DNA-encoded library

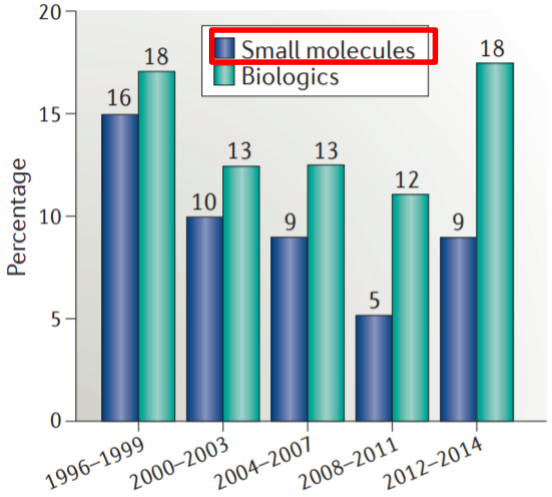
171125

D2 Yuri Takada

contents

Drug development

clinical success rates from Phase I to launch



- ***Early 1990*: high-through-put screening (HTS) technologies have evolved (1-2 million compounds)**

  Chemical space, however, is much larger (for example, >1 × 10^{25}), perhaps unknowably so.

- **There is substantial interest in the development of approaches capable of exploring large chemistry spaces more deeply**

  - **Split-and-pool (Furuka *et al.* 1989, solid-phase synthesis of peptide libraries)**

1) Smietana, K.; Siatkowski, M.; Møller, M. *Nat. Rev.* **2016**, *15*, 379.

Collaboration of pharmaceutical companies

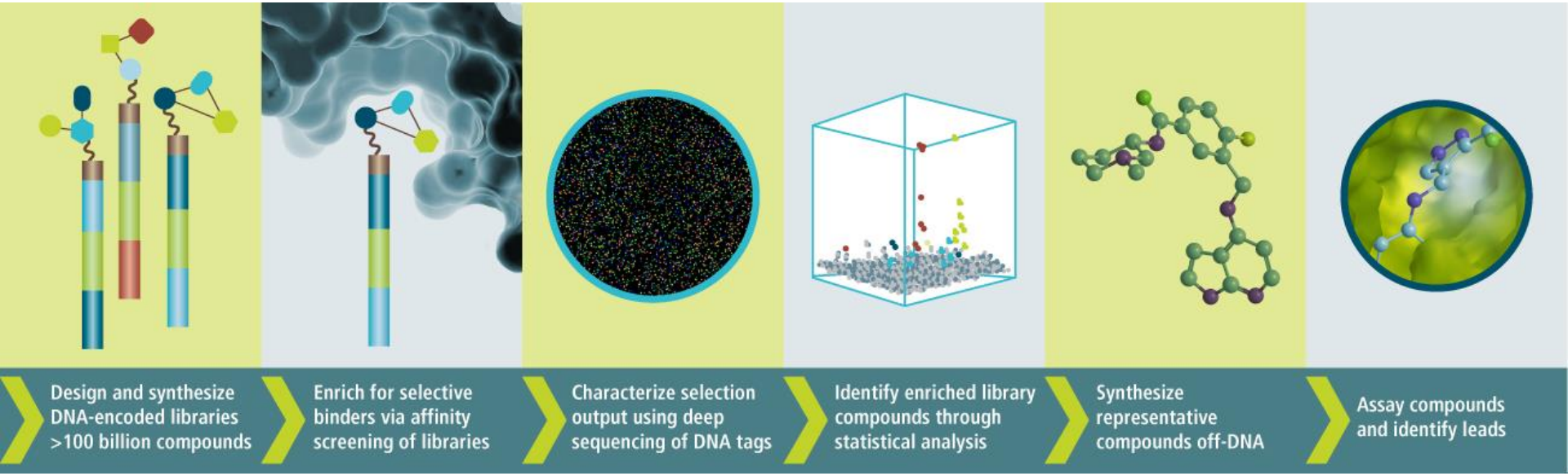
2017. 3.21

X-Chem and certain Japanese pharmaceutical companies enter into drug discovery collaboration

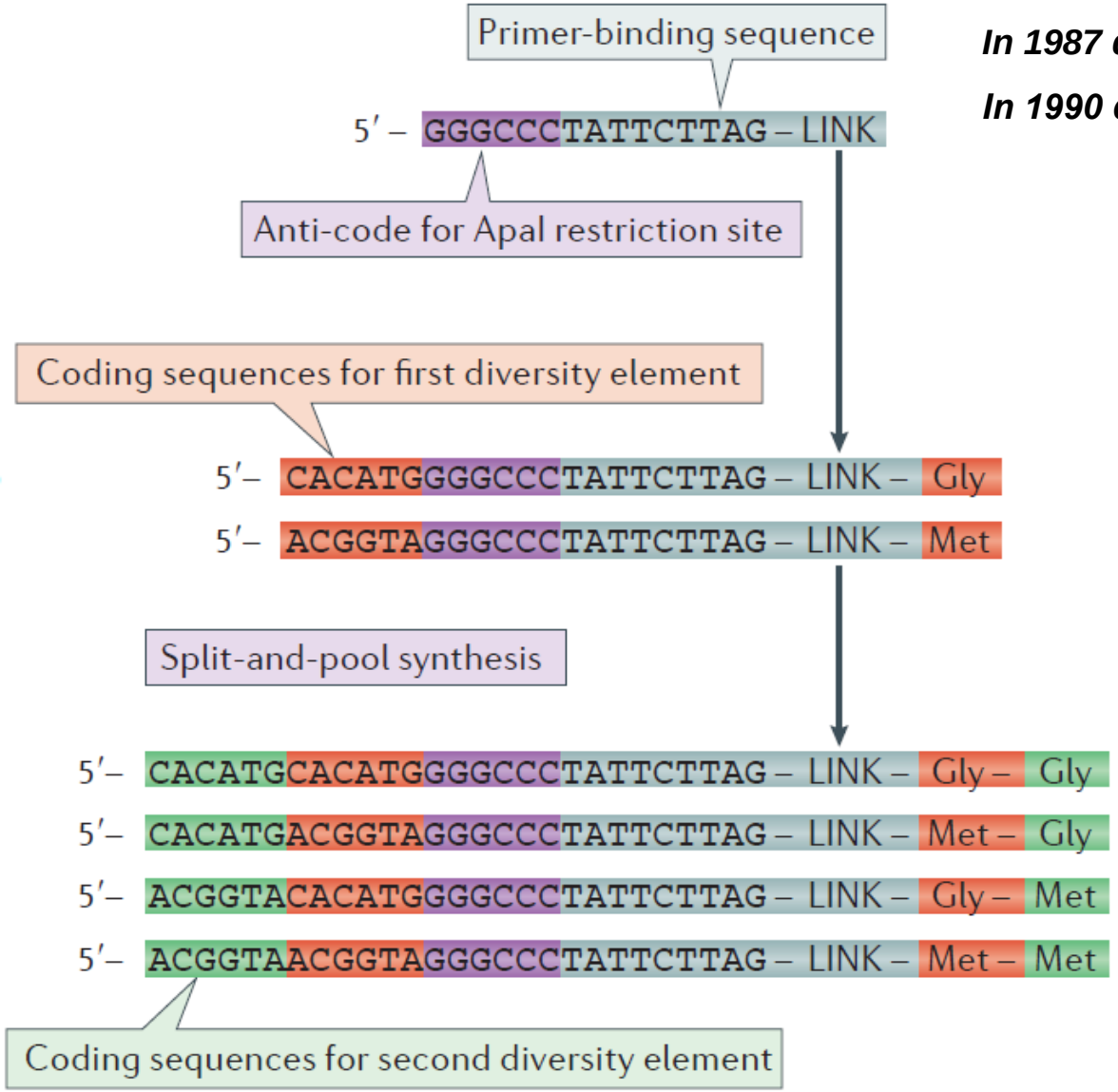
→ **X-Chem contain over 120 billion small molecules libraries**

↓

That Japanese company will have the option to license identified lead compounds and will be responsible for further development and commercialization of any resulting programs

