

# Designing protein- protein interfaces

John Karanicolas  
David Baker

# Designing protein- protein interfaces

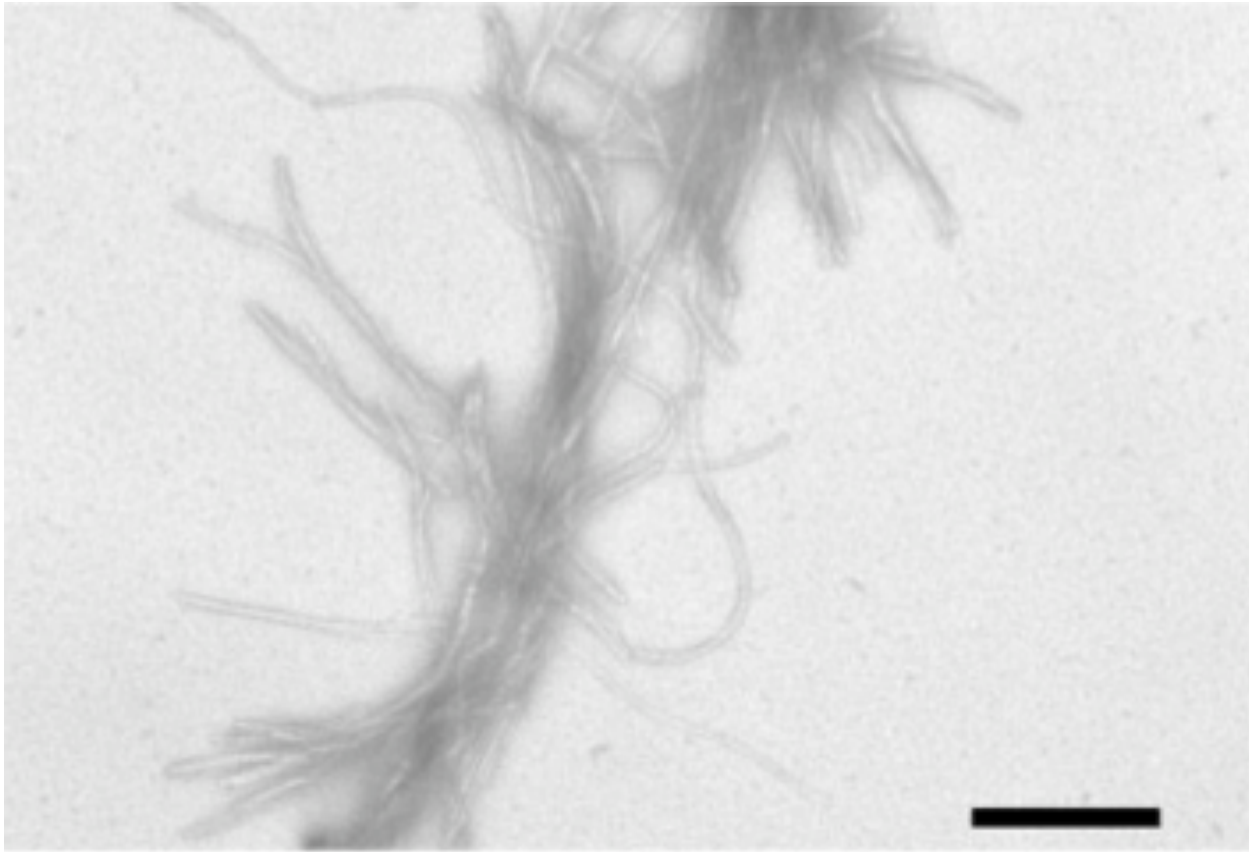
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# Selecting a binding mode

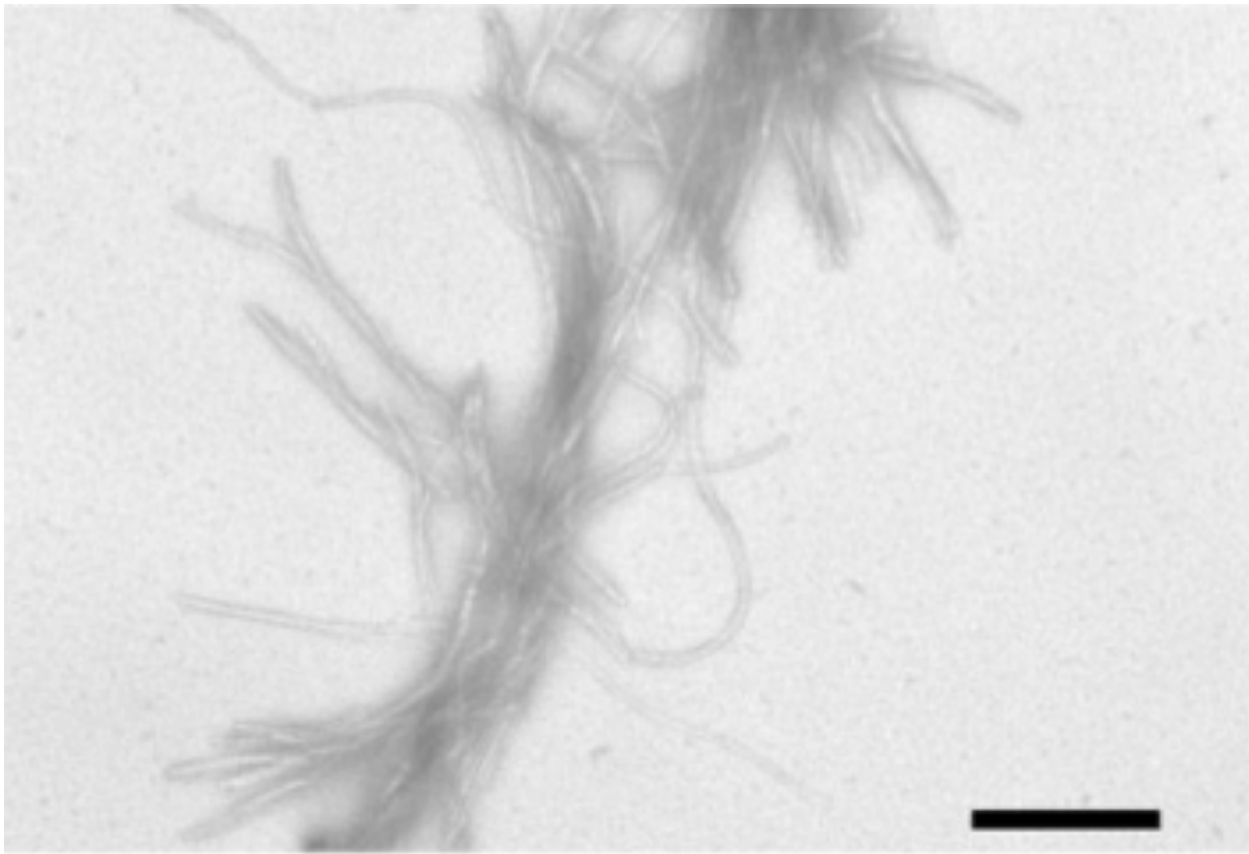
- Redesign a pair of proteins known to bind
- Build model using some prior information (eg. epigraft)
- Random docking (completely *de novo*)

# Tau protein

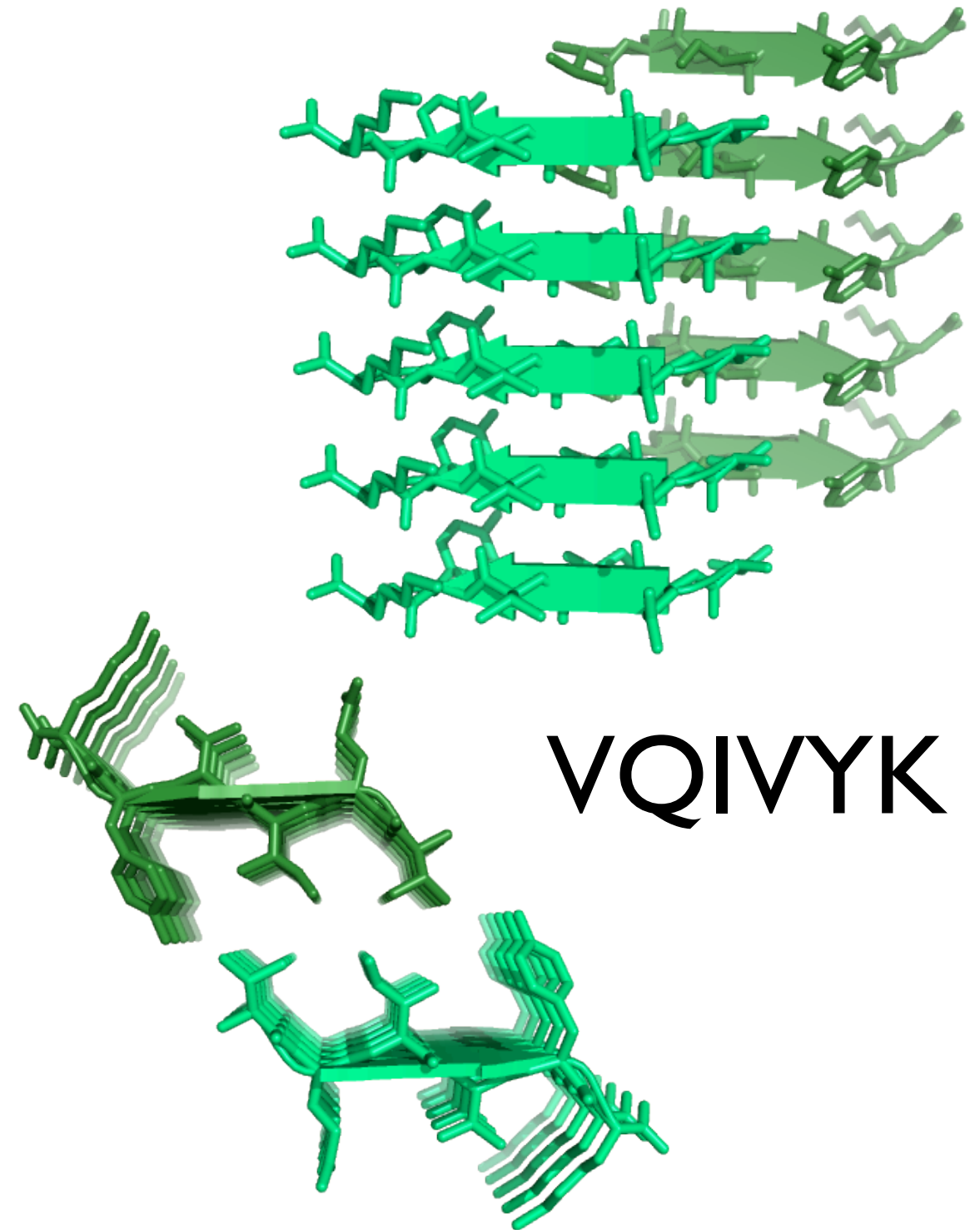


Fibril formation associated with various “tau-opathies” (Alzheimer’s, Parkinsons)

