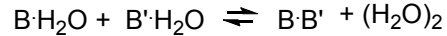


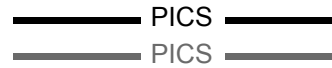
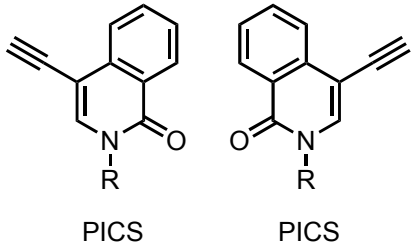
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Hydrophobic Base Pairs

Orthogonal H-bond Base Pairs



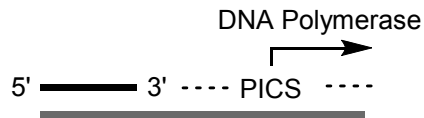
Hydrophobic Base Pairs



Base Pair	TM (°C)
PICS/PICS	62.6
PICS/A	55.5
PICS/T	53.7
PICS/G	51.4
PICS/C	54.5
A:T	59.2
C:G	60.7

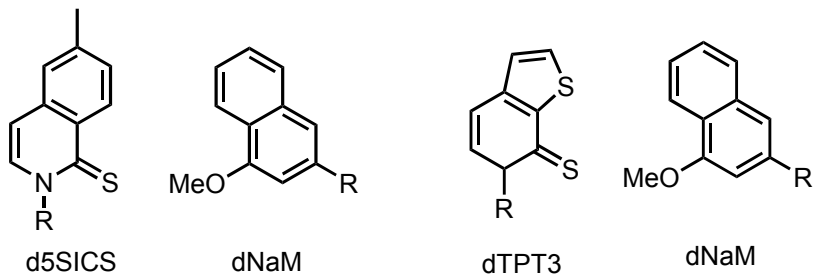
Excellent thermodynamic stability

Potential Problems

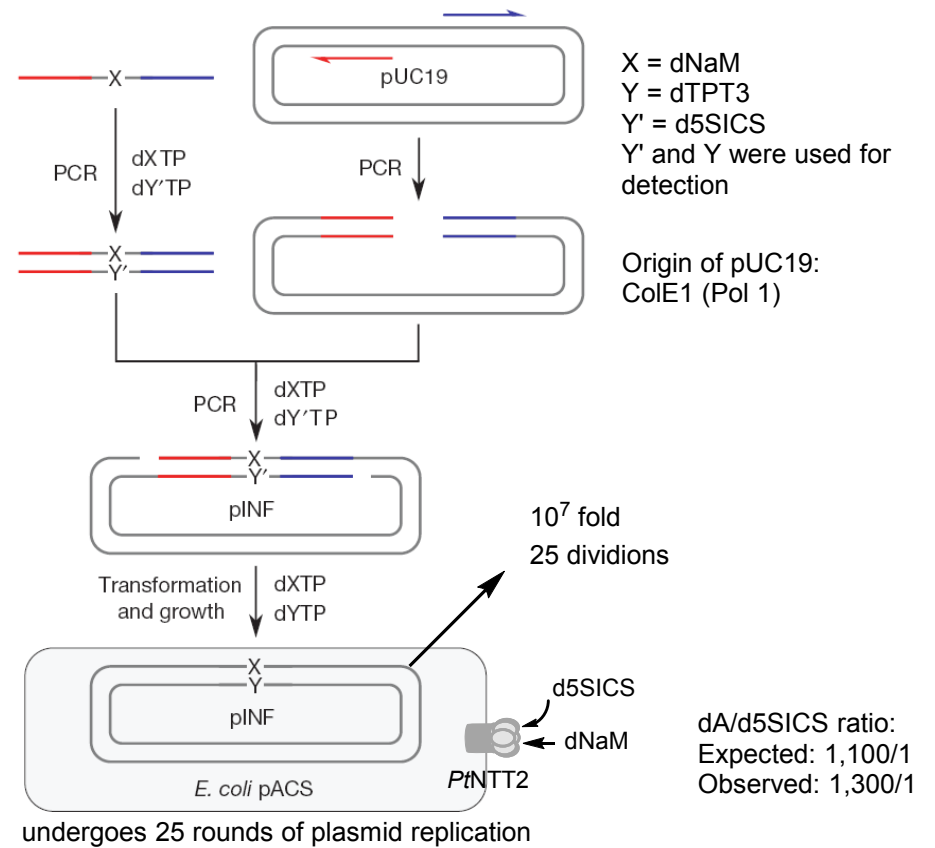


- extension is inefficient once a PICS is incorporated
- more than one PICS is challenging

