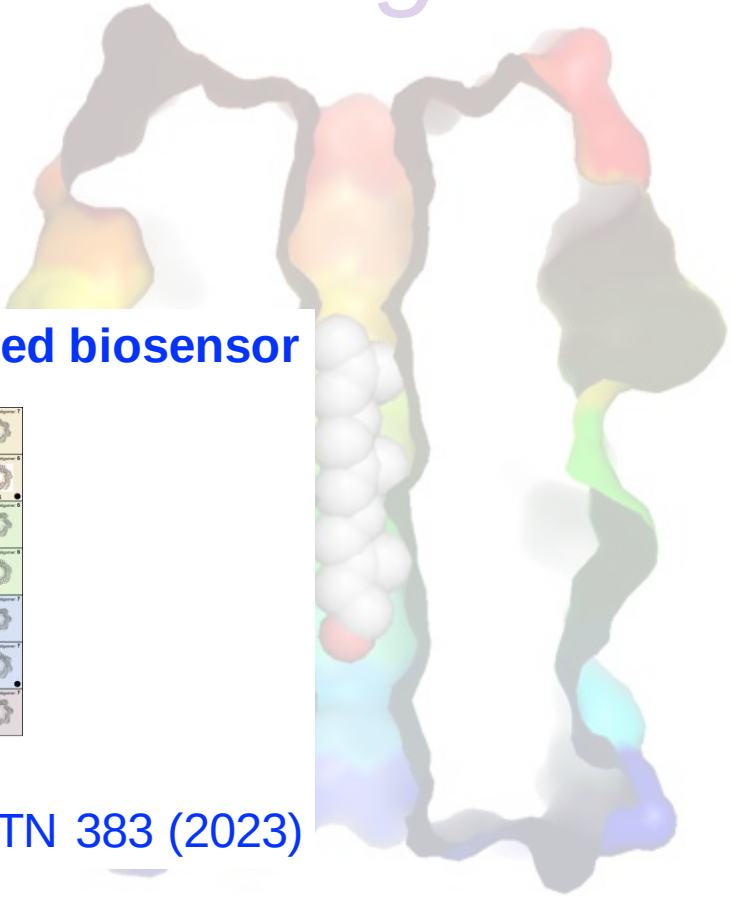




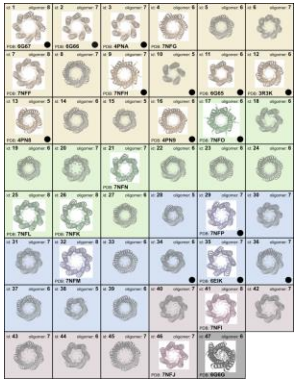


… & displaced by *interesting* moles.

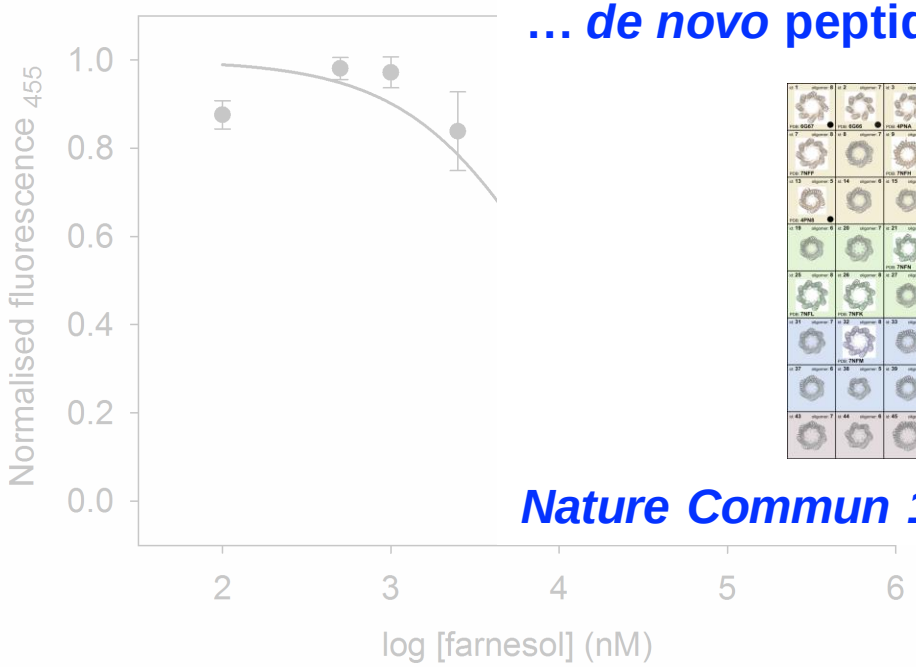




… *de novo* peptide-based biosensor



Nature Commun 14, ARTN 383 (2023)