# Tau protein

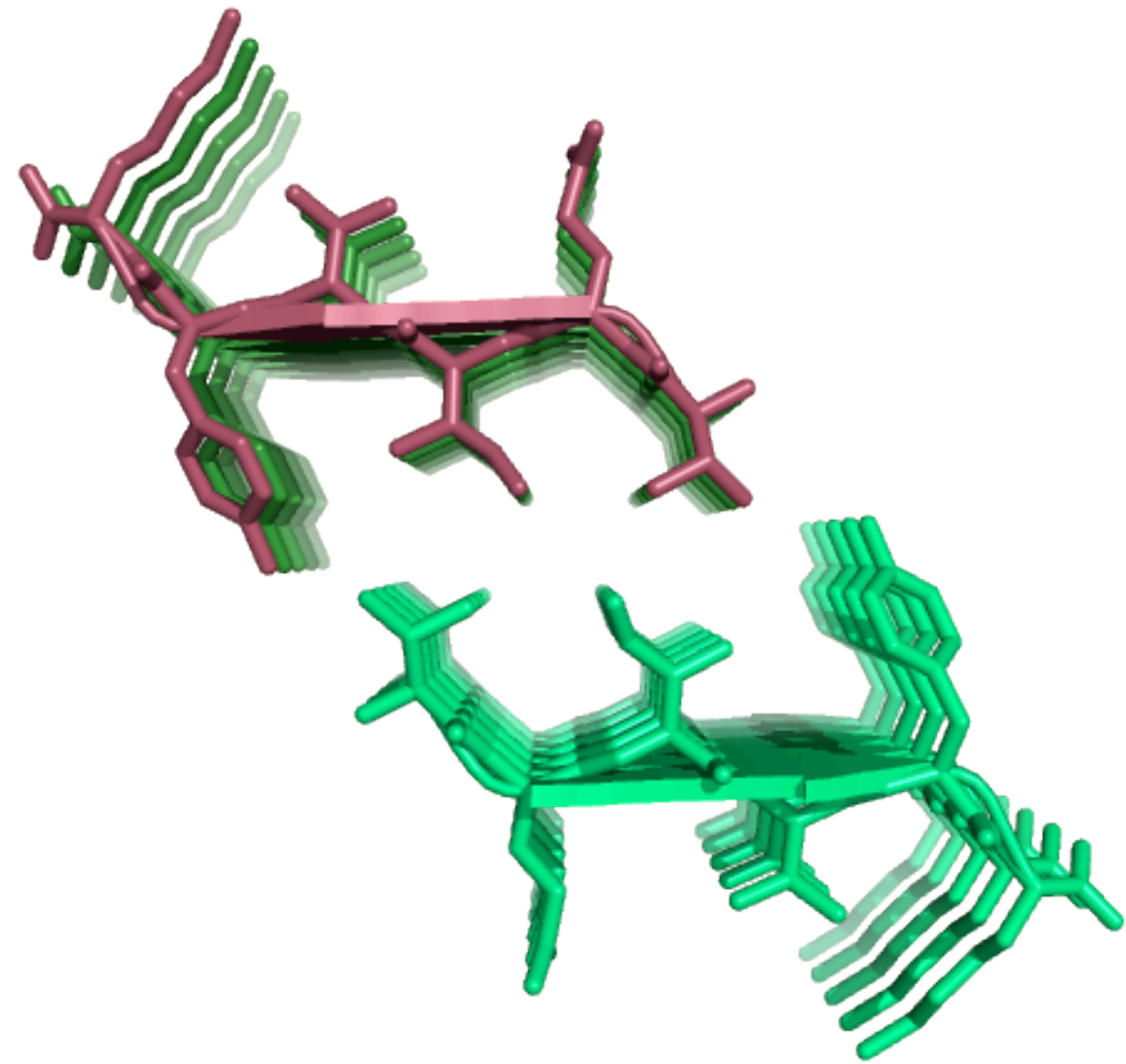
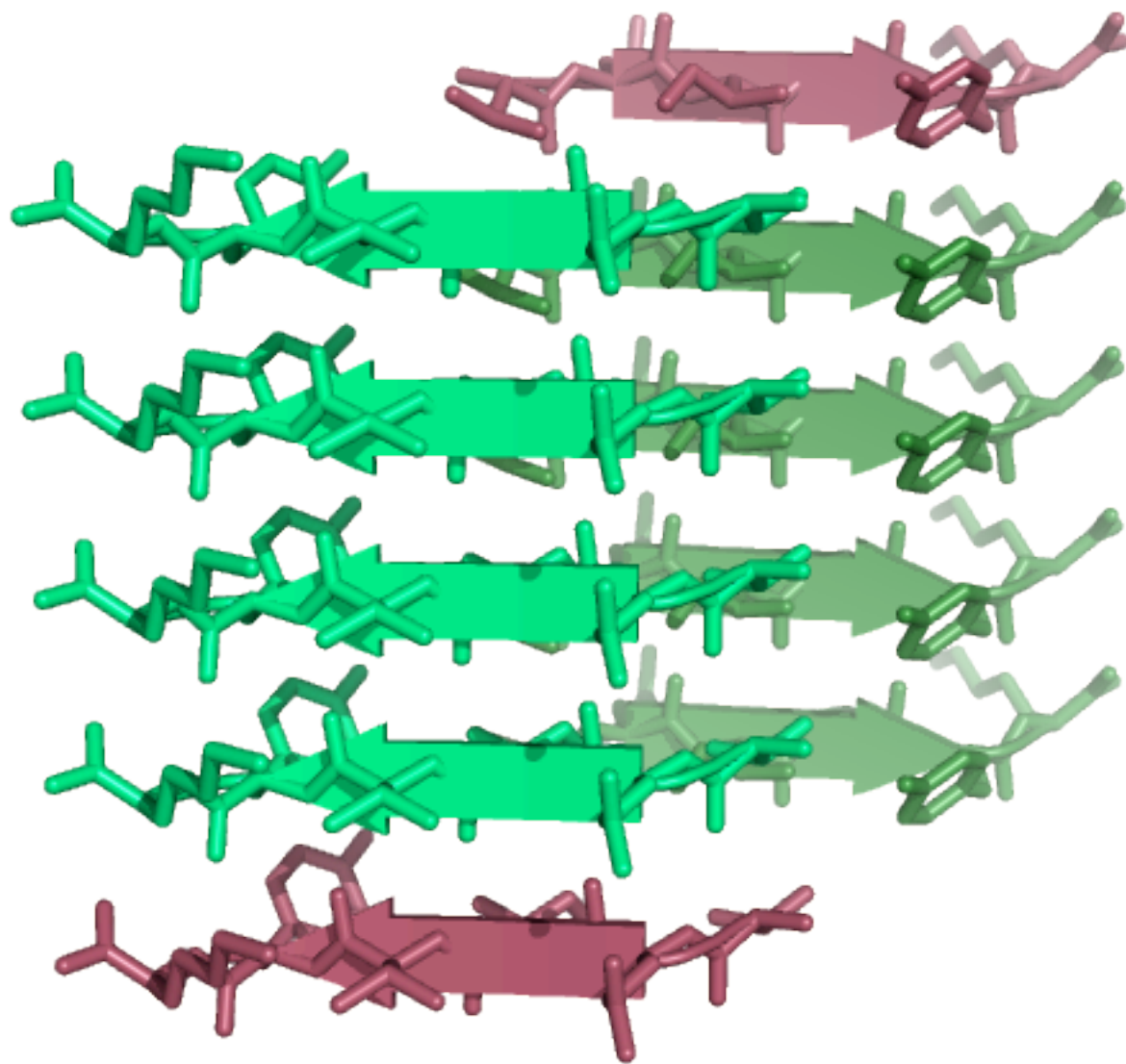


Fibril formation associated with various “tau-opathies” (Alzheimer’s, Parkinsons)