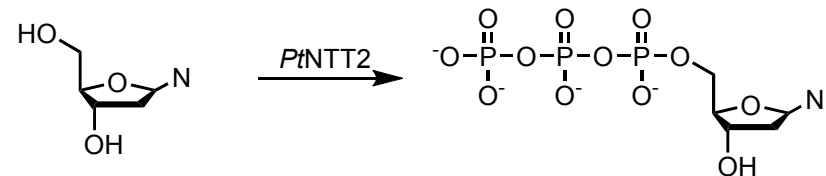
DNA Pol 1 Substrates



Genetic expansion of alphabet: unnatural base pairs (UBP)



PtNTT2 : nucleotide triphosphate transporter

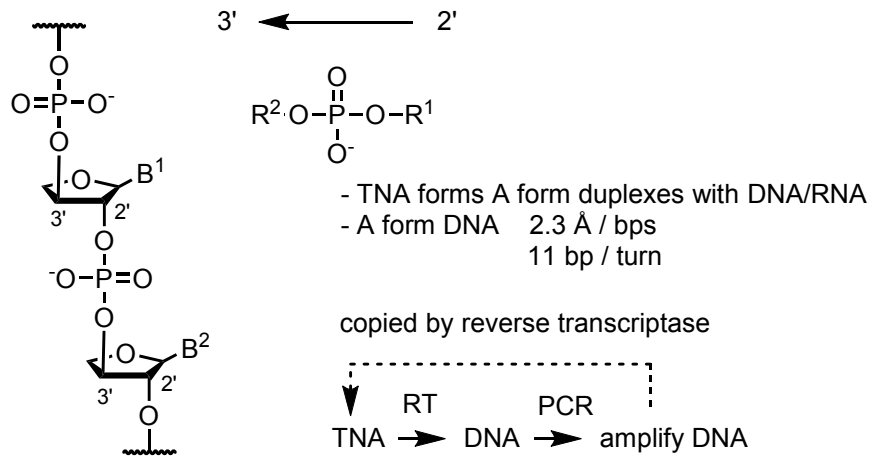


challenge remains : incorporation multiple UBPs

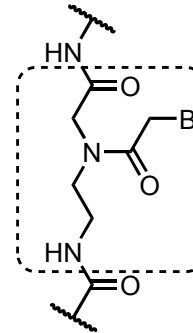
Malyshev, D. A.; Dhami, K.; Lavergne, T.; Chen, T.; Dai, N.; Foster, J. M.; Correa, I. R., Jr.; Romesberg, F. E., A semi-synthetic organism with an expanded genetic alphabet. *Nature* 2014, 509 (7500), 385-8.

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Threose nucleic acid (TNA)



Peptide nucleic acid (PNA)



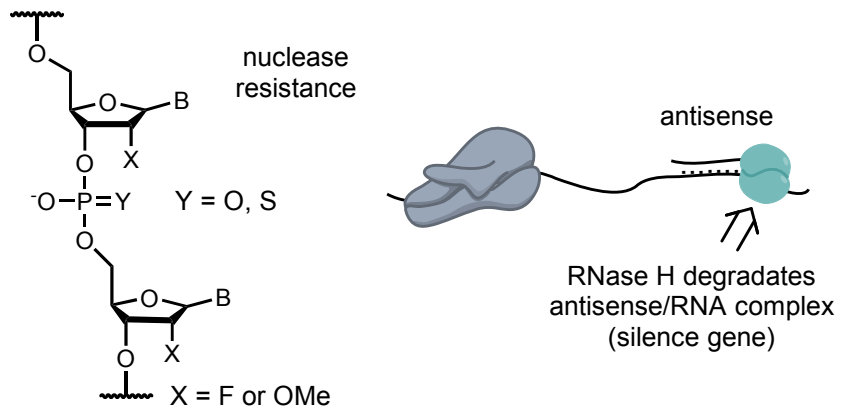
Peptide nucleic acid (PNA)

- $dA_{10}dT_{10} \sim 23 \text{ }^\circ\text{C}$
- $dA_{10}dT_{10} \text{ (PNA)} \sim 75 \text{ }^\circ\text{C}$

higher T_m of PNA hybrid due to loss of phosphate-phosphate repulsion

(not very cell permeable)