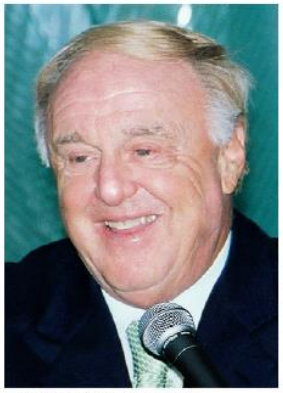


combinatorial chemistry and in vitro-directed evolution methods

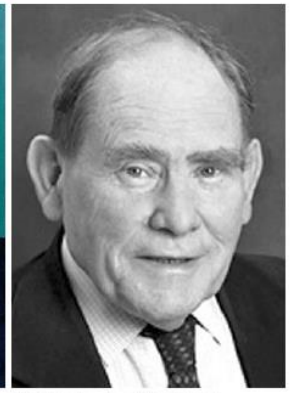


In 1987 development of PCR

In 1990 development of combinatorial chemistry



Richard A. Lerner
Institute Professor
The Scripps Research Institute



Sydney A. Brenner
Professor
The Scripps Research Institute

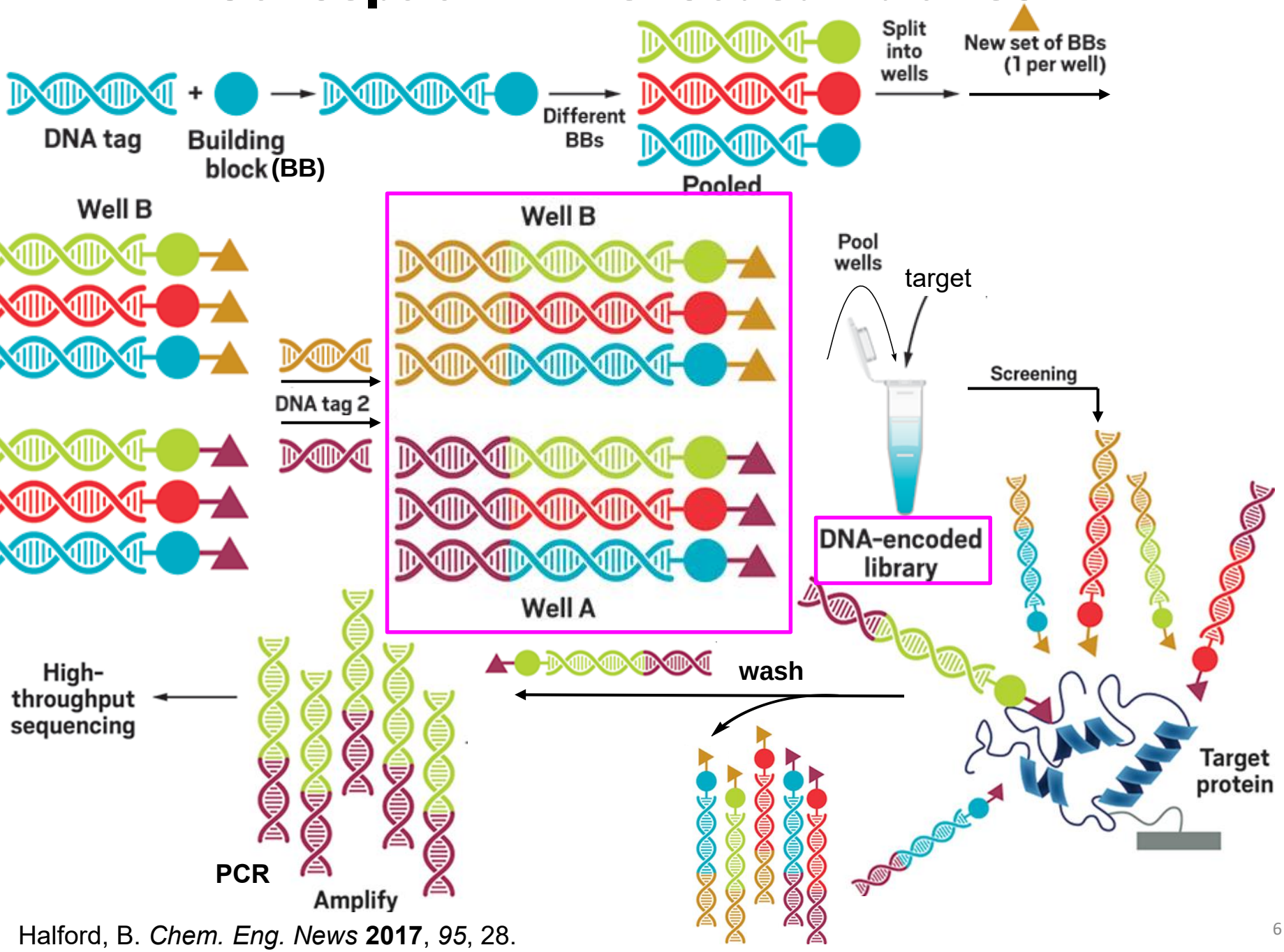
In 1992

the use of DNA sequences as a means to encode the synthesis of a peptide on a solid-phase support

DNA-encoded methods have evolved to the extent that libraries larger than 100 million compounds are regularly synthesized and screened.

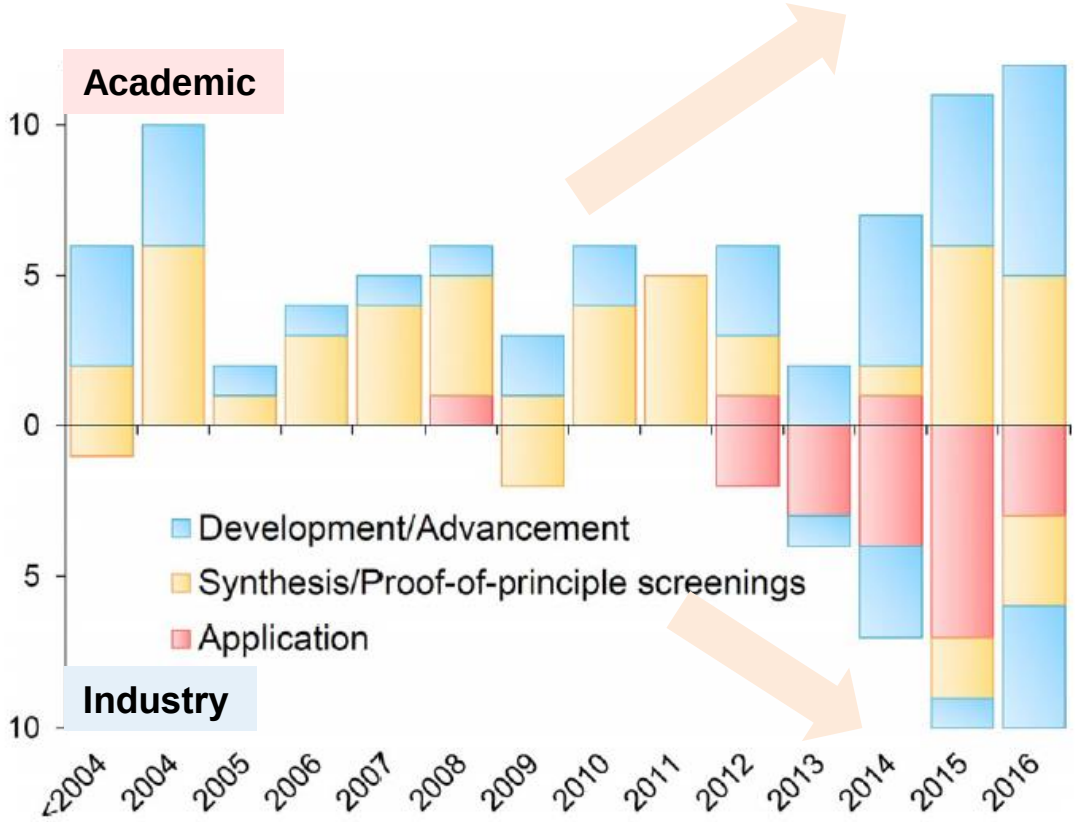
1) Brenner, S.; Lerner, R. A. Proc. Natl Acad. Sci. *USA* **1992**, *89*, 5381.
2) Lener, R. A.; Brenner, S. *Angew. Chem. Int. Ed.* **2017**, *56*, 1164.

Concept of DNA-encoded libraries



1) Halford, B. *Chem. Eng. News* **2017**, *95*, 28.

Publications related to DNA-encoded libraries



HTS	DEL
1 ~ 2 million	Up to 40 trillion
1000000	40000000000000
	Increase of spices

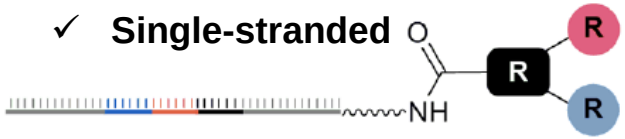
1) Yuen, L. H.; Franzini, R. M. *ChemBioChem* **2017**, *18*, 829.

Construction methods of DNA-encoded libraries

✓ Double-stranded

primer codons primer building blocks

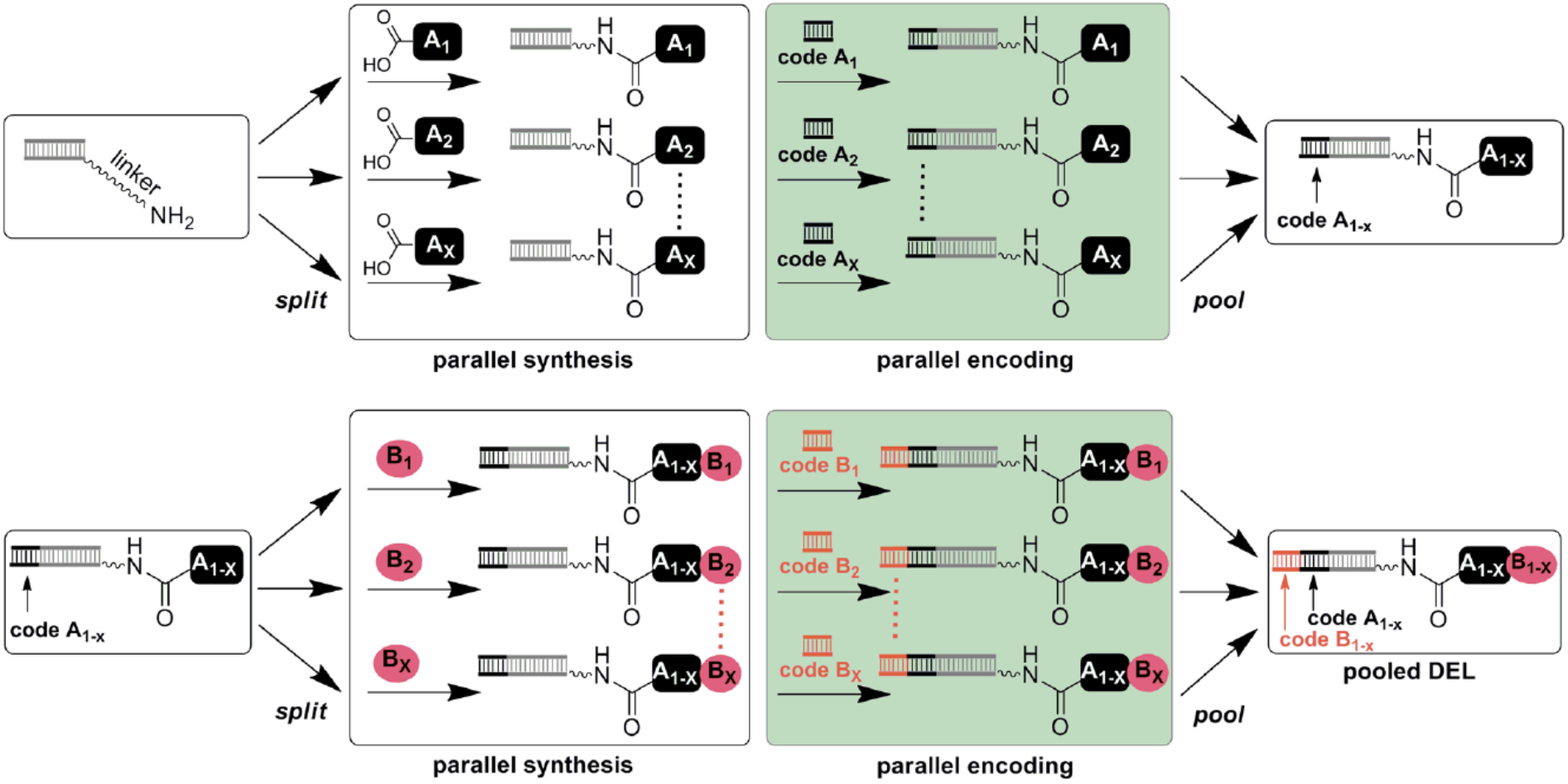
✓ Single-stranded



primer codons primer building blocks

DNA-encoded compound

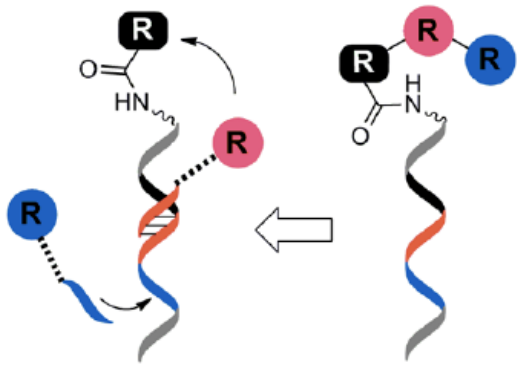
☐ DNA-recorded split-and-pool combinatorial synthesis



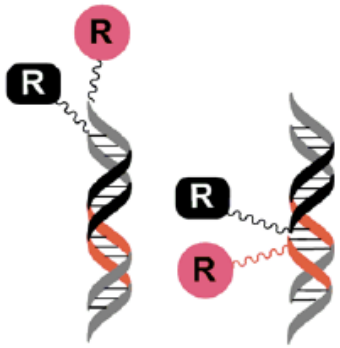
1) Salamon, H.; Škopic, M. K.; Jung, K.; Bugain, O.; Brunschweiger, A. *ACS Chem. Biol.* **2016**, *11*, 296.