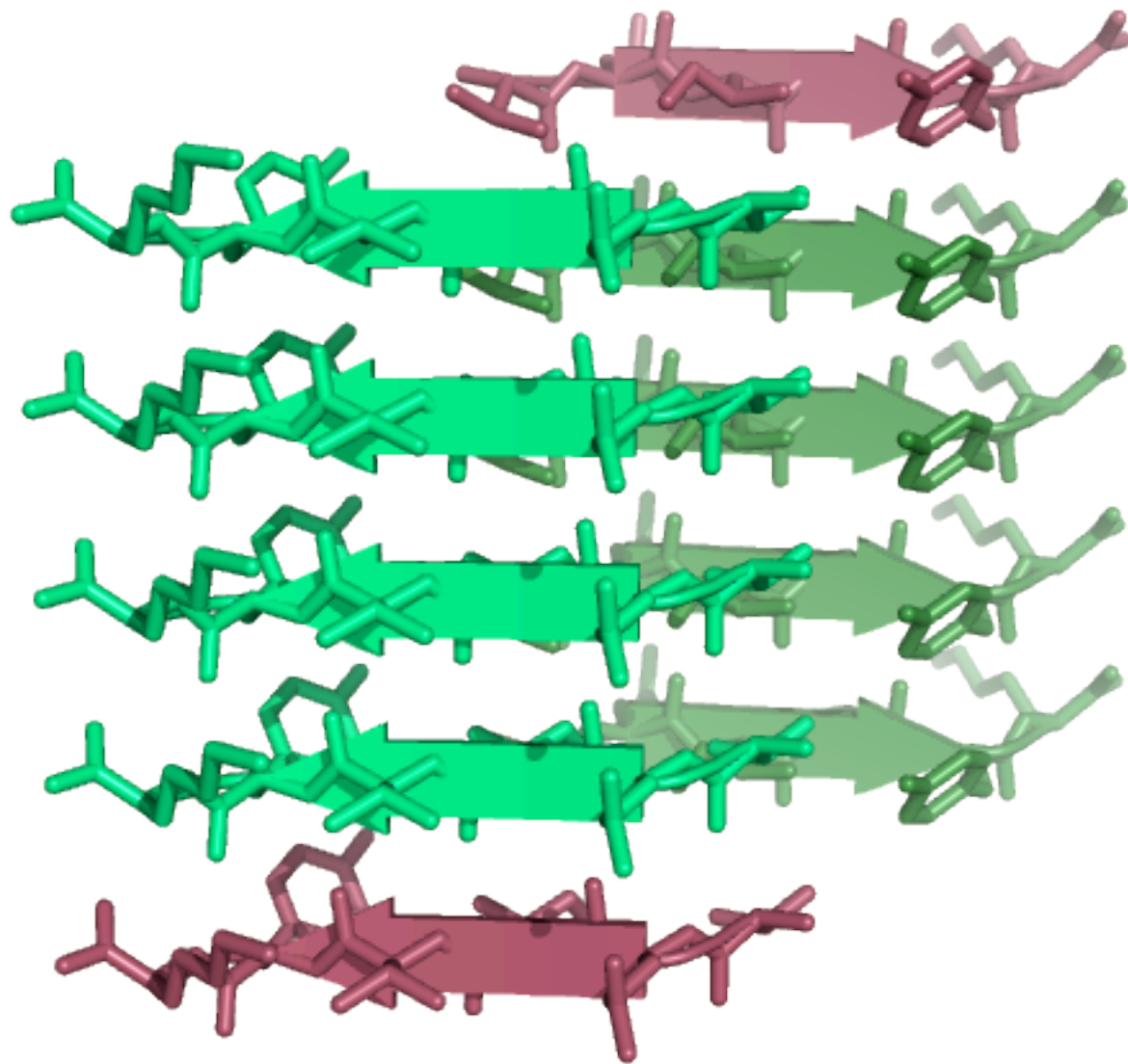
VQIVYK

# Strategy for intervention

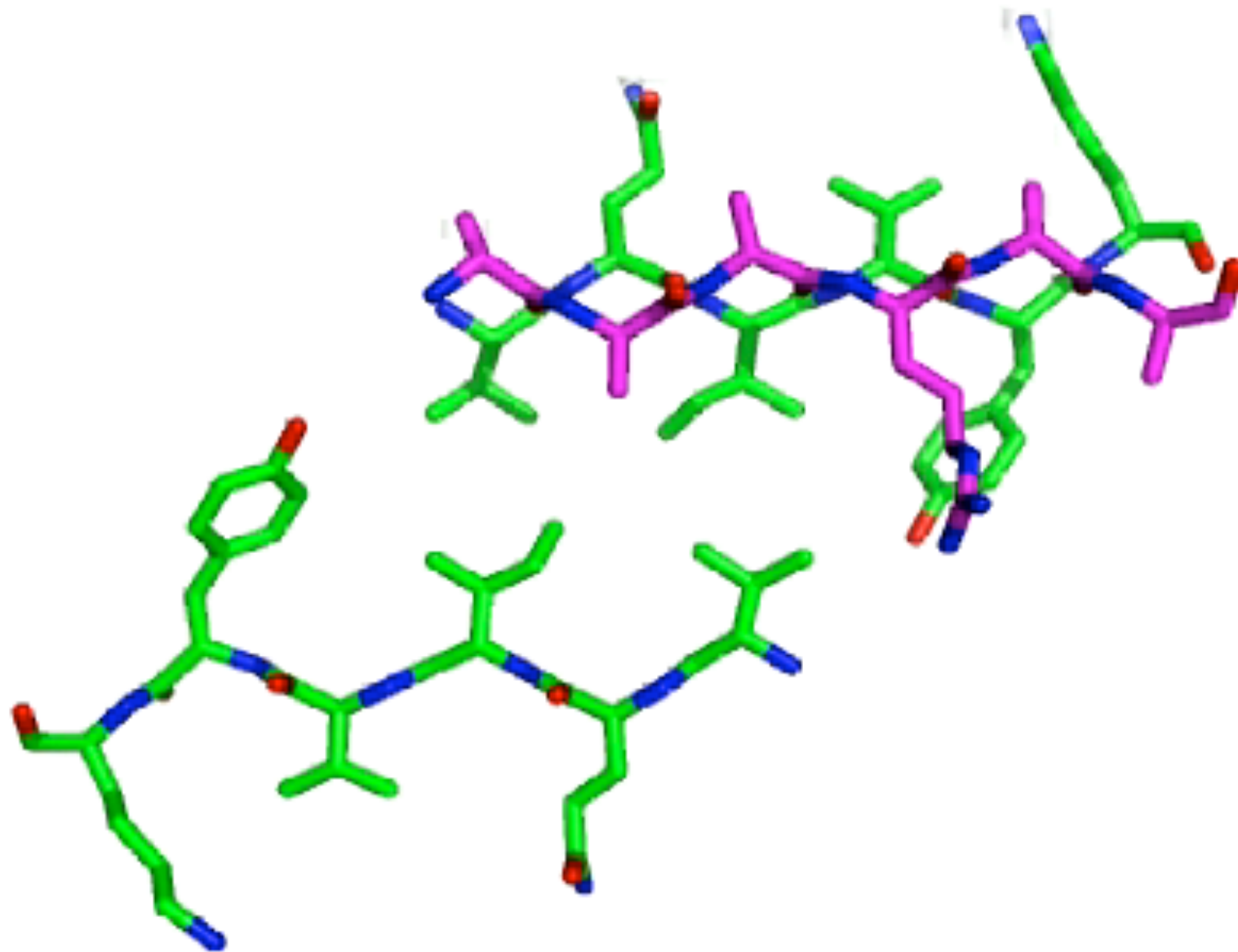




# Strategy for intervention

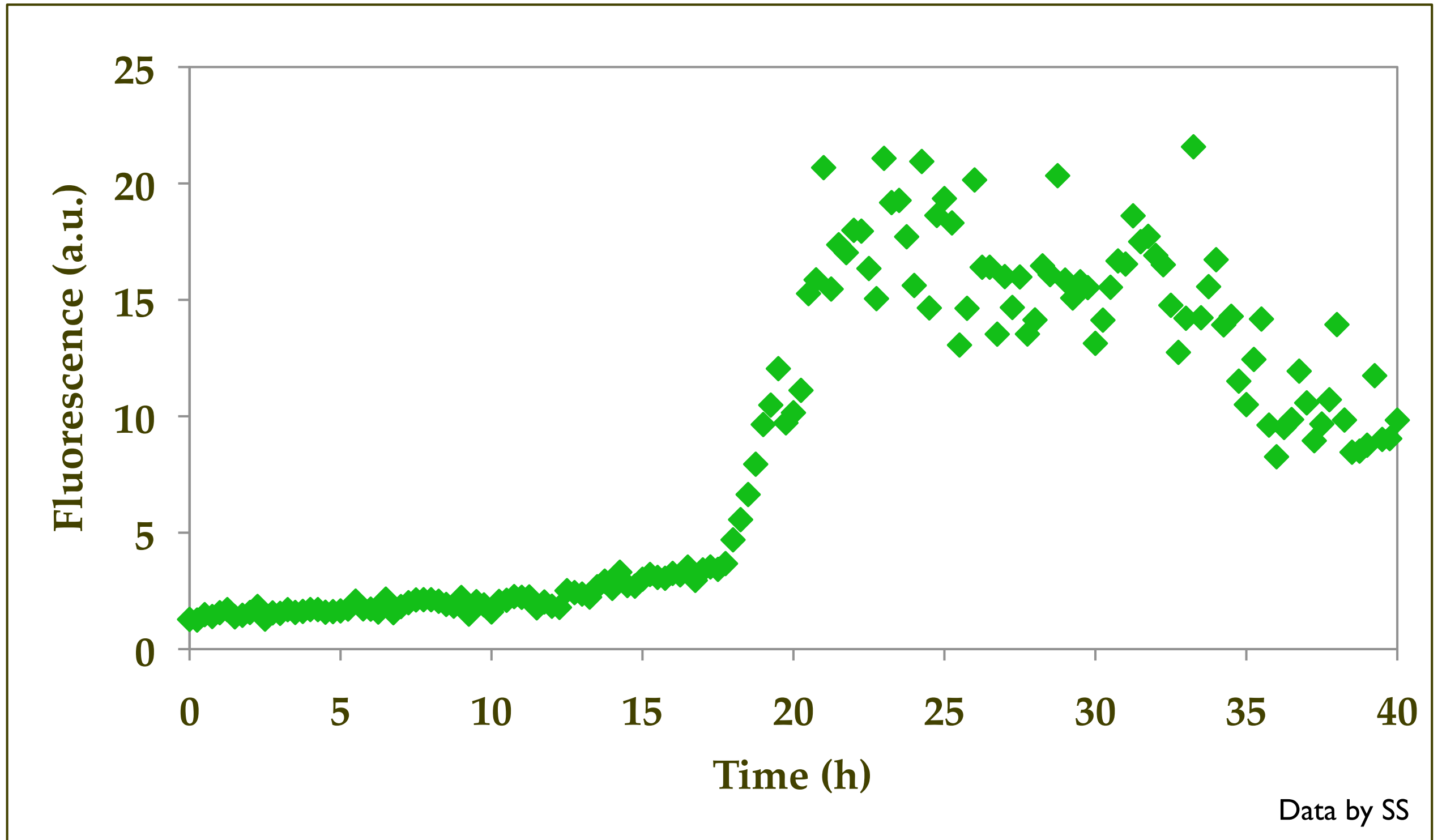


# Designing D-peptides in r++

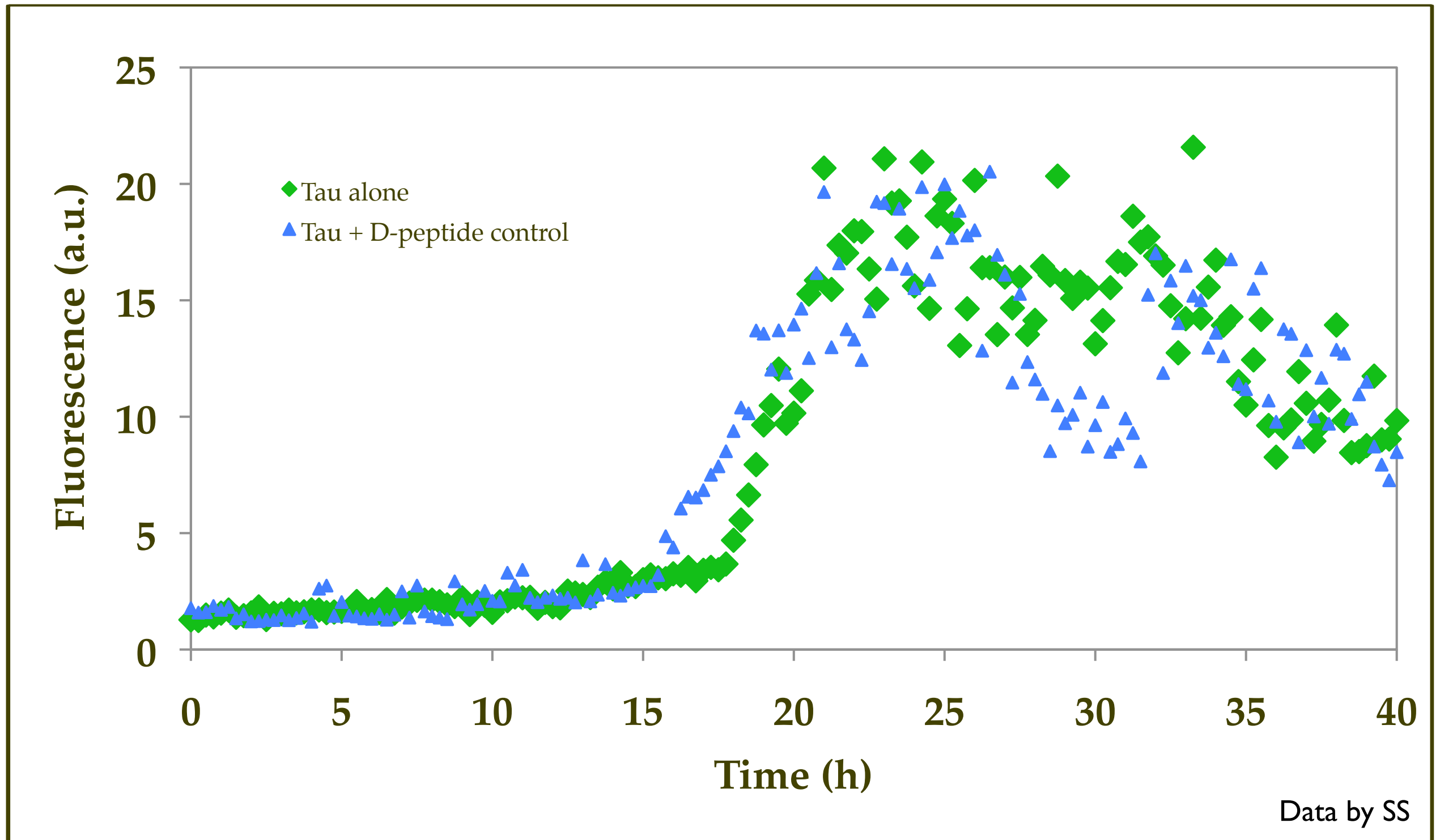