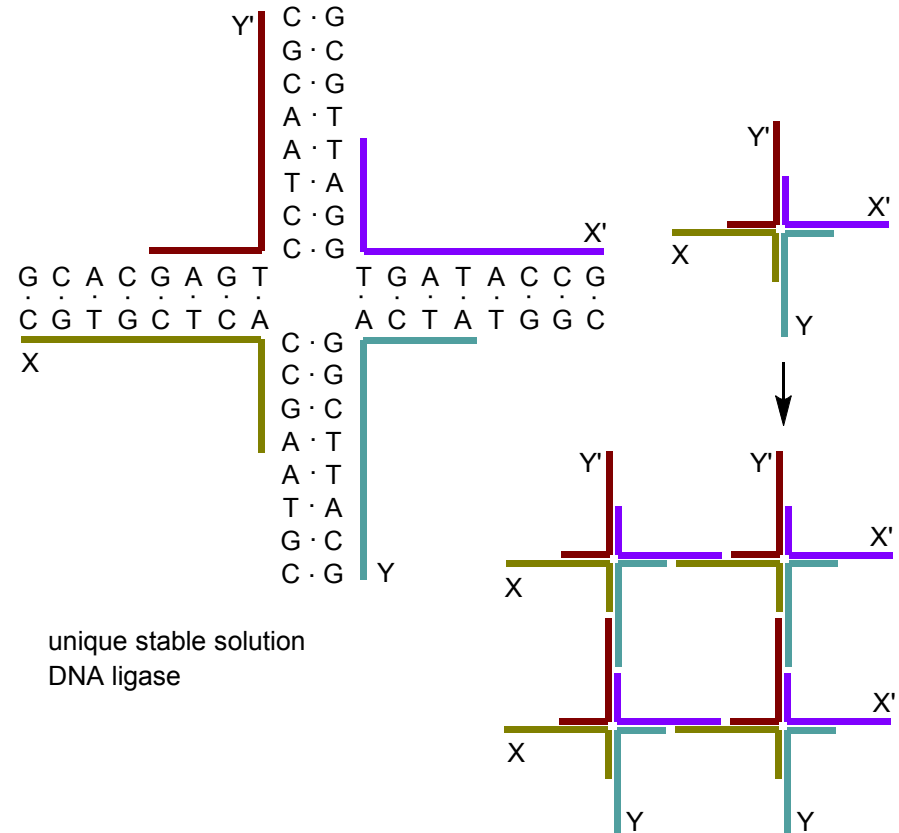
Therapeutic applications of unnatural nucleic acid



antisense therapeutics

Challenge: negative charged RNA cannot easily get into cells.

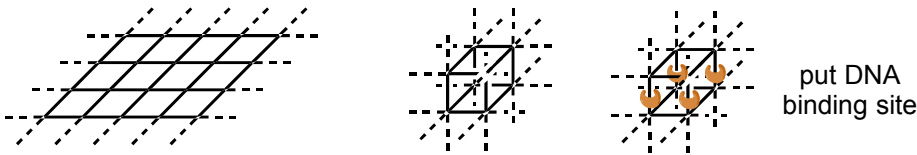
Stable DNA branched junction



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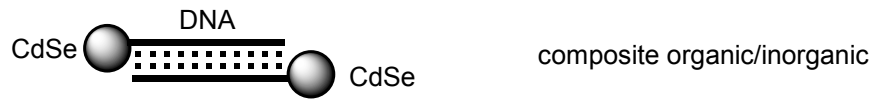
Stable DNA branched junction

Scaffolding of structural DNA nanotechnology



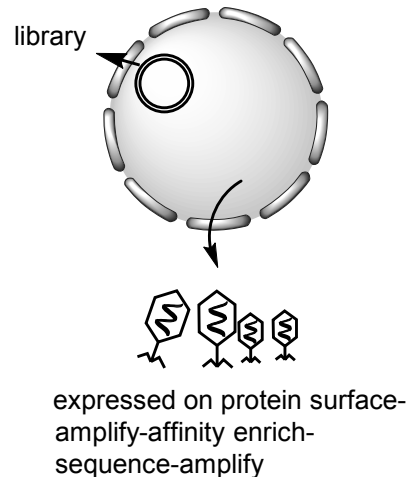
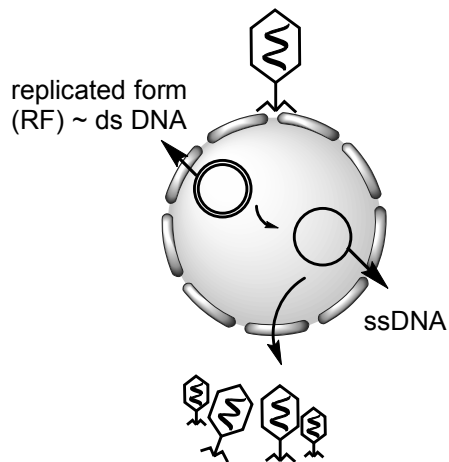
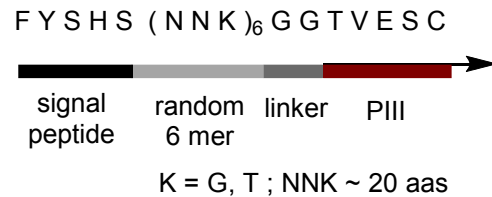
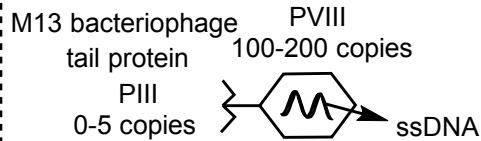
2 and 3 dimensional structures

