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Mirror Therapeutics:

Empowering Nature's Fragile Warriors

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<u>Disclosures</u>
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SAB member: Aizen Therapeutics

ABC's of D-peptides

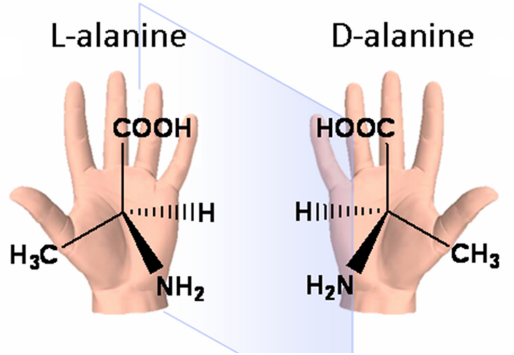
- D-peptides are composed of D-amino acids (mirror-images of natural L-amino acids)

  -Key benefit: not degraded by proteases

    -less frequent/lower dosing

    -poorly recognized by immune system

- No examples in nature – so how do we design them?



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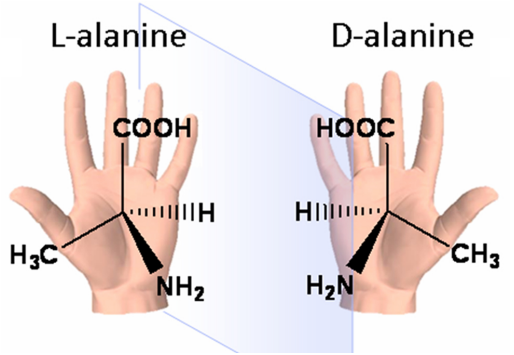
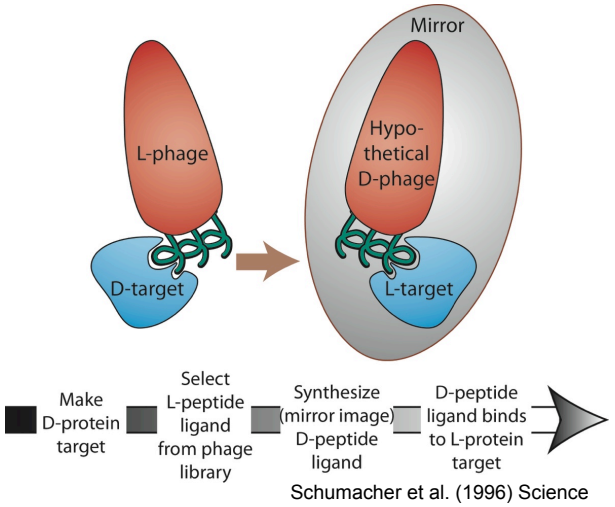


Mirror-image phage display

-screens library of >10^{10} peptide sequences against a mirror-image (D-protein) target

-hit optimization via structure-guided design & additional rounds of phage display



Schumacher et al. (1996) Science

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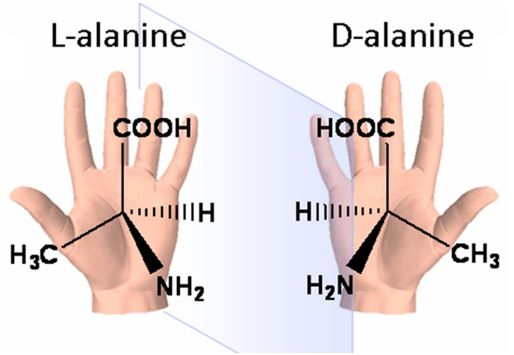

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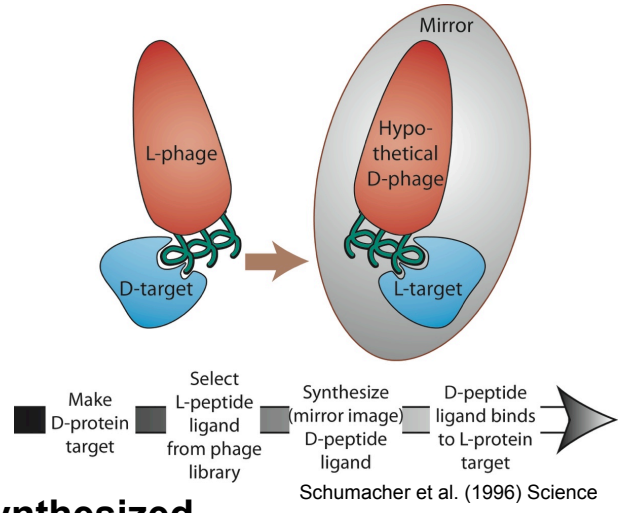