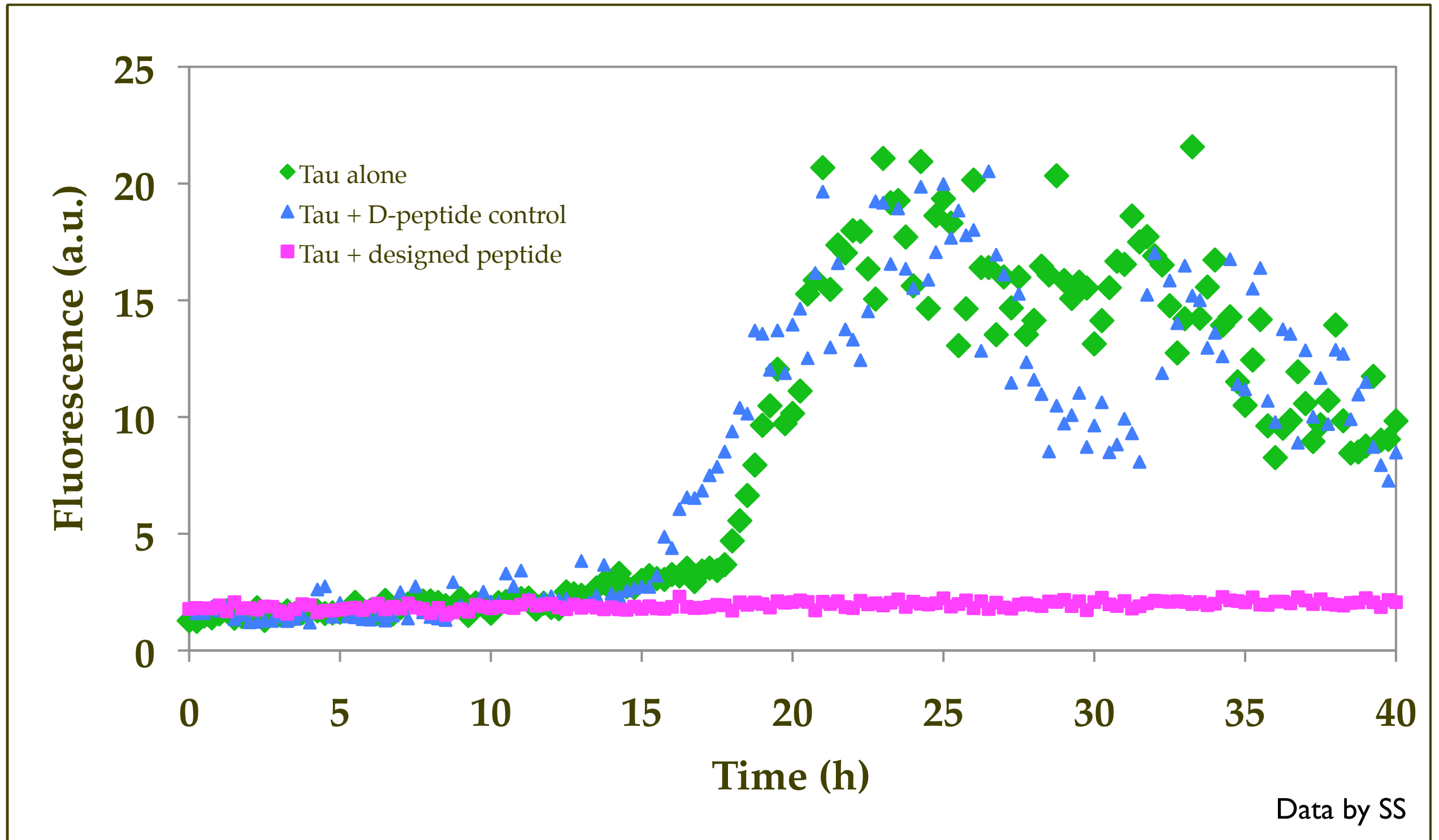
# Assaying fibril formation



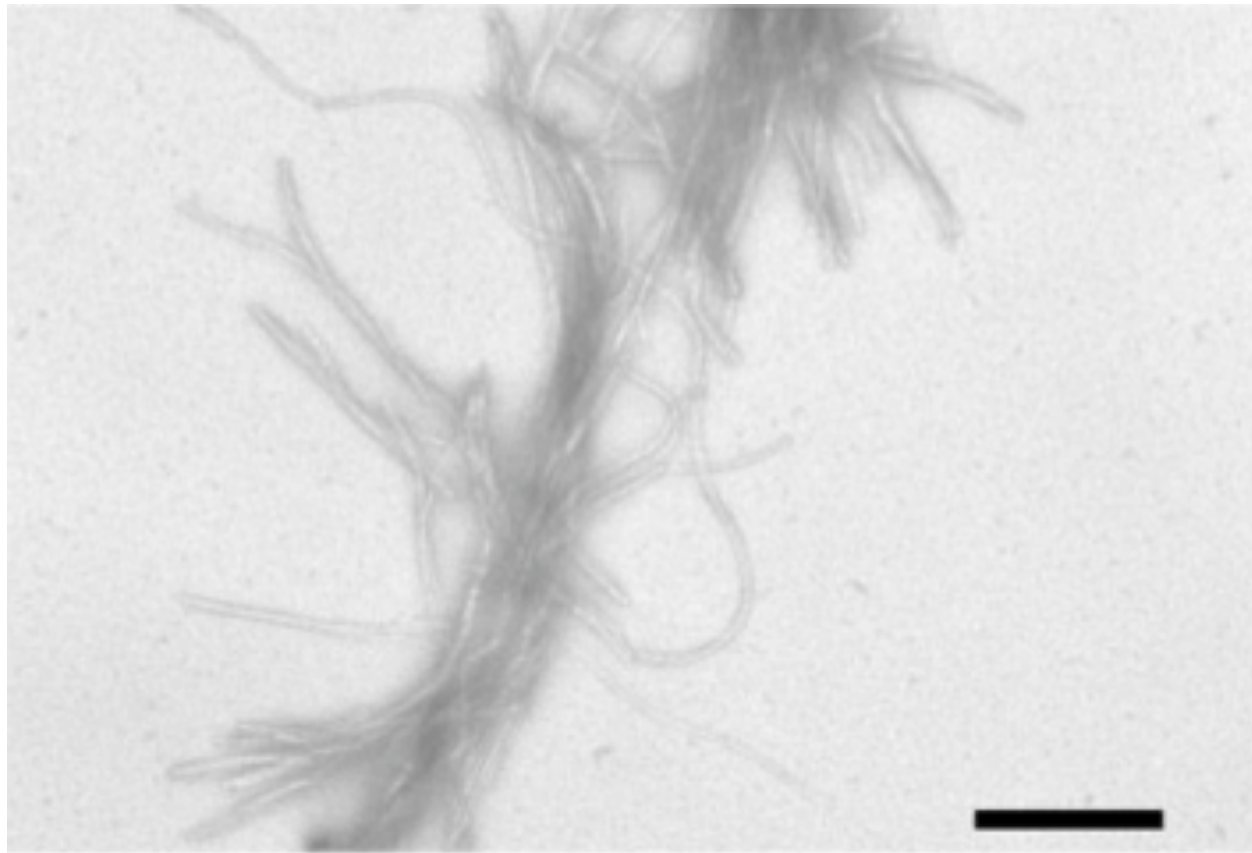
# Assaying fibril formation



# Assaying fibril formation



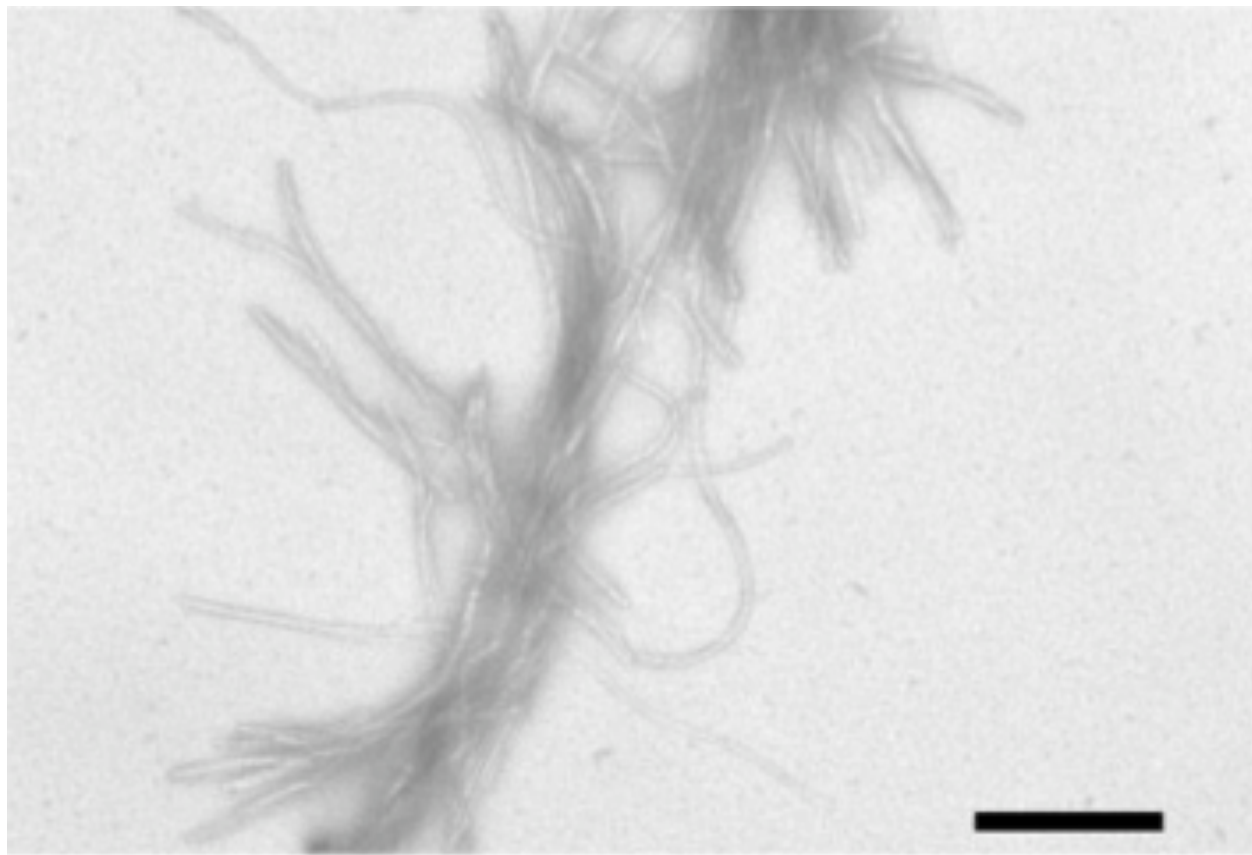