$K_I = 0.6 \pm 0.2$ µM

1.8 Å X-ray crystal structure

$R_{work} = 0.2120$; $R_{free} = 0.2635$

Franziska Thomas *et al.* ***ACS Synth Biol 7*** 1808-1816 (2018)

- Redacted slides from here as this was all unpublished work. Sorry.

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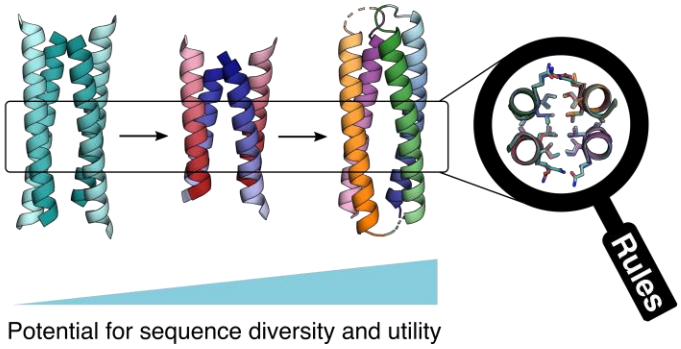
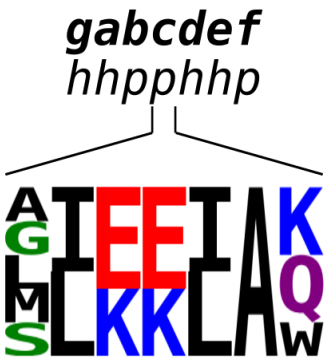


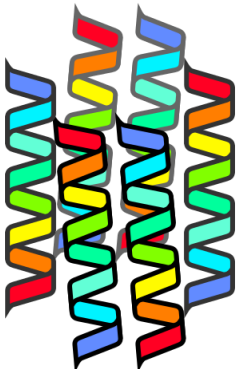
Chem Sci 13, 11330-40 (2022)
& some unpublished work

