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, Parkinson’s)
Tau protein

Fibril formation associated with various “tau-opathies” (Alzheimer’s, Parkinsons)
Strategy for intervention
Strategy for intervention
Designing D-peptides in r++
Assaying fibril formation

Fluorescence (a.u.)

Time (h)

Data by SS
Assaying fibril formation

Data by SS
Assaying fibril formation

Fluorescence (a.u.) vs. Time (h)

- Tau alone
- Tau + D-peptide control
- Tau + designed peptide

Data by SS
Assaying fibril formation

Tau alone

Data by SS
Assaying fibril formation

Tau alone

Tau + designed peptide

Data by SS
Accuracy of design model

- L-TLKIVW doesn’t work
- D-TIKWLV, D-TIWKVL, and D-LKTWIV 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

A. Random docking

B. Pdar surface design

C. Prb surface design

Pdar-Prb complex

Figure by JEC.
“Pdar-Prb”

23 mutations to AR
17 mutations to PH1109
They co-elute!

Redesigned PH1109
Redesigned AR
1:1 mixture
Excess AR

Data by LJ and WH.
They really bind great!

Kd = 130 nM

Data by JEC
They really bind great!

![Graphs showing binding affinity with Kd = 130 nM]

Kd = 130 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
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