# Assaying fibril formation



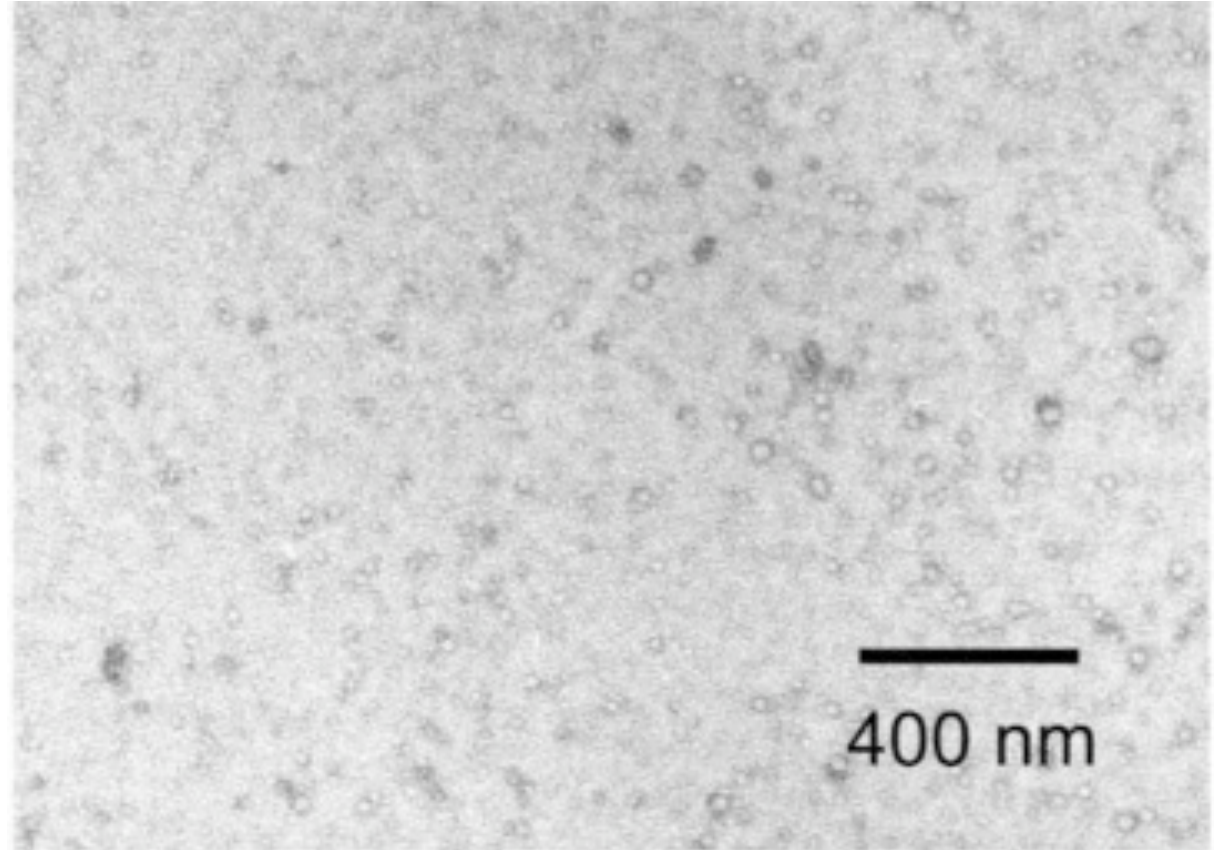
Tau alone



# Assaying fibril formation

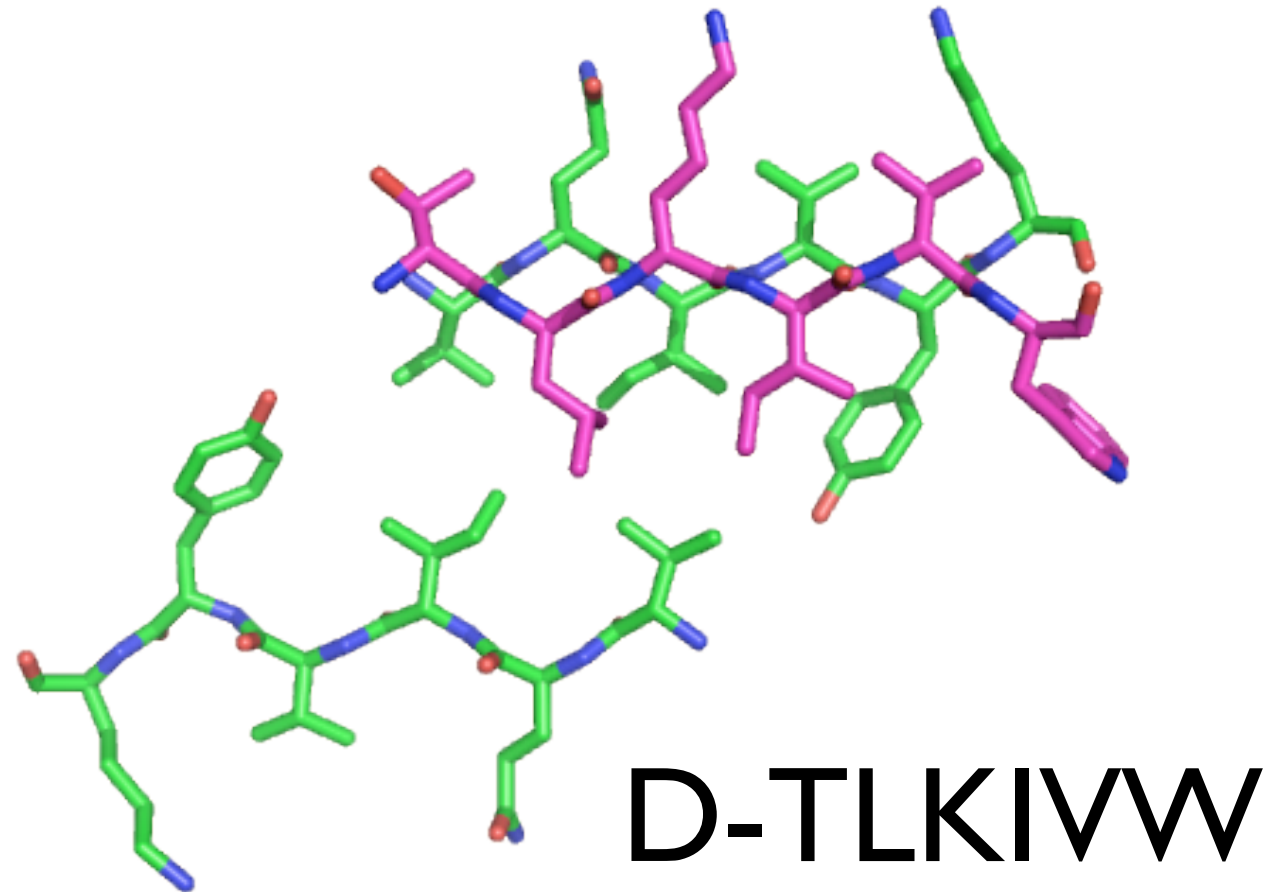
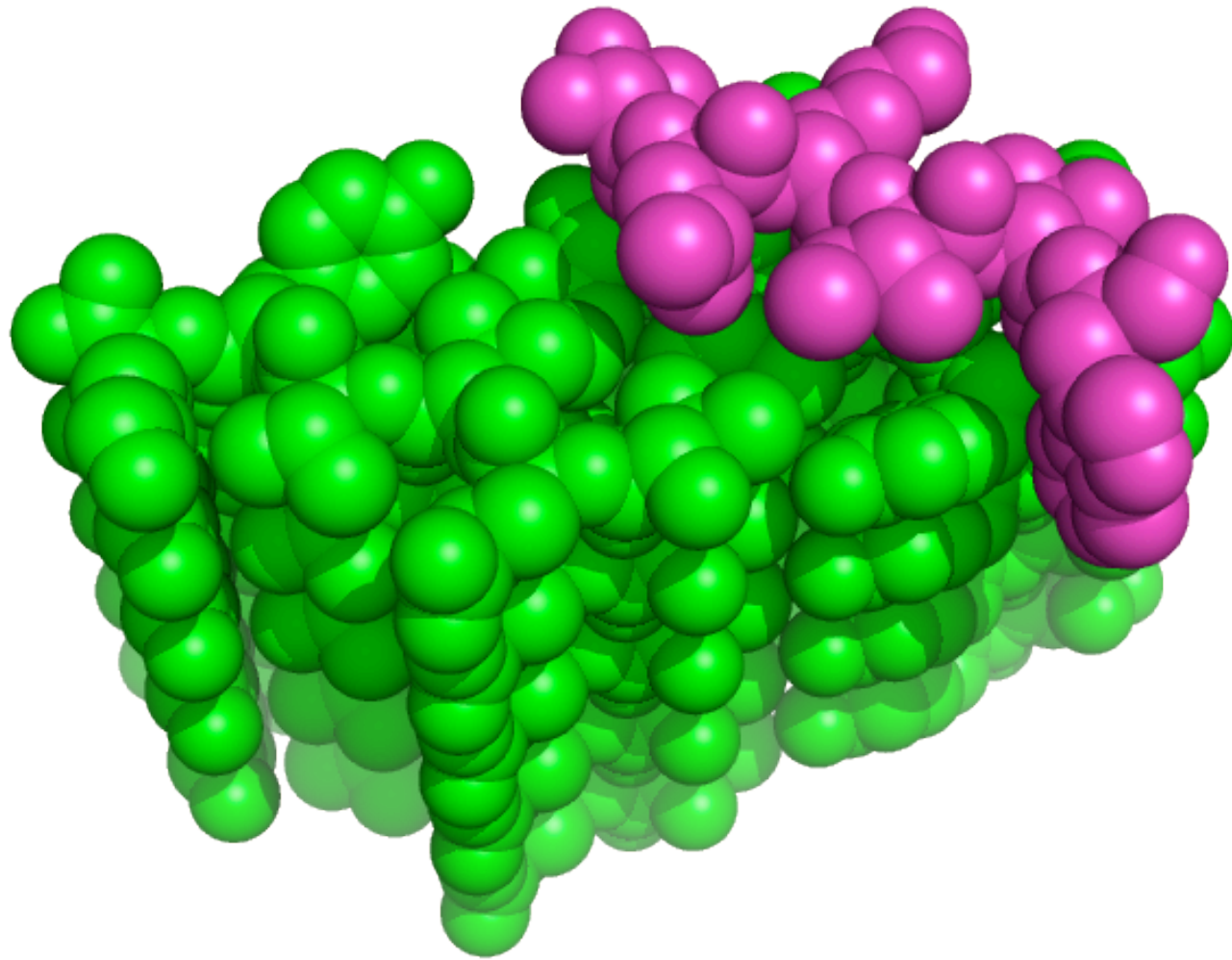


Tau alone



Tau  
+ designed peptide

# Accuracy of design model



- L-TLKIVW doesn't work