Rationally seeded computational design



de novo peptide design

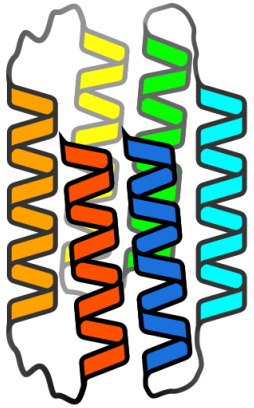
coiled-coil rules



rational seed

loop search

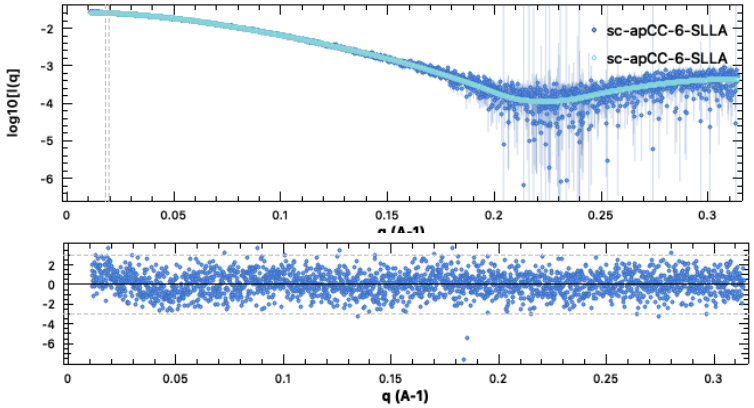
MASTER

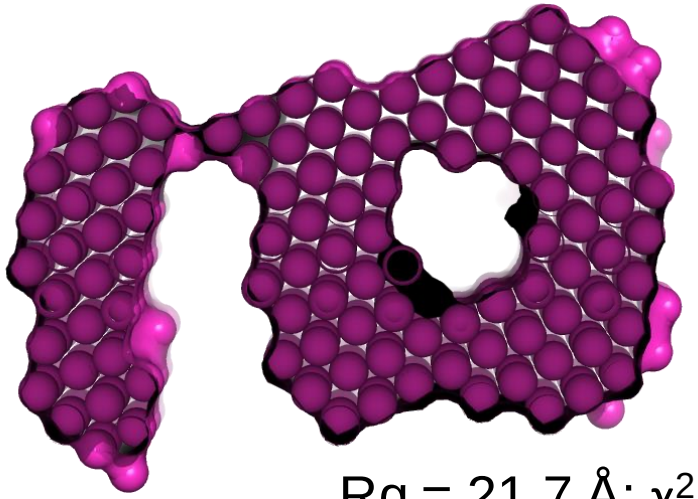


anti-parallel targets

→ single-chain anti-parallel 6HB

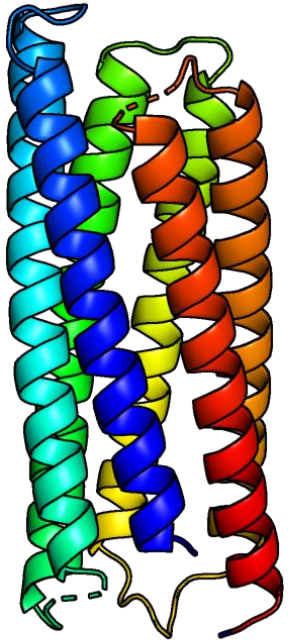
SAXS model

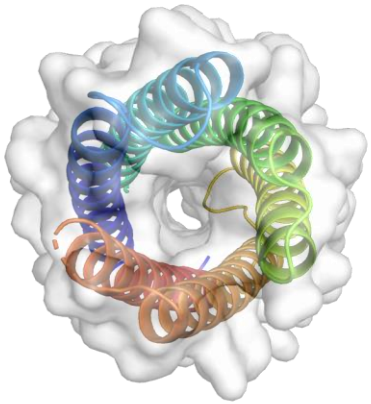




Rg = 21.7 Å; χ^2 =1.3