Construction methods of DNA-encoded libraries

- DNA-templated chemistry (ex. macrocycles)

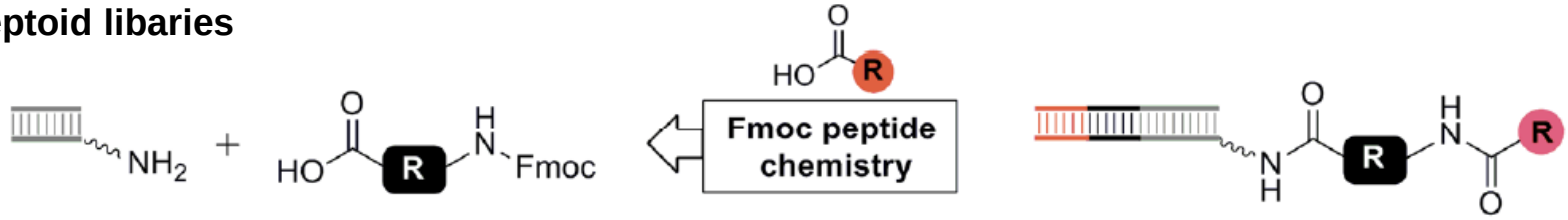


- assembly of DNA-small molecule fragment conjugates

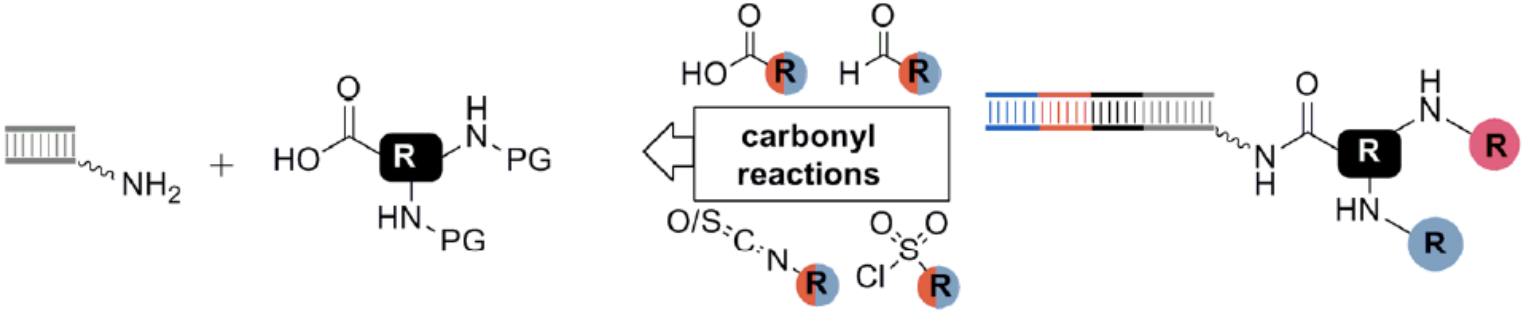


Construction reactions of DNA-encoded compounds

(a) Peptoid libaries



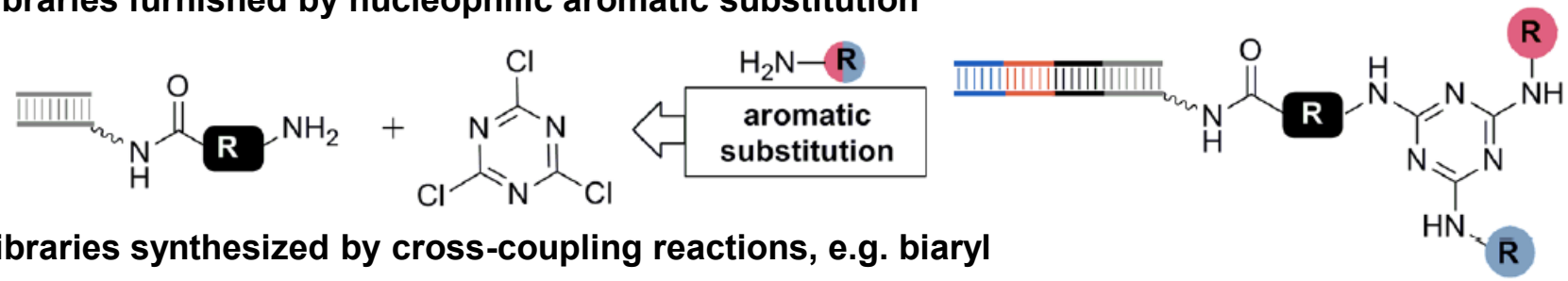
(b) libraries based on diamino substituted scaffolds



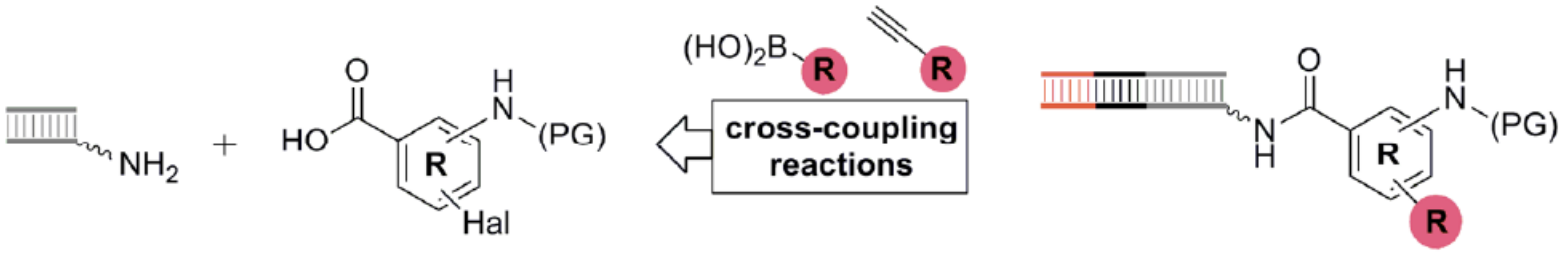
1) Salamon, H.; Škopic, M. K.; Jung, K.; Bugain, O.; Brunschweiger, A. *ACS Chem. Biol.* **2016**, *11*, 296.

Construction reactions of DNA-encoded libraries

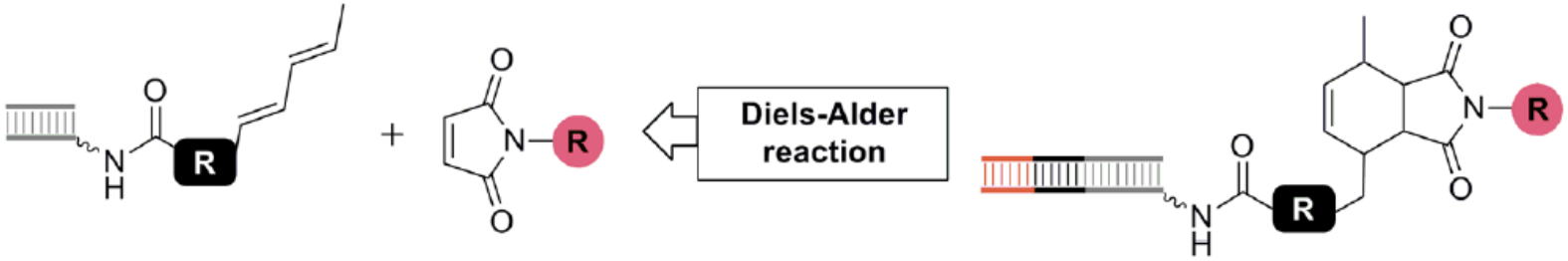
(c) libraries furnished by nucleophilic aromatic substitution



(d) libraries synthesized by cross-coupling reactions, e.g. biaryl



(e) cyclohexene-based libraries synthesized by Diels−Alder cycloaddition



(f) benzimidazole libraries

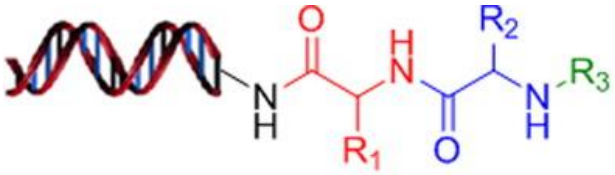
1) Salamon, H.; Škopic, M. K.; Jung, K.; Bugain, O.; Brunschweiger, A. *ACS Chem. Biol.* **2016**, *11*, 296.

“success stories” DNA-encoded libraries hits

By GlaxoSmith-Kline (GSK)

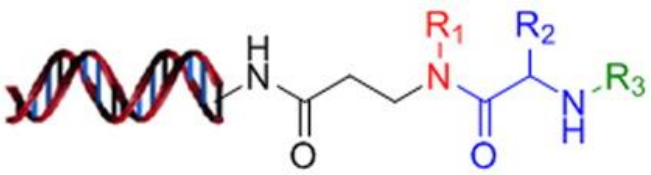
Development of highly potent and mono-selective receptor Interacting protein 1 (RIP1) kinase inhibitors

- 7.7 billion compounds -



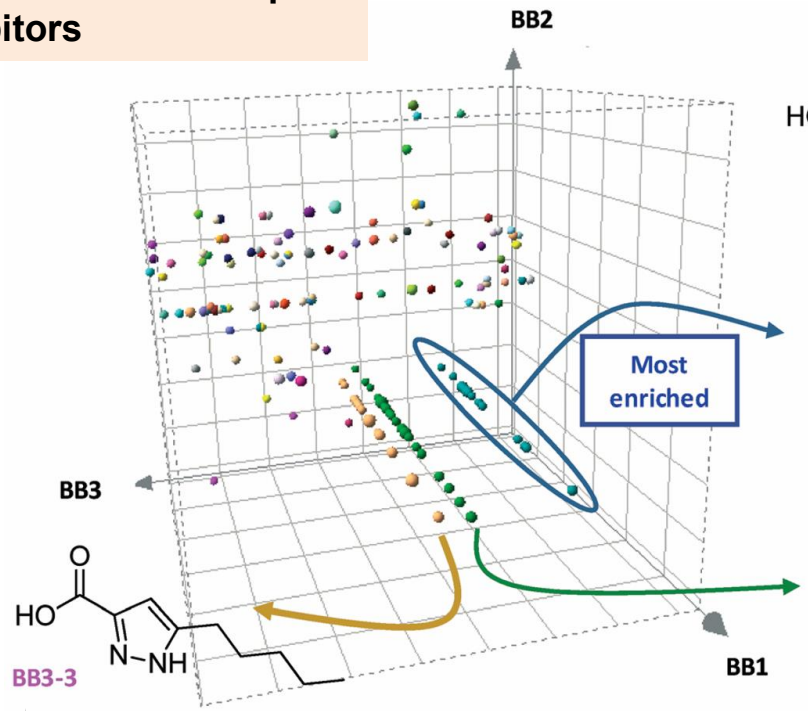
BB1 = 632 amino acids
BB2 = 632 amino acids
BB3 = 6594 amine caps