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Major limitation: D-targets must be chemically synthesized

Longing for larger targets: tools of the trade

Solid-phase peptide synthesis
(robust up to ~50 aa)

Dawson, Muir, Clark-Lewis, & Kent, *Science* 266: 776 (1994)
Weinstock et al., *PNAS* 111: 11679 (2014)

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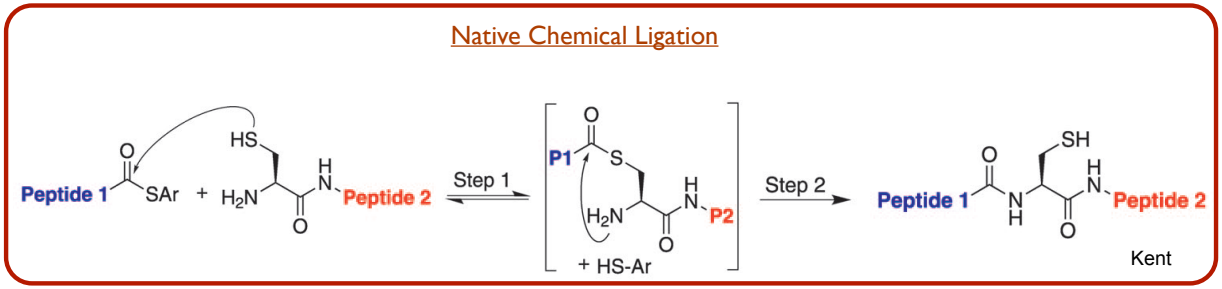

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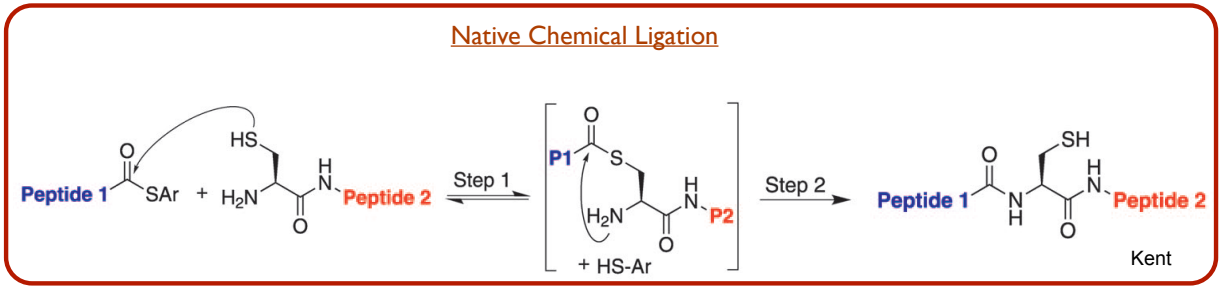

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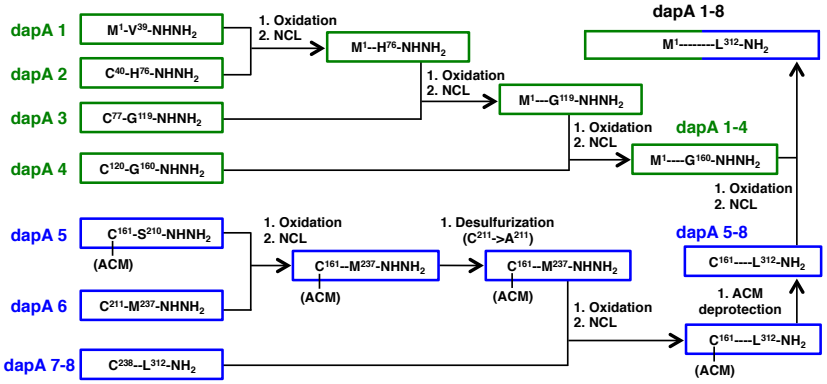
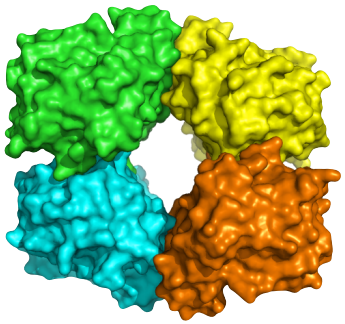


ligation "bracket"