X-ray crystal structure

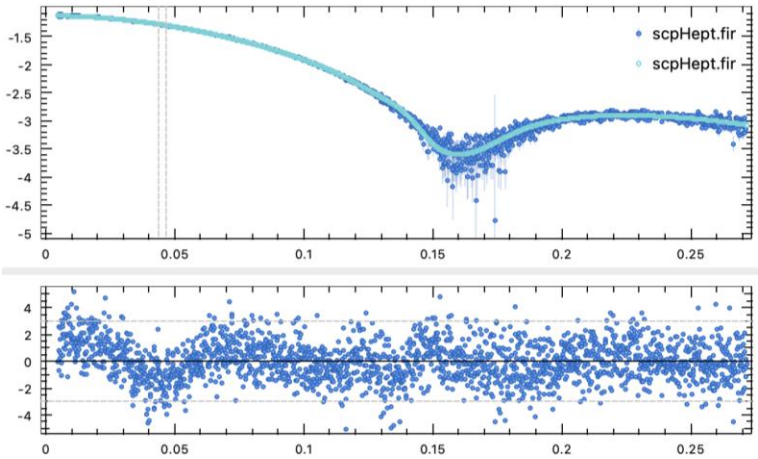


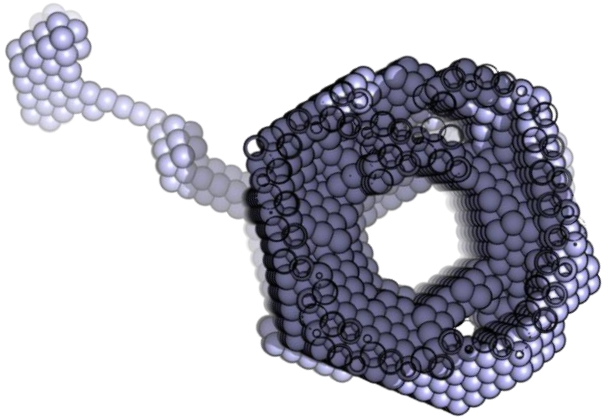


crystal structure
for sc-apCC-6
1.7 Å
R_{work}= 0.24, R_{free} = 0.30

→ single-chain parallel 7+6HB

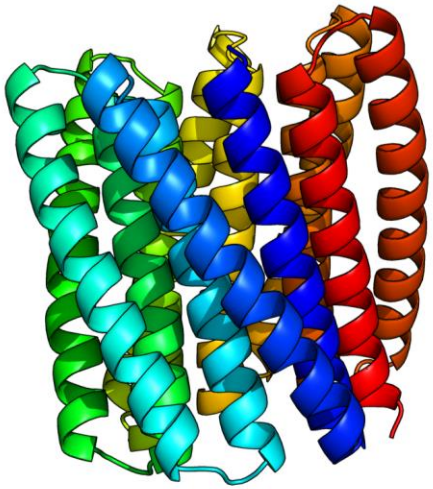
SAXS model

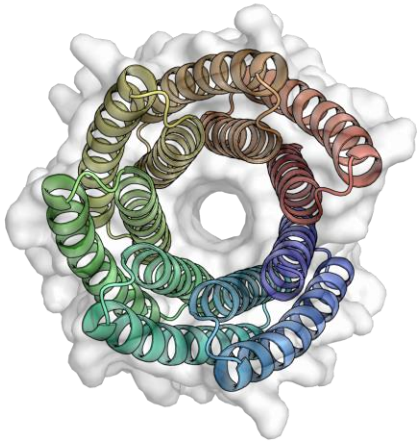




Rg = 23.9 Å; χ^2 = 2.1

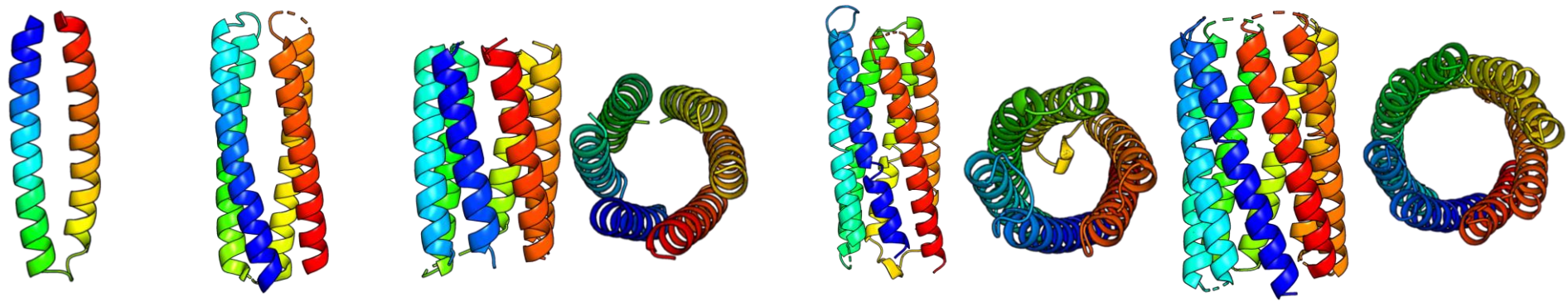
X-ray crystal structure



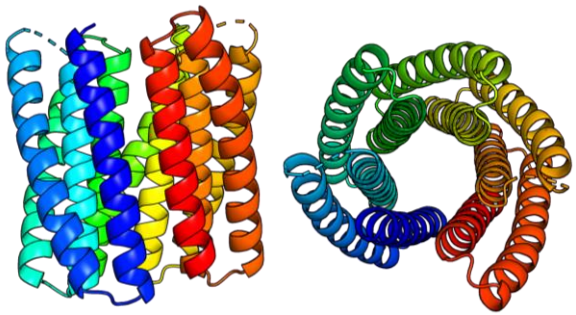