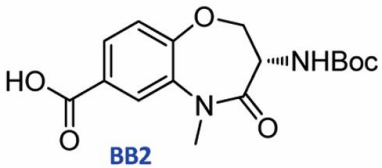
632 × 632 × 6594 = 2633801856



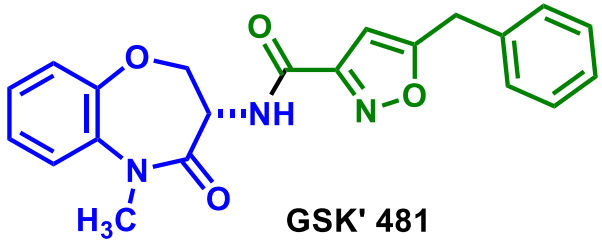
BB1 = 1222 amines
BB2 = 632 amino acids
BB3 = 6594 amine caps

1222 × 632 × 6594 = 5092572576





Selection output



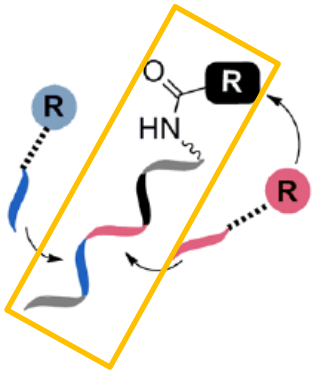
GSK' 481

DNA-encoded chemical library (DECL) technologies are increasingly being adopted in drug discovery for hit and lead generation

1) Harris, P. A. *et al. J. Med. Chem.* **2016**, 59, 2163.

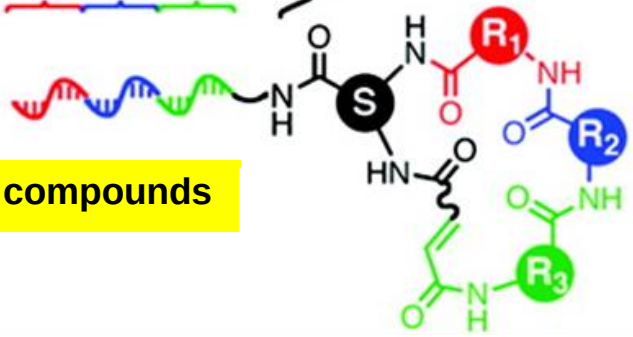
Application for small macrocyclic peptide

macrocycle libraries synthesized by DNA-templated chemistry

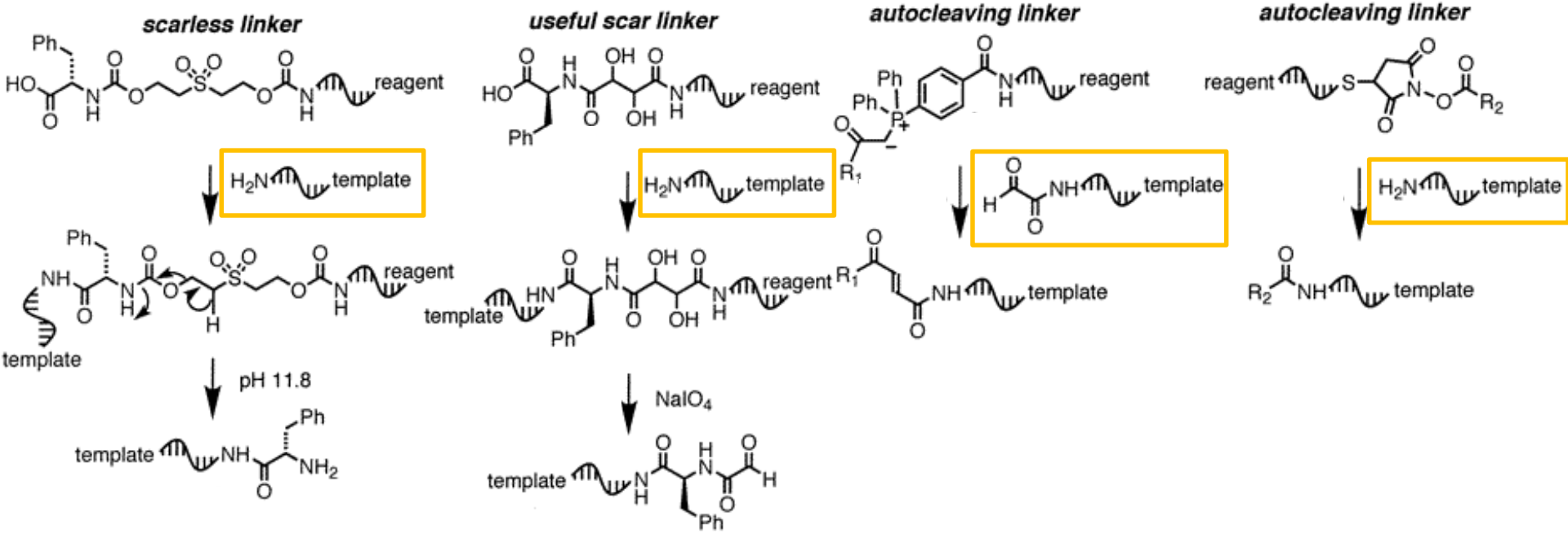


macrocycle synthesis

12 x 12 x 12 x 8

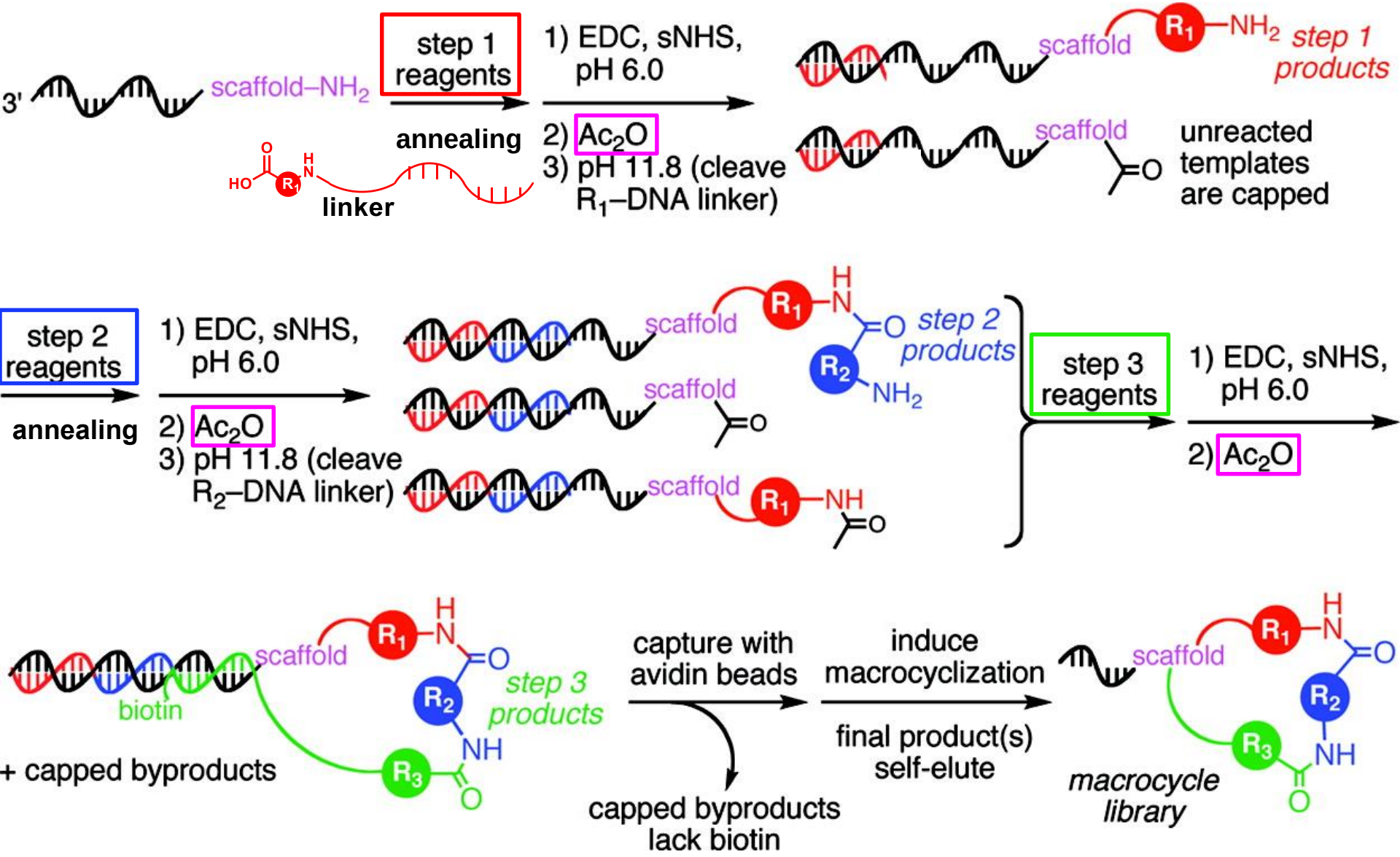


8 × 12 × 12 × 12 = 13824 compounds



1) Salamon, H.; Škopic, M. K.; Jung, K.; Bugain, O.; Brunschweiger, A. *ACS Chem. Biol.* **2016**, *11*, 296.
2) Tse, B. N.; Snyder, T. M.; Shen, Y. Liu, D. R. *J. Am. Chem. Soc.* **2008**, *130*, 15611.
3) Gartner, Z. J.; Kanan, M. W.; Liu, D. R. *J. Am. Chem. Soc.* **2002**, *124*, 10304.