- D-TIKWLV, D-TIWKVL, and D-LKTIWV don't work

# Followup questions

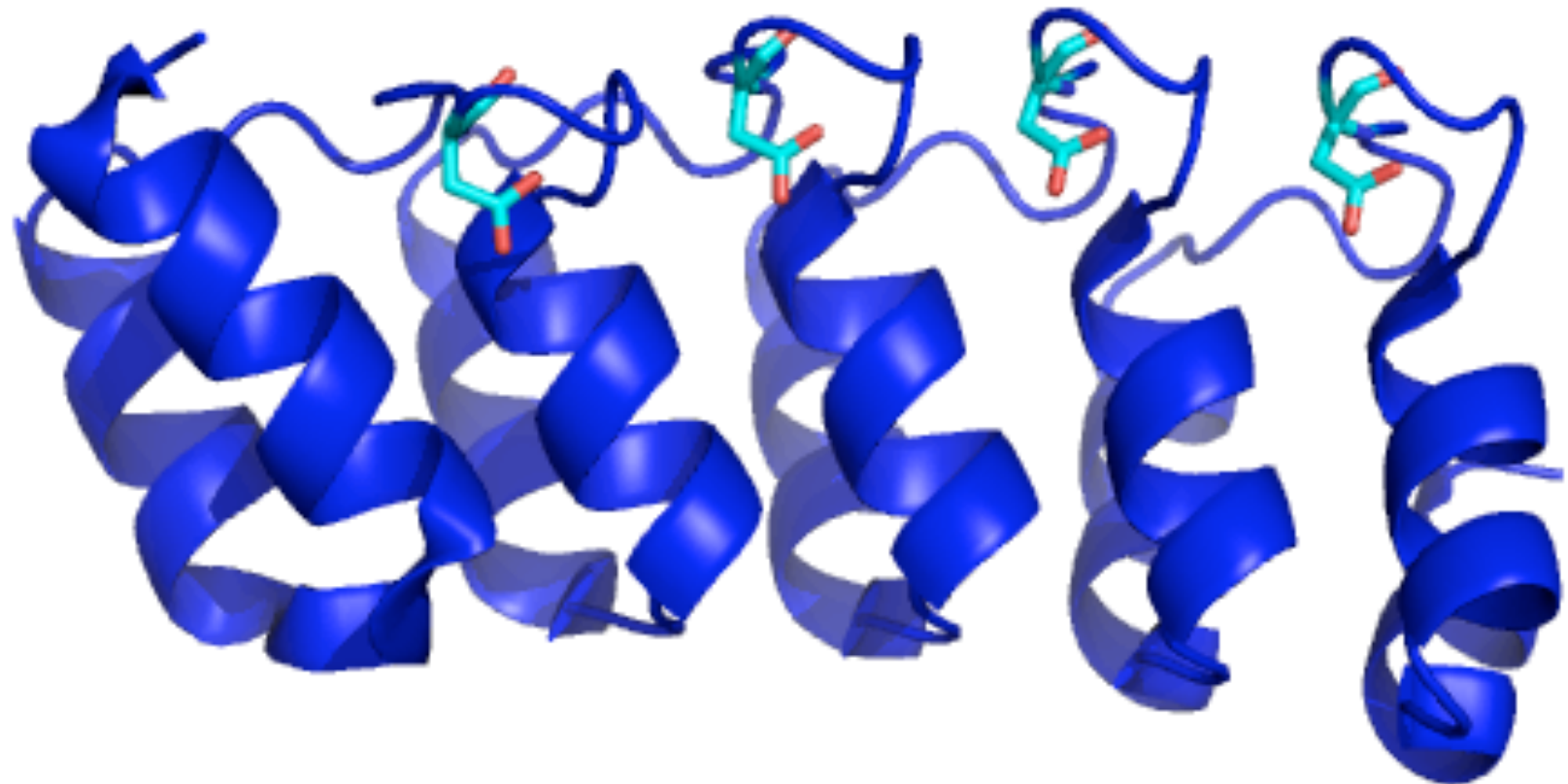
- What's the mechanism of action?
- Can we design peptides against other fibril-forming proteins?
- How will these behave *in vivo?* *in situ?*