crystal structure
for sc-pCC-7
2.3 Å
R_{work} = 0.19, R_{free} = 0.24

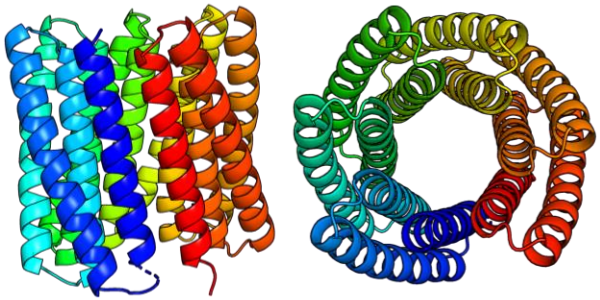
Single-chain *de novo* proteins so far…



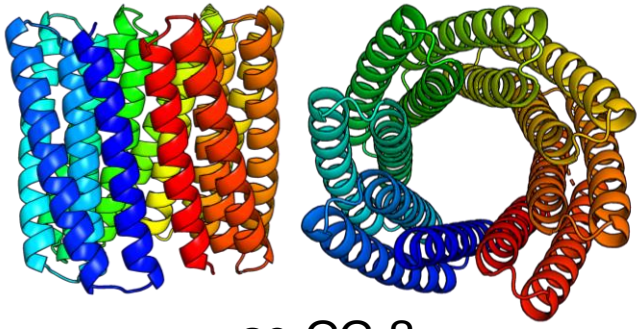
<5 constructs each; 80% success



sc-CC-6
8QAG



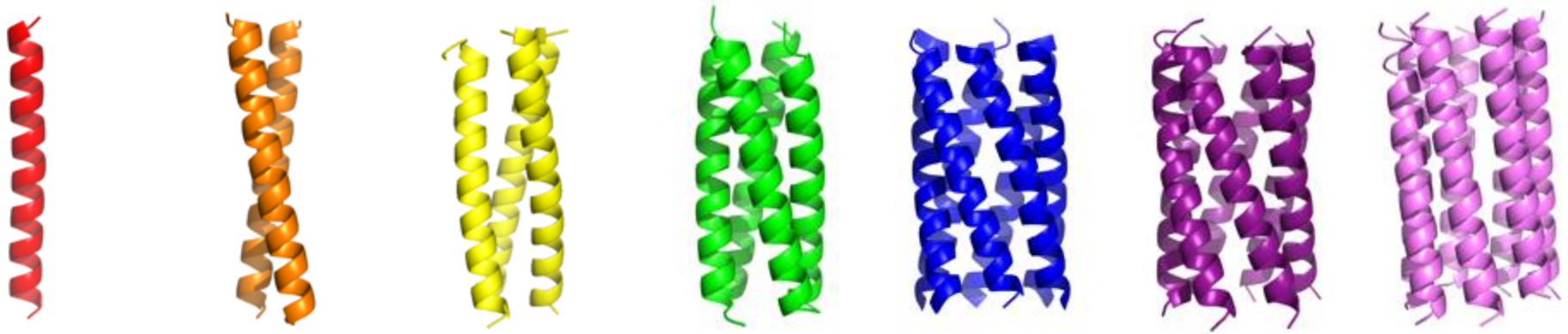
sc-CC-7
8QAI



sc-CC-8
8QAH

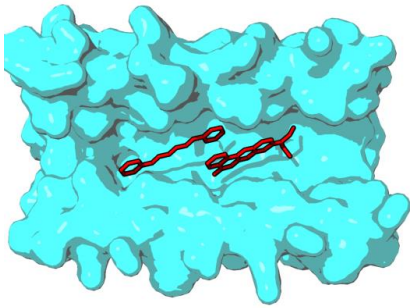
Katherine Albanese, Rokas Petrenas, & Bram Mylemans