Capping-based strategy for construction of libraries



The use of a capping reagent (Ac_2O) prevents unreacted or improperly reacted material from participating in further reactions. The final streptavidin bead capture and macrocyclization steps achieve effective purification of the final product

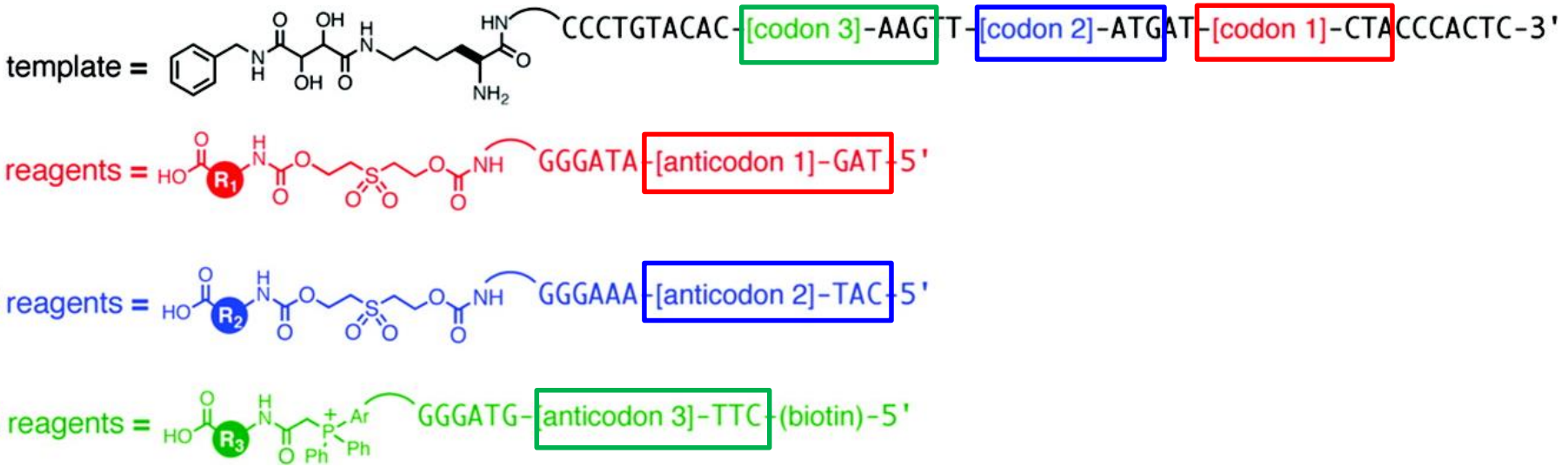
1) Tse, B. N.; Snyder, T. M.; Shen, Y. Liu, D. R. *J. Am. Chem. Soc.* **2008**, *130*, 15611.

Library of codon

code	codon 1	anticodon 1
1A	5'- GGCTTT	5'- AAAGCC
1B	5'- AGGCTT	5'- AAGCCT
1C	5'- GCCAAA	5'- TTTGGC
1D	5'- AGGAAC	5'- GTTCCT
1E	5'- CGTATG	5'- CATACG
1F	5'- CATGAG	5'- CTCATG
1G	5'- GCAGTA	5'- TACTGC
1H	5'- GCGTAT	5'- ATACGC
1I	5'- GAGACA	5'- TGTCTC
1J	5'- CTGTAG	5'- CTACAG
1K	5'- GGAATC	5'- GATTCC
1L	5'- TAGCTG	5'- CAGCTA

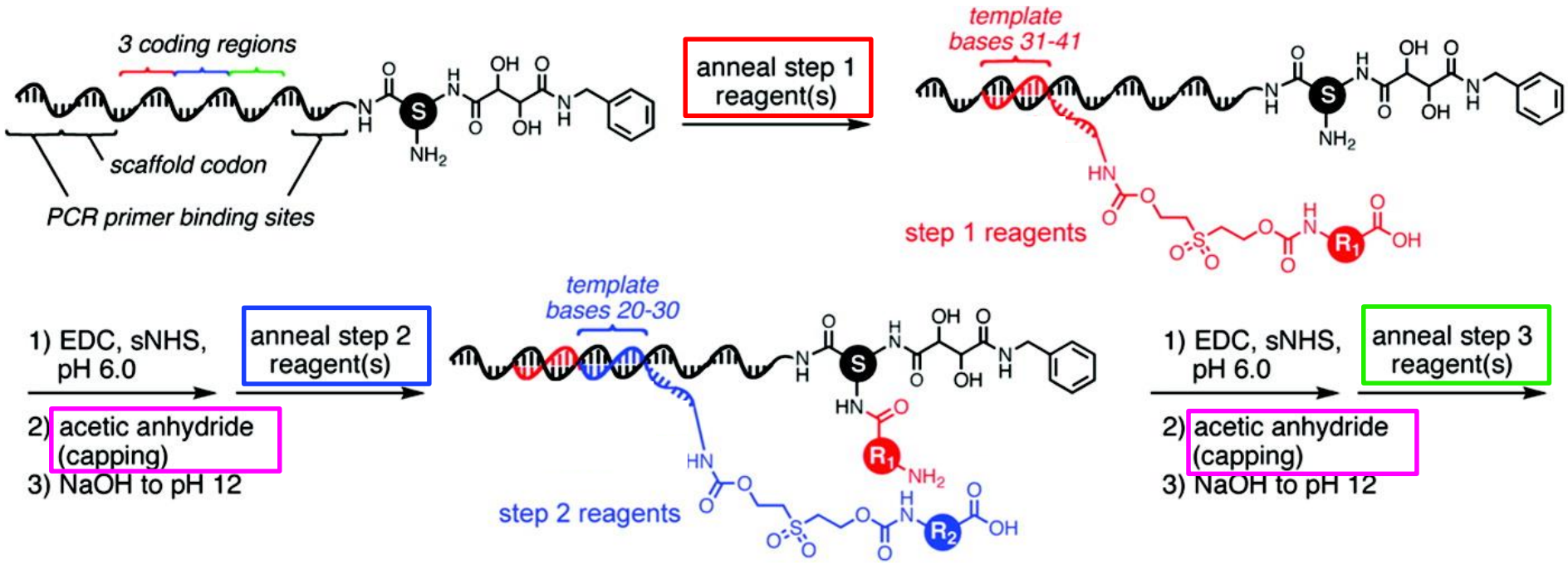
code	codon 2	anticodon 2
2A	5'- GCTGAA	5'- TTCAGC
2B	5'- AACGGT	5'- ACCGTT
2C	5'- GTCGAT	5'- ATCGAC
2D	5'- GATTGC	5'- GCAATC
2E	5'- GGACTT	5'- AAGTCC
2F	5'- ACGGAT	5'- ATCCGT
2G	5'- AGGACT	5'- AGTCCT
2H	5'- TCGAGT	5'- ACTCGA
2I	5'- GCAAGA	5'- TCTTGC
2J	5'- CTTGTG	5'- CACAAG
2K	5'- GGCTAA	5'- TTAGCC
2L	5'- CTGGAA	5'- TTCCAG

code	codon 3	anticodon 3
3A	5'- TTCCTC	5'- GAGGAA
3B	5'- AGCTCA	5'- TGAGCT
3C	5'- ATCGGA	5'- TCCGAT
3D	5'- TGTGCA	5'- TGCACA
3E	5'- AGACTC	5'- GAGTCT
3F	5'- CTTCAG	5'- CTGAAG
3G	5'- AGTCGA	5'- TCGACT
3H	5'- ATGACG	5'- CGTCAT
3I	5'- ACTAGC	5'- GCTAGT
3J	5'- CAACCT	5'- AGGTTG
3K	5'- TCCGTA	5'- TACGGA
3L	5'- GCTTAC	5'- GTAAGC



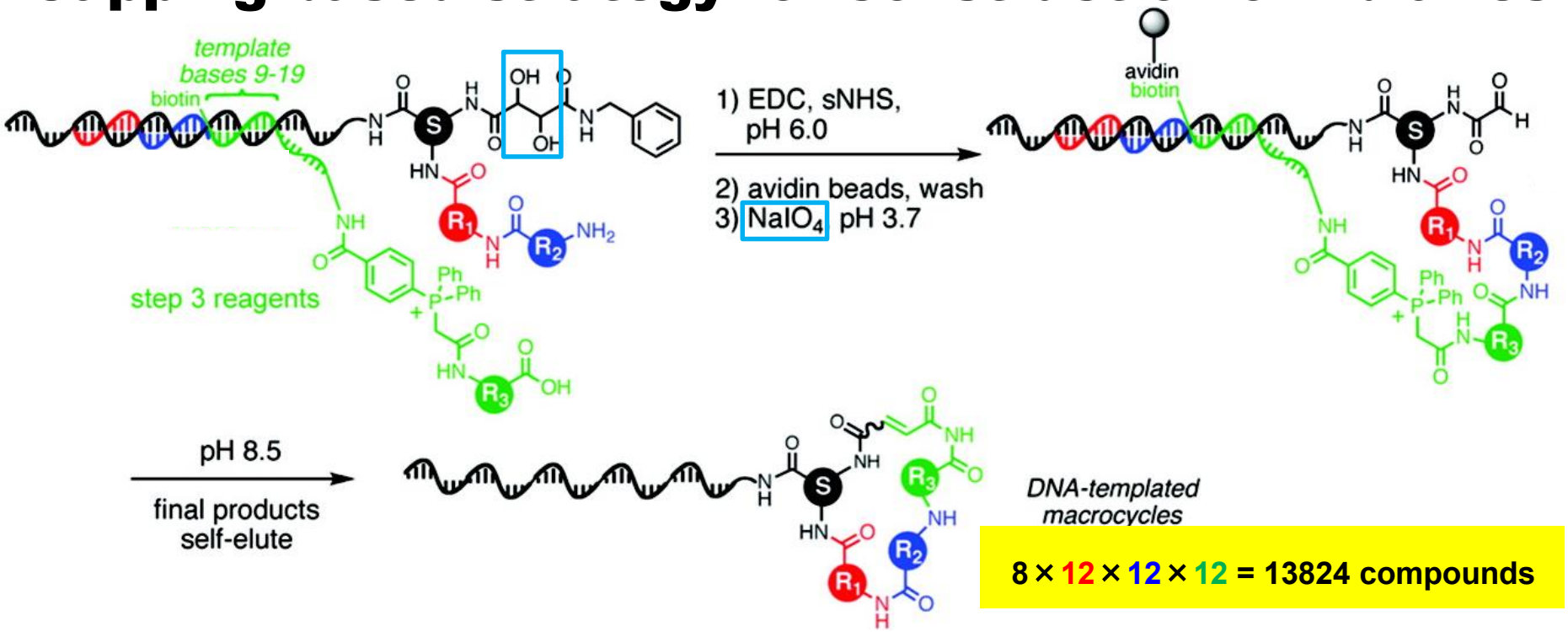
1) Tse, B. N.; Snyder, T. M.; Shen, Y. Liu, D. R. *J. Am. Chem. Soc.* **2008**, *130*, 15611.