DNA origami



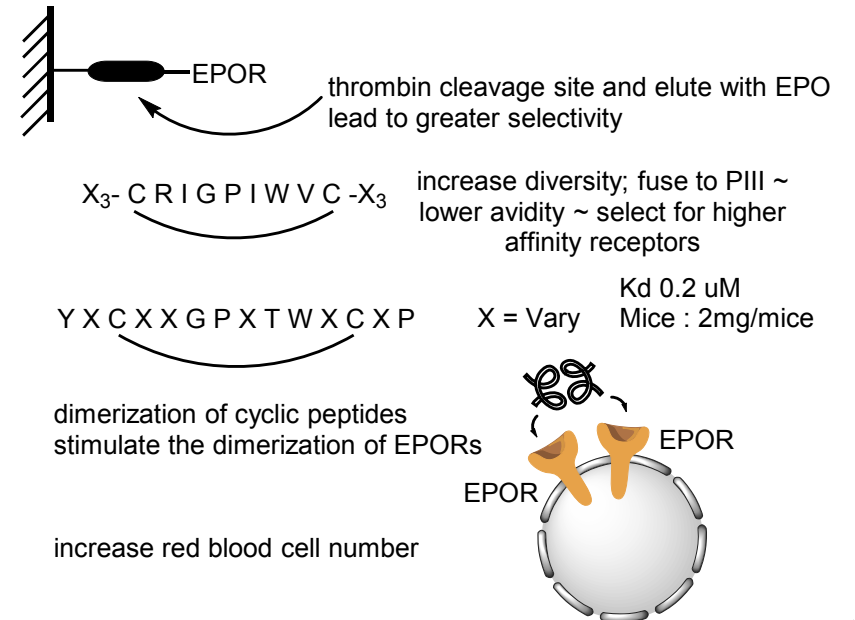
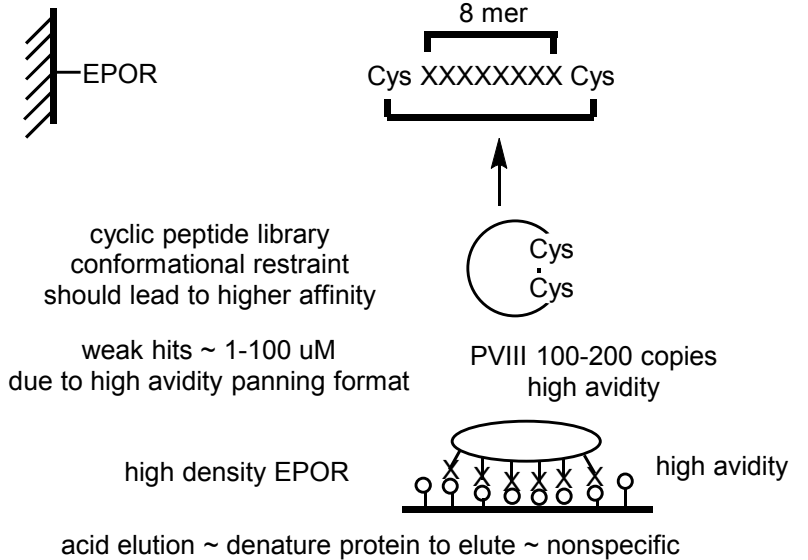
Peptide libraries

recombinant peptide libraries
- library members can be amplified



EPOR (EPO receptor)