Summary

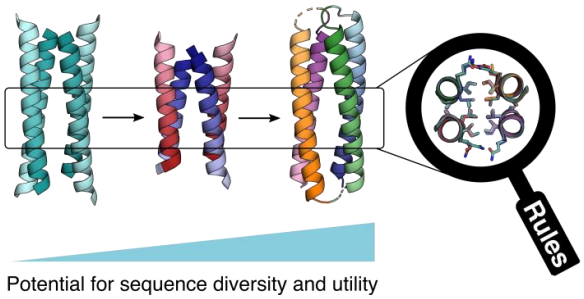


ACS Synth Biol 2012

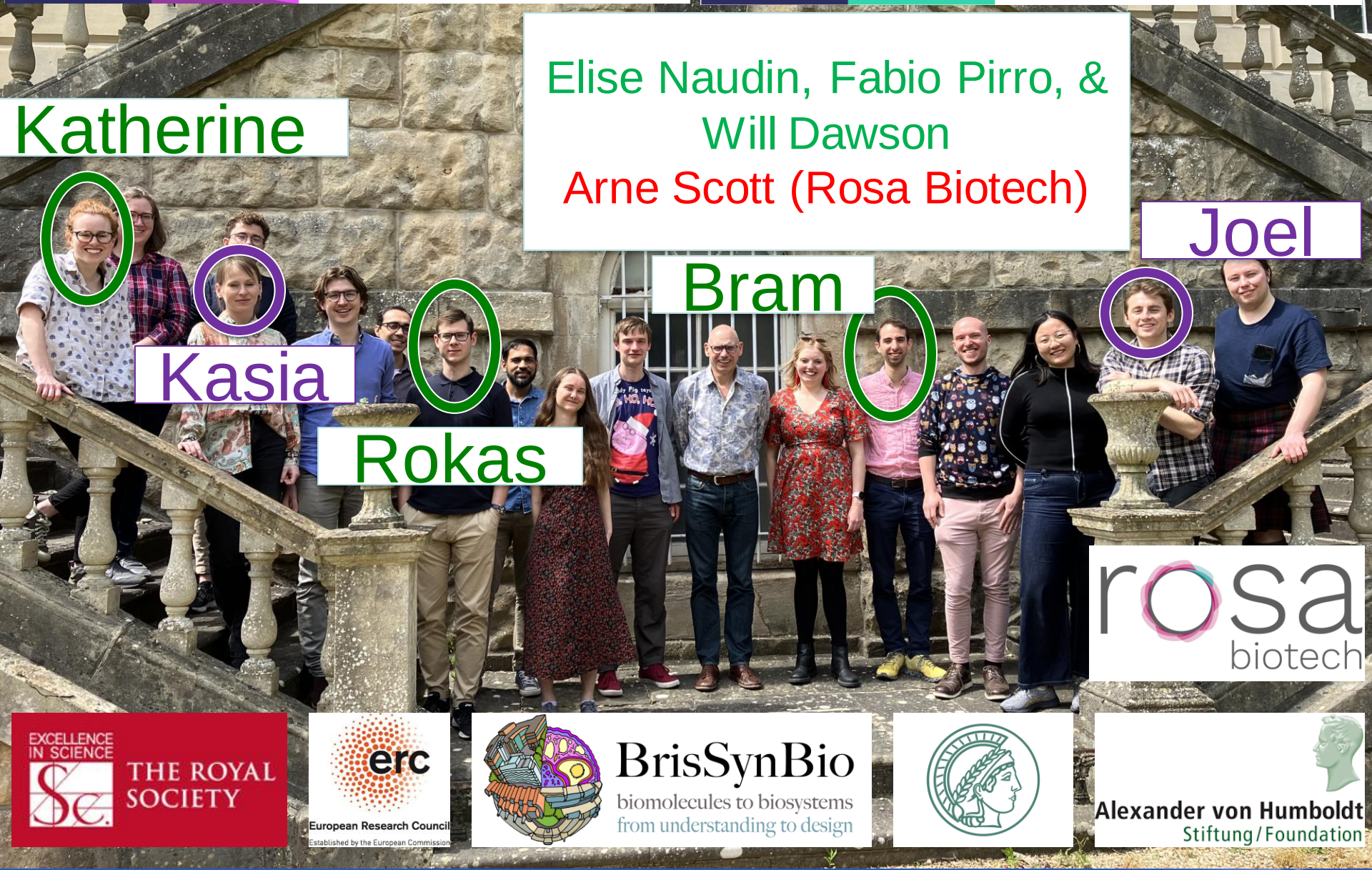
Nature Chem Biol 2011;
Science 2014; Nature Commun 2018



Unpublished



Chem Sci 2022 & Unpublished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