Capping-based strategy for construction of libraries

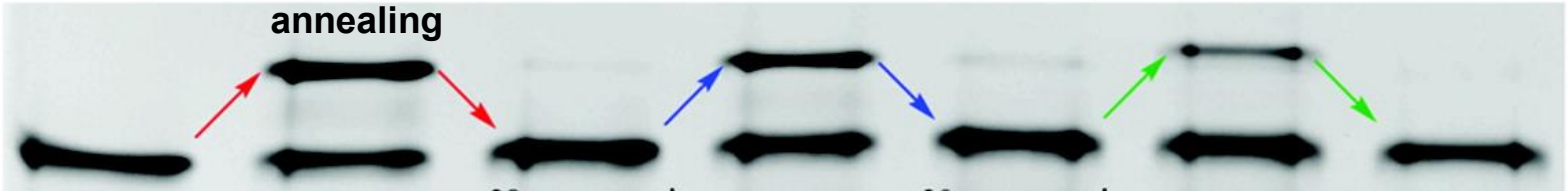


1) Tse, B. N.; Snyder, T. M.; Shen, Y. Liu, D. R. *J. Am. Chem. Soc.* **2008**, *130*, 15611.

Capping-based strategy for construction of libraries

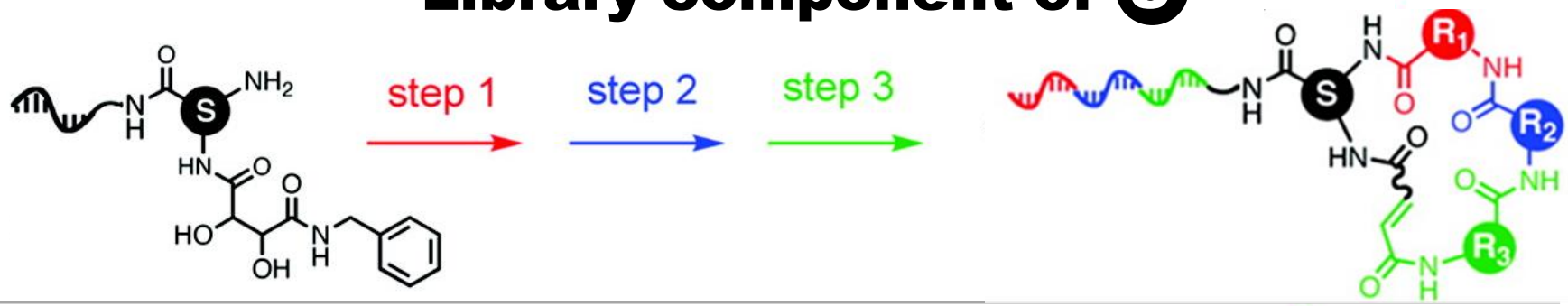


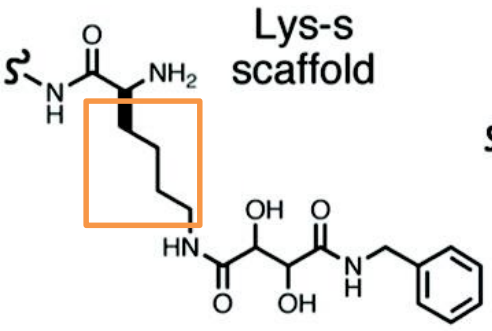
8 × 12 × 12 × 12 = 13824 compounds

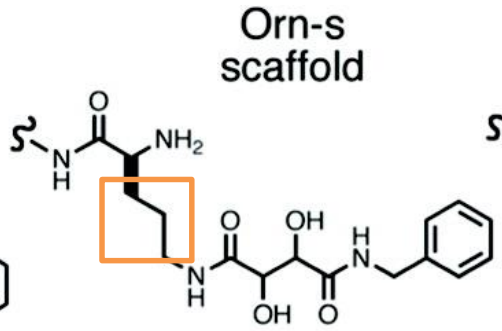


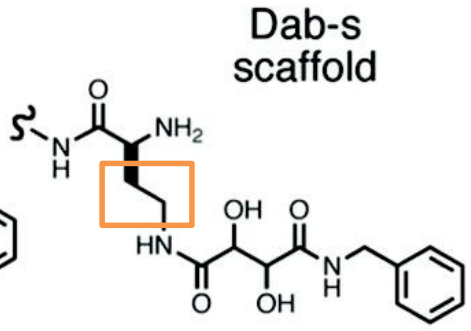
1) Tse, B. N.; Snyder, T. M.; Shen, Y. Liu, D. R. *J. Am. Chem. Soc.* **2008**, *130*, 15611.

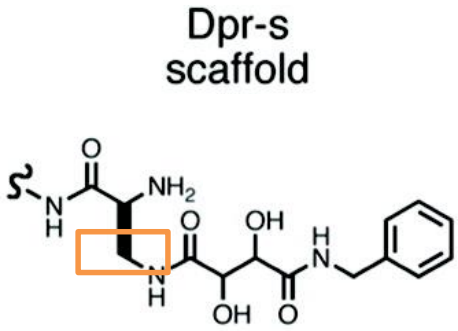
Library component of S

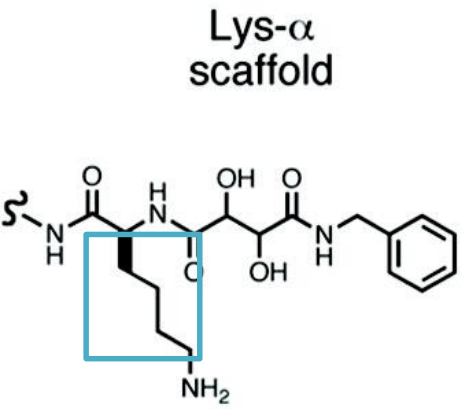


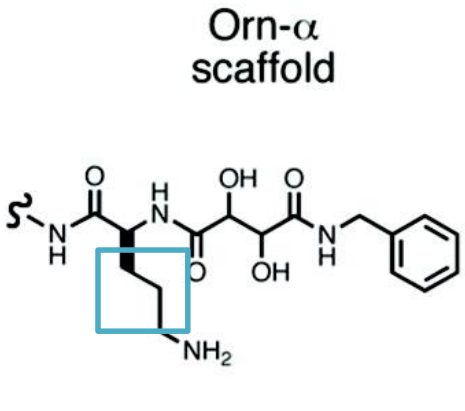


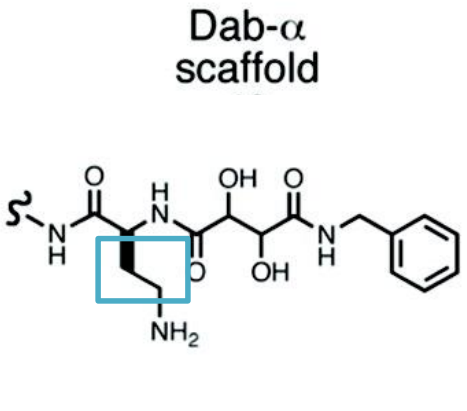


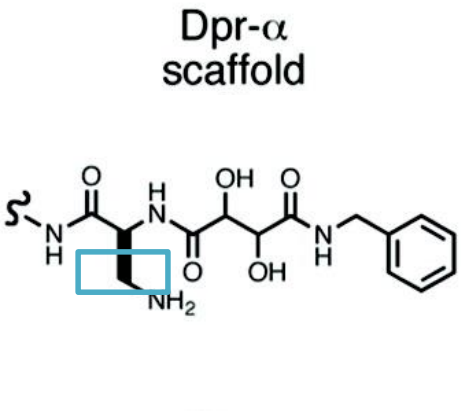






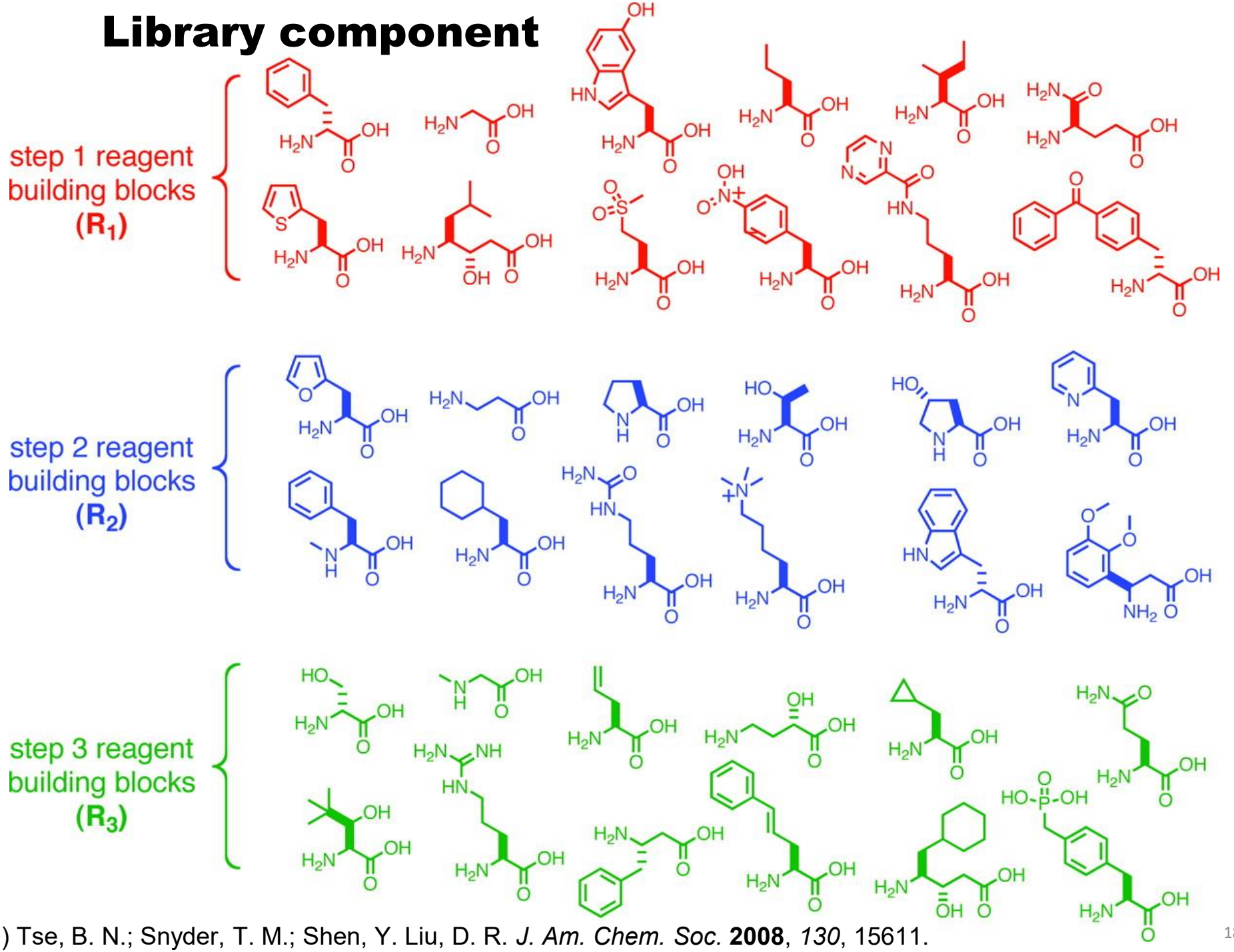






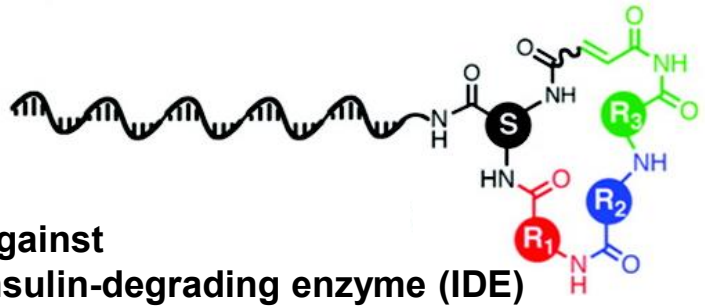
1) Tse, B. N.; Snyder, T. M.; Shen, Y. Liu, D. R. *J. Am. Chem. Soc.* **2008**, *130*, 15611.