Purely *de novo* design



# Aim

- Take two proteins which don't normally interact, redesign them to bind
- Use a consensus Ankyrin Repeat as our scaffold



# Motif-based design

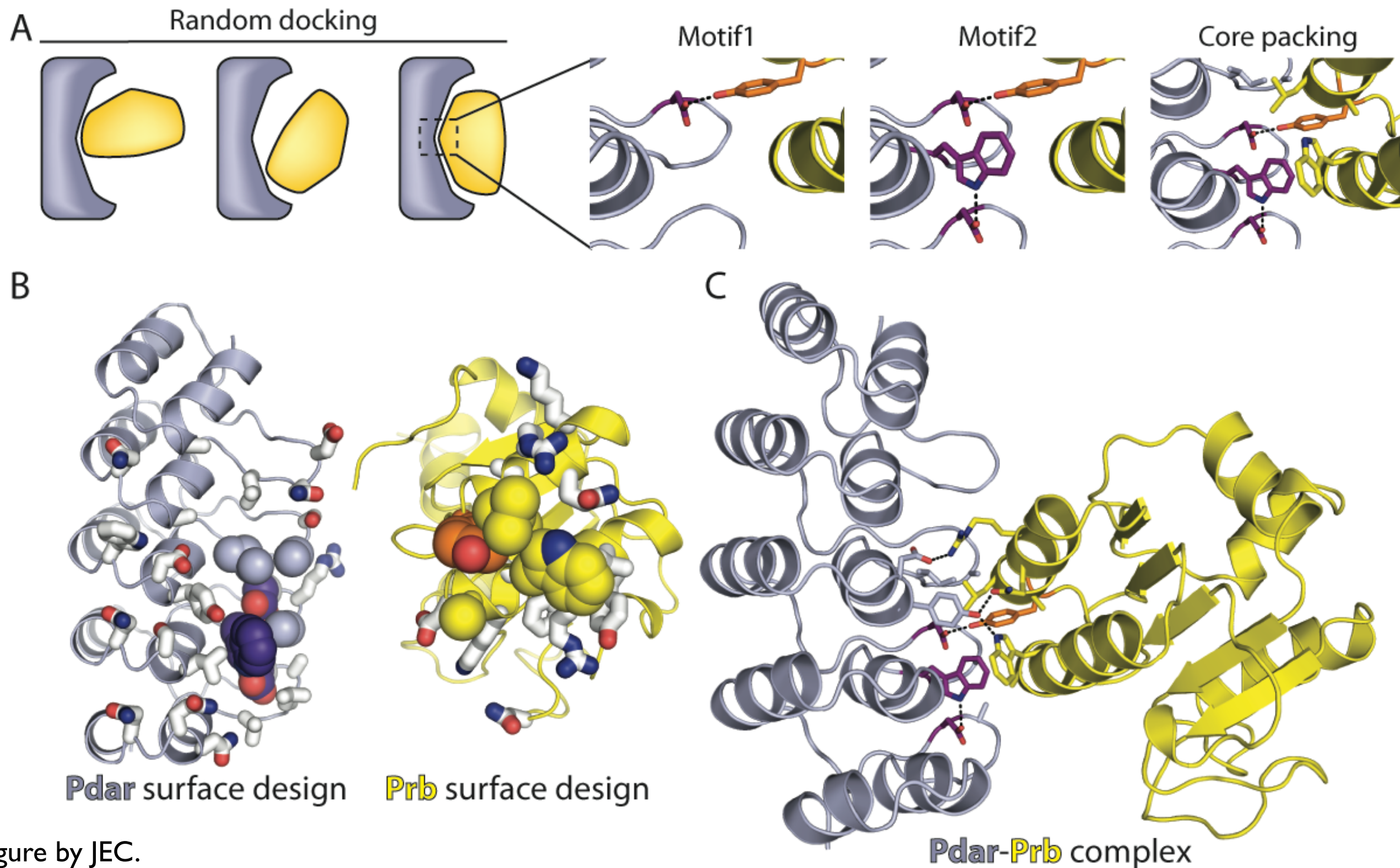
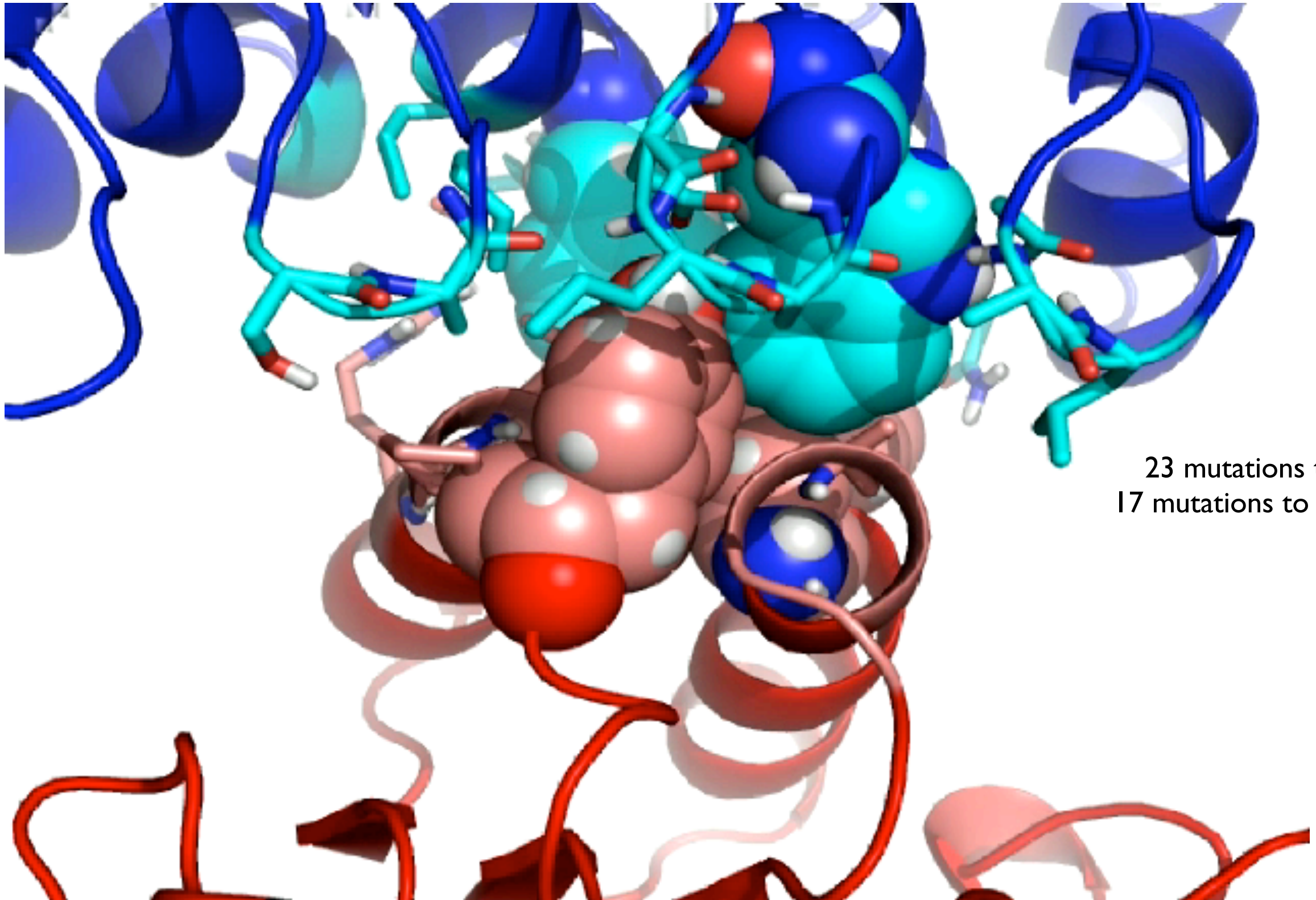


Figure by JEC.