312-AA
DapA
PDB: 1DHP

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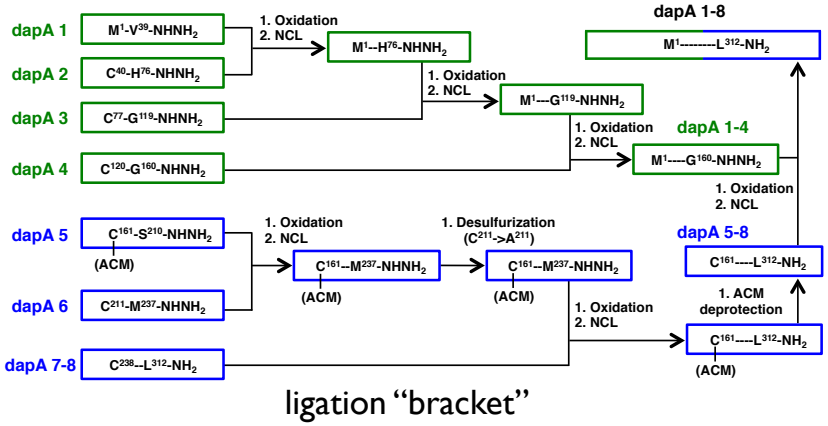

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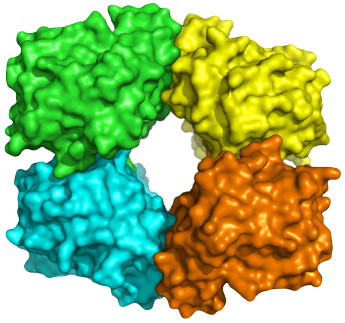

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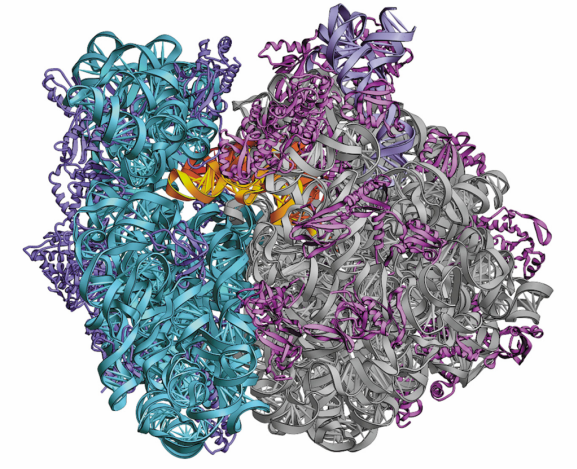
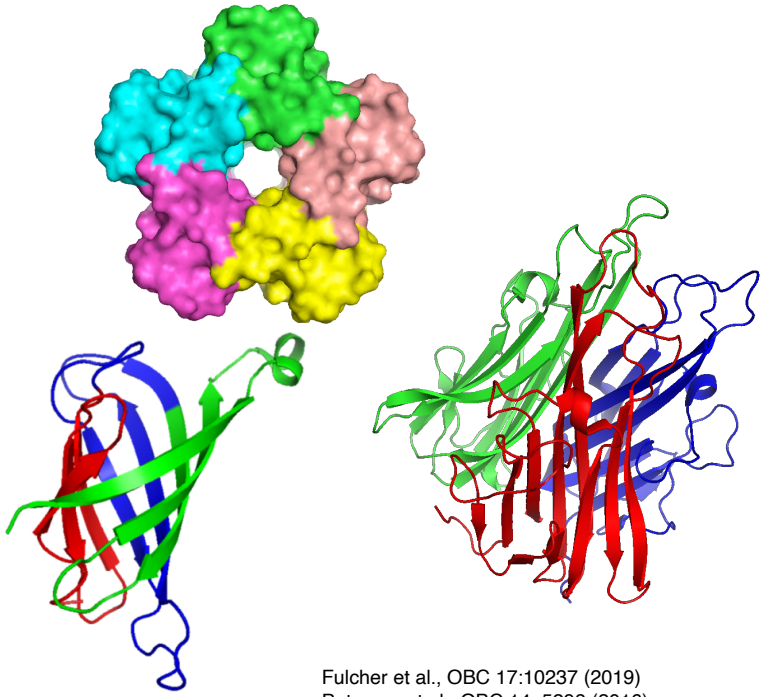
Driving Demand for Efficient Production of Larger D-proteins

- Larger targets for mirror drug screening
- Mirror proteins for diagnostics/therapeutics (most demanding)
- Mirror proteins for mirror manufacturing (e.g., polymerases, ligases)
- D-ribosome
- Recombinant mirror protein manufacturing



2.3 MDa complex, 3 RNAs, 54 proteins

Ribosome image from Noller Lab



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Giesler RJ et. al. ChemRxiv 20r8k (2025)