Library component



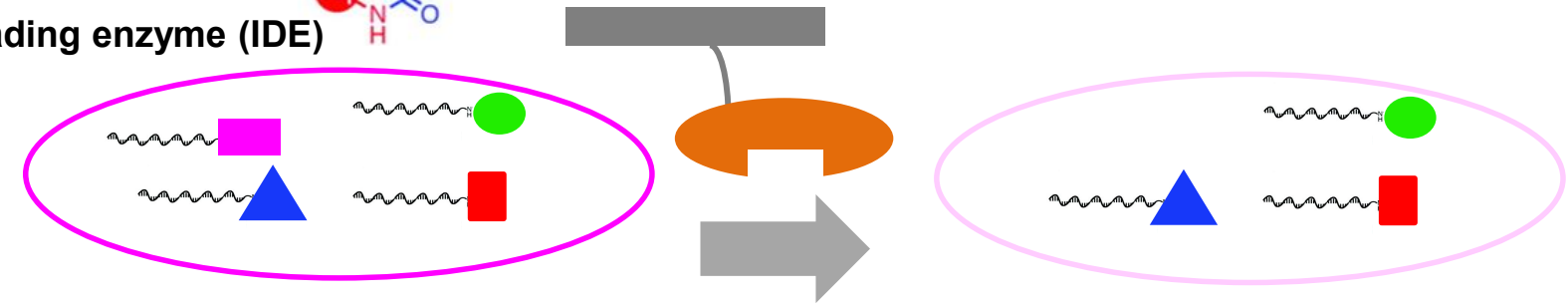
1) Tse, B. N.; Snyder, T. M.; Shen, Y. Liu, D. R. *J. Am. Chem. Soc.* **2008**, *130*, 15611.

in vitro selection of a DNA-templated library

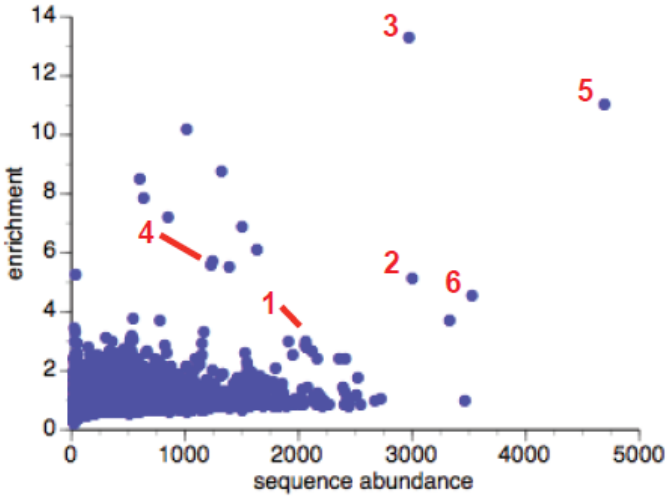


8 × 12 × 12 × 12 = 13824 compounds

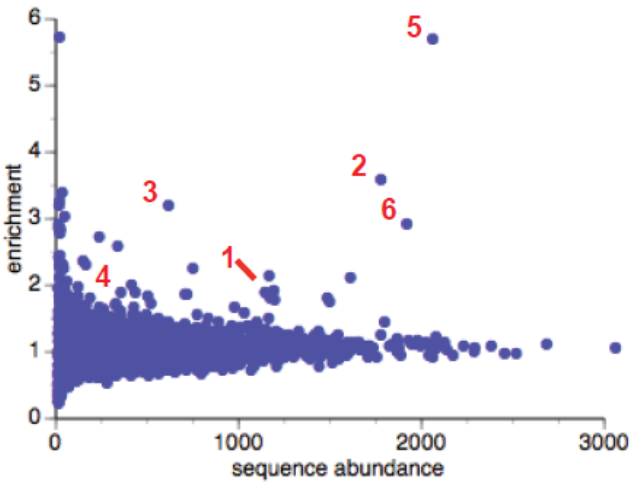
Against insulin-degrading enzyme (IDE)



IDE *in vitro* selection 1 results



IDE *in vitro* selection 2 results

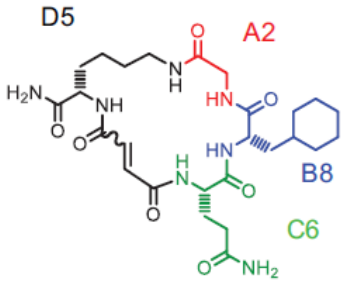


1) Maianti, J. P.; McFedries, A.; Foda, Z. H.; Kleiner, R. E.; Du, X. Q.; Leissring, M. A.; Tang5, W.-J.; Charron, M. J.; Seeliger, M. A.; Saghatelian, A.; Liu, D. R.; *Nature* **2014**, 511, 94.

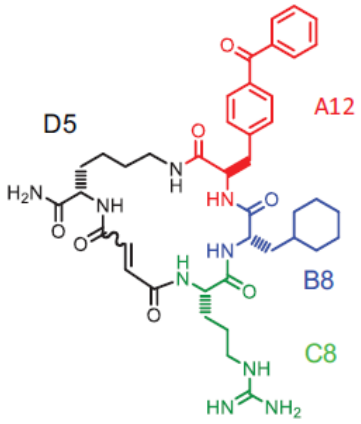
2) Kleiner, R. E.; Dumelin, C. E.; Tiu, G. C.; Sakurai, K.; Liu, D. R. *J. Am. Chem. Soc.* **2010**, *132*, 11779.

Selected hit compounds

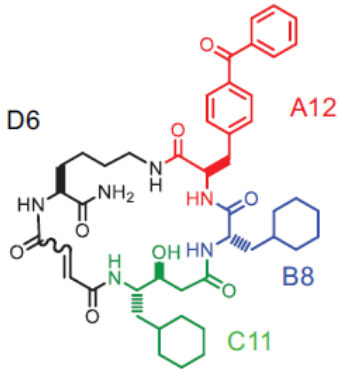
Selection of 6 compounds



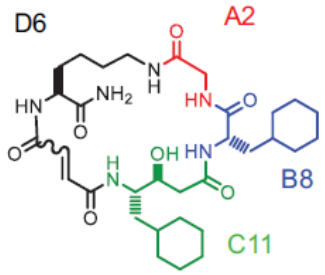
1a (*cis* olefin) IC_{50}>100 μM
1b (*trans* olefin) IC_{50}=5.0 μM



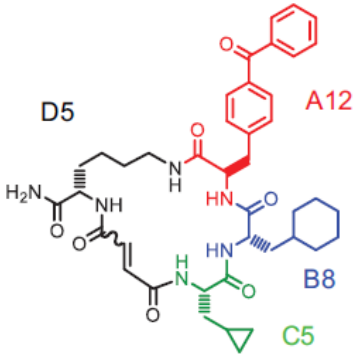
2a (*cis* olefin) IC_{50}=10 μM
2b (*trans* olefin) IC_{50}=0.14 μM



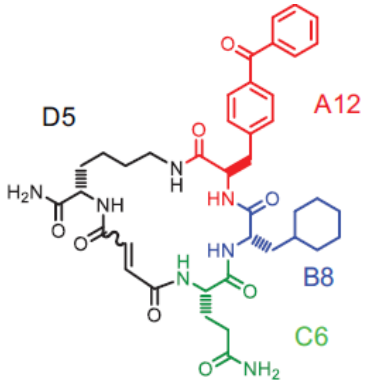
3a (*cis* olefin) IC_{50}>20 μM
3b (*trans* olefin) IC_{50}=1.5 μM