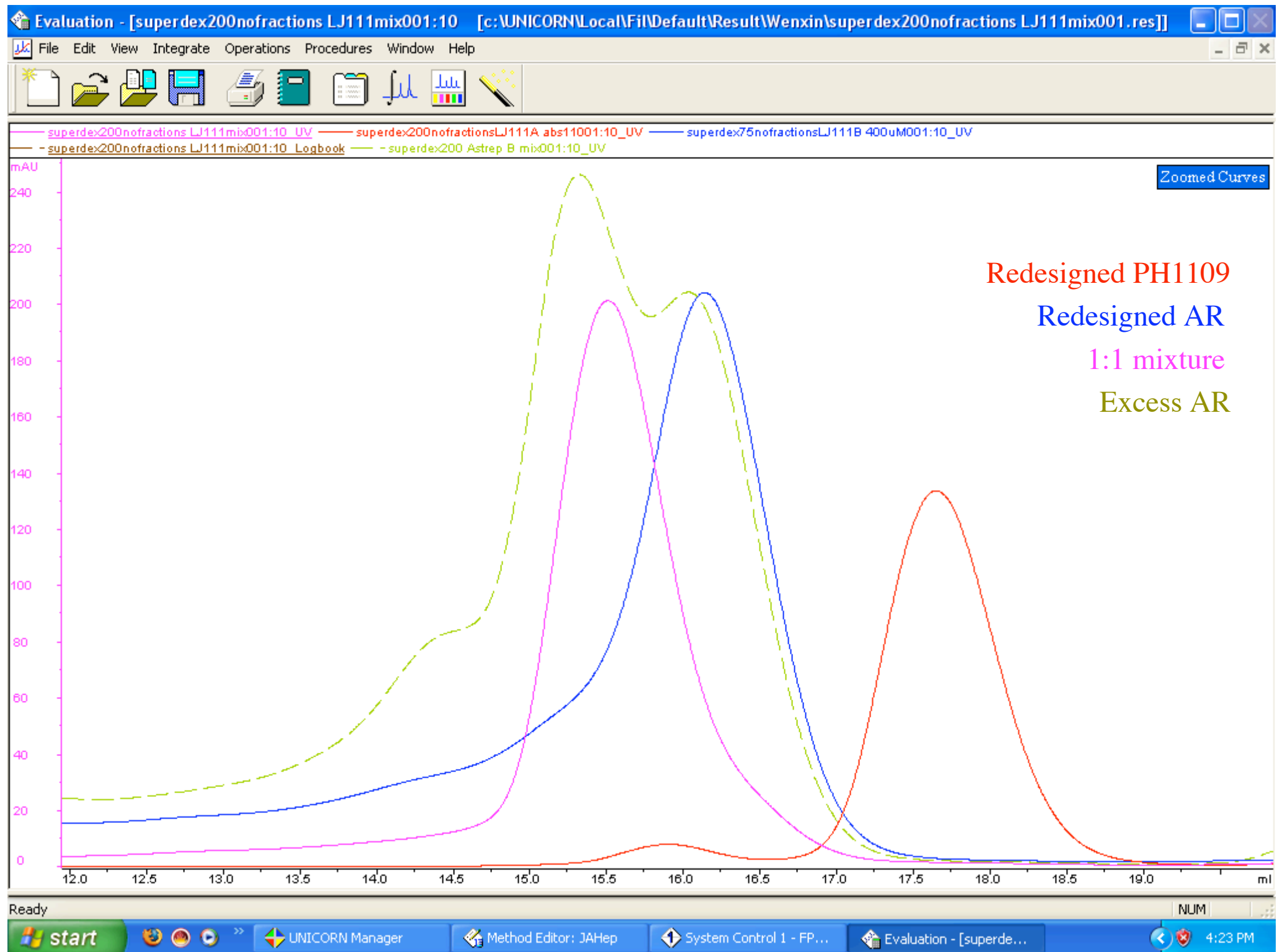


# “Pdar-Prb”



23 mutations to AR  
17 mutations to PHI 109

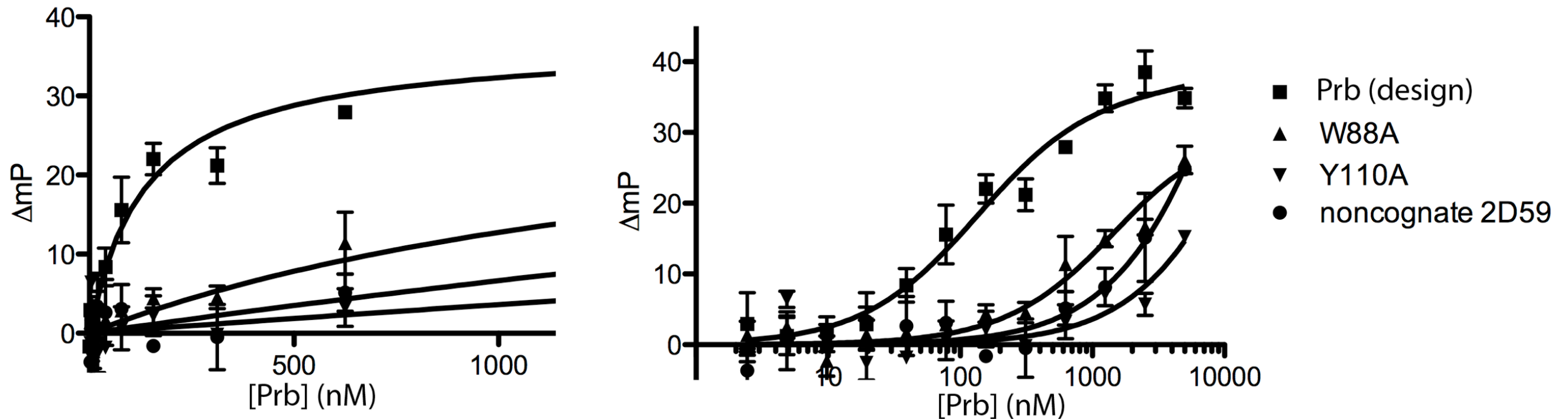
# They co-elute!



Data by LJ  
and WH.

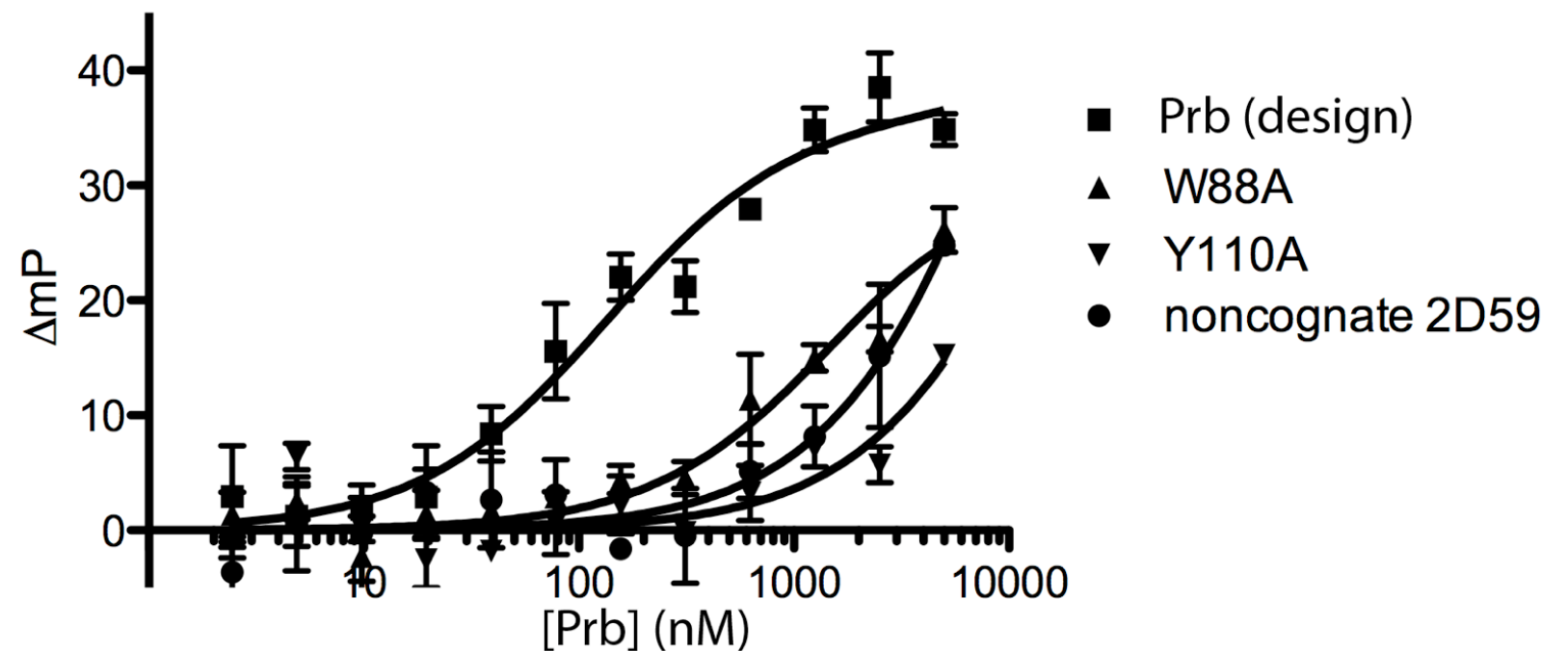
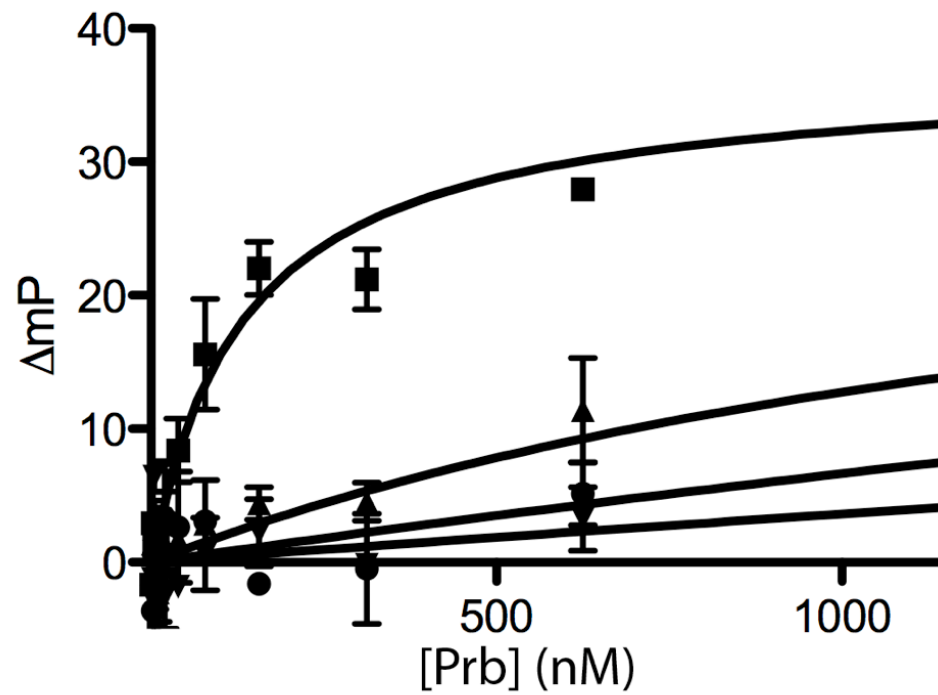


# They really bind great!



$K_d = 130 \text{ nM}$

# They really bind great!



$$K_d = 130 \text{ nM}$$



Data by JEC

# Gazing ahead...



- Further abstraction of motif-based design, with SJF, JEC, EMS (cool things ahead!)
- Application to cytokine biology
  - Restrict a pleiotropic cytokine to a single function
  - We have a binding partner, but we want a binder on a different scaffold

# Acknowledgments

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