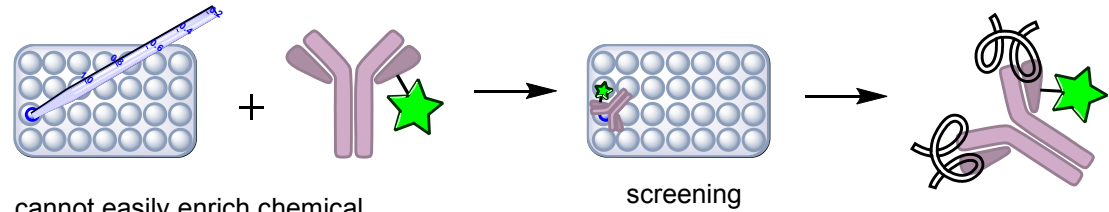
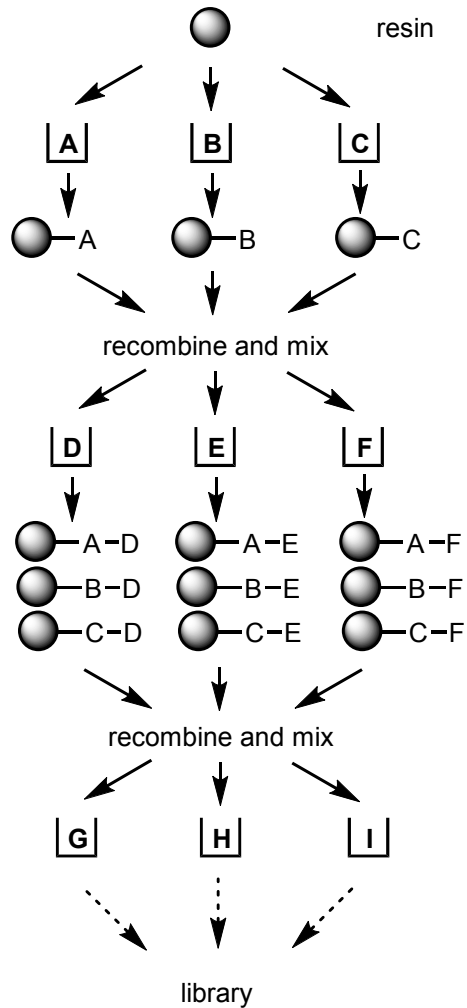
EC50 200 pM EPO 34 kDa
erythropoiesis - red blood cell formation



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Synthetic peptide library

split/mix bead-based library synthesis

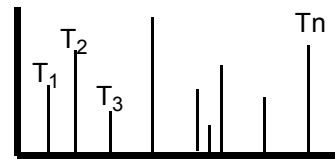
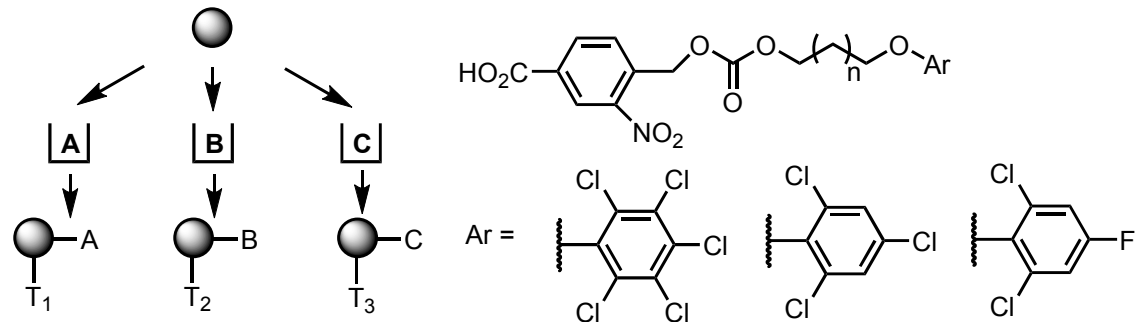


cannot easily enrich chemical libraries so must directly screen wells with fluorescently tagged receptors

Deconvolute: peptide sequencing -Chem
-MS

relatively large amount of materials typically required ~ limited by bead capacity
electron capture GC <1 pmol

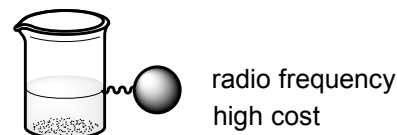
Tagging approach - couple a tag to bead each time couple a monomer



	T ₁	T ₂	T ₃
Ser	0	0	1
Asp	0	1	0
	1	0	0
	0	1	1
	1	0	1
	0	1	1
Lys	1	1	1

Binary Tags
7 building blocks
6 mers ~ 18 tags

Radio labelled tags



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Library of small synthetic drug like molecules