4a (*cis* olefin) IC_{50}>100 μM
4b (*trans* olefin) IC_{50}>100 μM



5a (*cis* olefin) IC_{50}>20 μM
5b (*trans* olefin) IC_{50}=1.0 μM



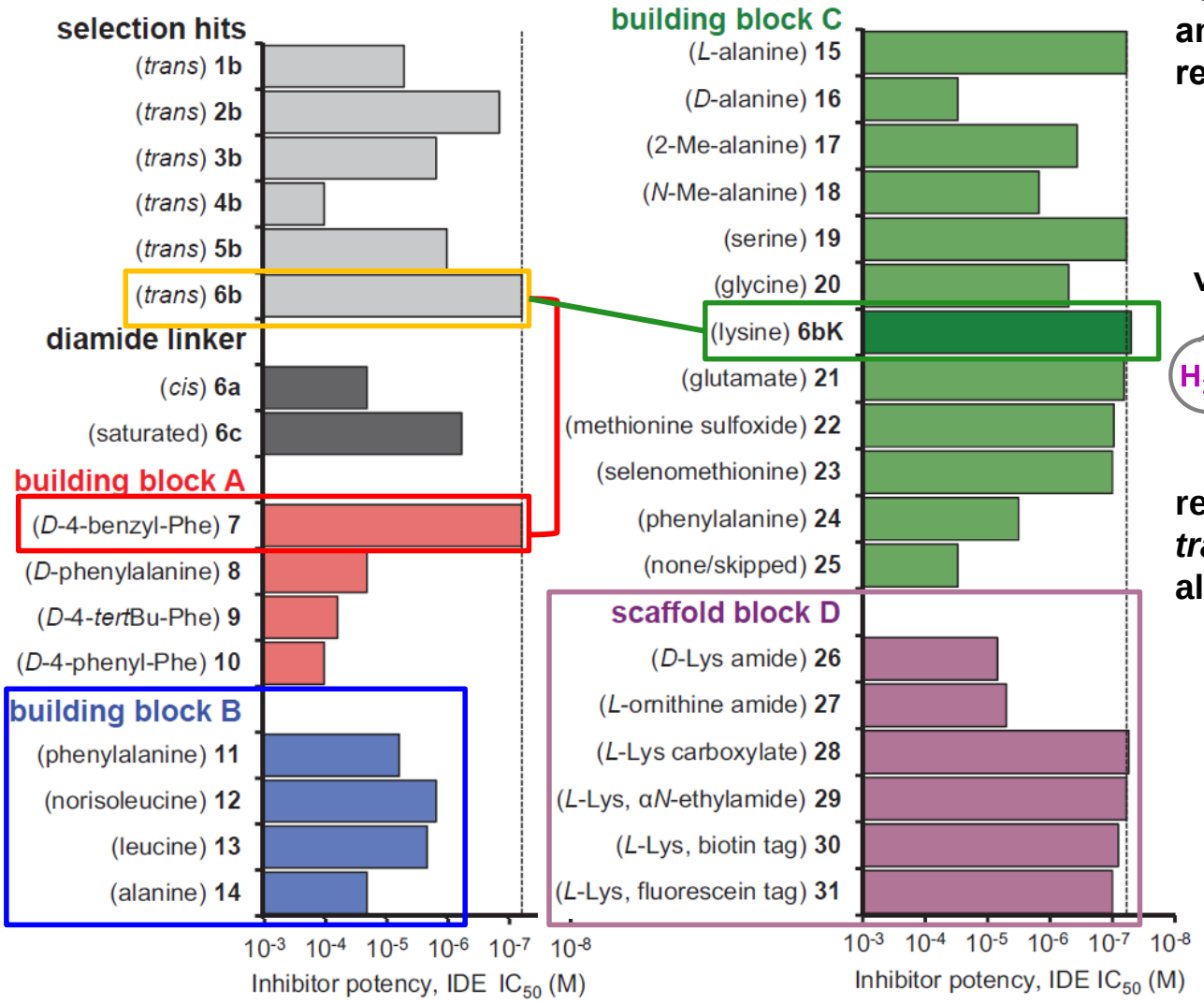
6a (*cis* olefin) IC_{50}=5.6 μM
6b (*trans* olefin) IC_{50}=0.06 μM

Potent and highly selective macrocyclic IDE inhibitors from the *in vitro* selection of a DNA-templated macrocycle library

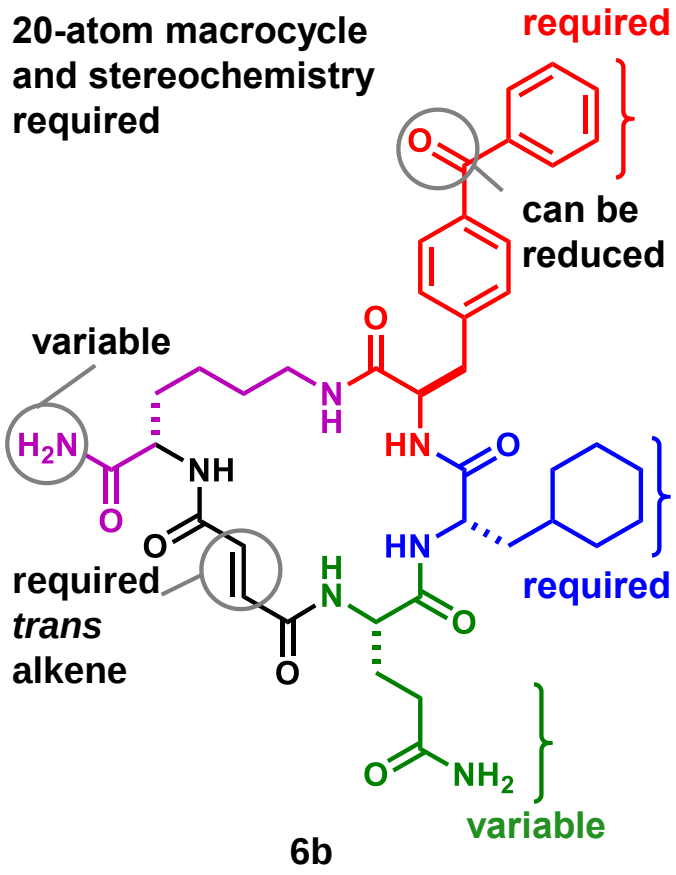
1) Maianti, J. P.; McFedries, A.; Foda, Z. H.; Kleiner, R. E.; Du, X. Q.; Leissring, M. A.; Tang5, W.-J.; Charron, M. J.; Seeliger, M. A.; Saghatelian, A.; Liu, D. R.; *Nature* **2014**, 511, 94.

Preparation of more 30 analogue

Against insulin-degrading enzyme (IDE)

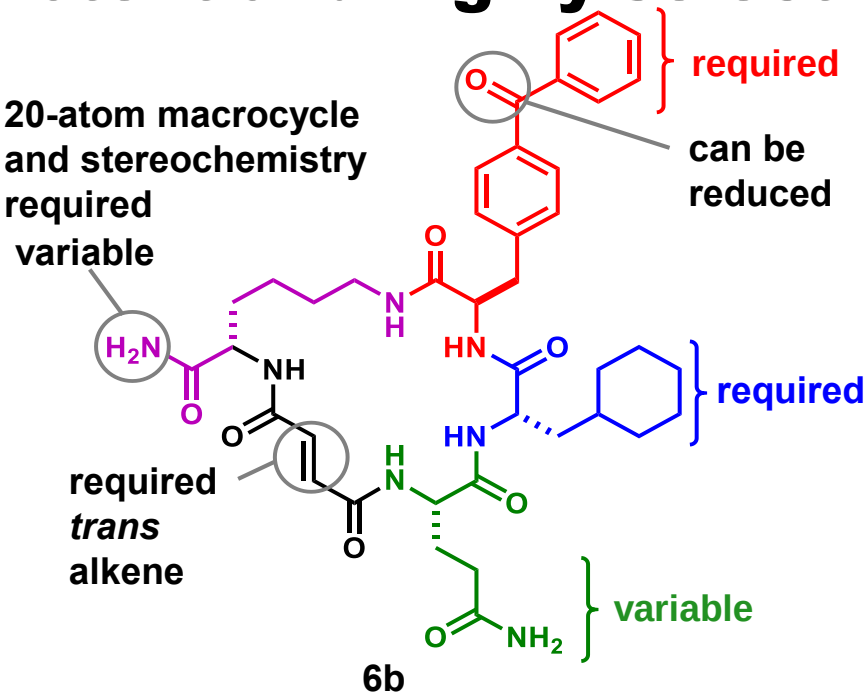


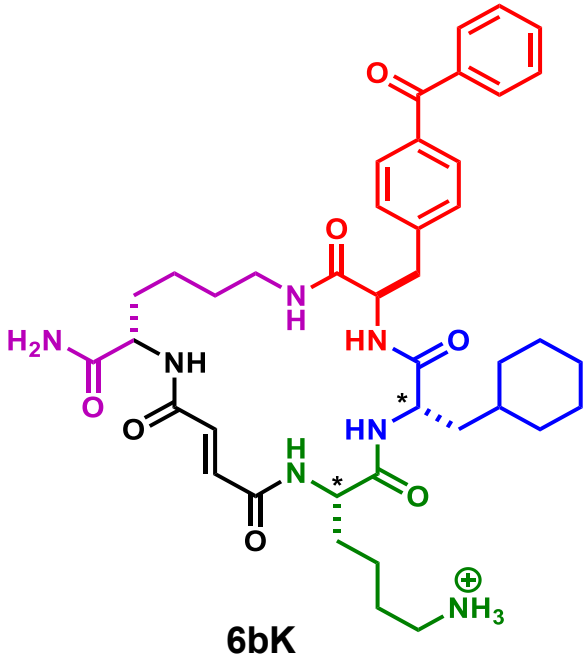
20-atom macrocycle and stereochemistry required



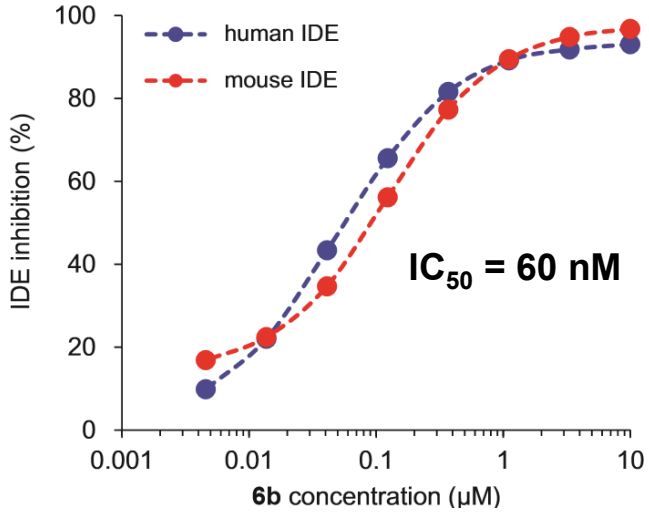
1) Maianti, J. P.; McFedries, A.; Foda, Z. H.; Kleiner, R. E.; Du, X. Q.; Leissring, M. A.; Tang5, W.-J.; Charron, M. J.; Seeliger, M. A.; Saghatelian, A.; Liu, D. R.; *Nature* **2014**, 511, 94.

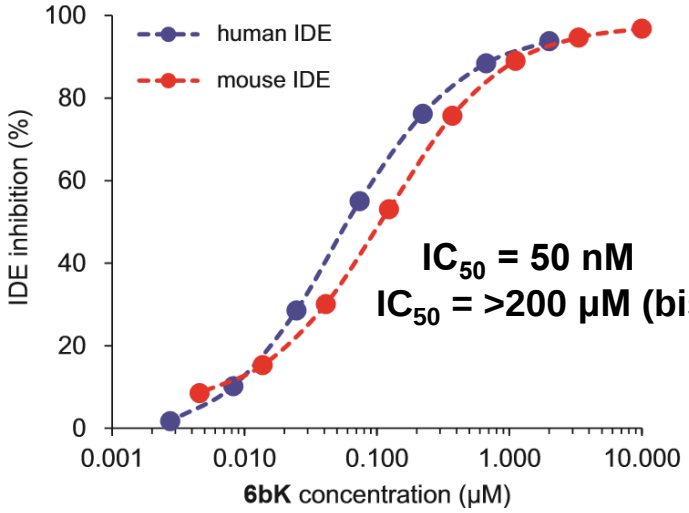
Potent and highly selective macrocyclic IDE inhibitors





Fluorogenic peptide degradation

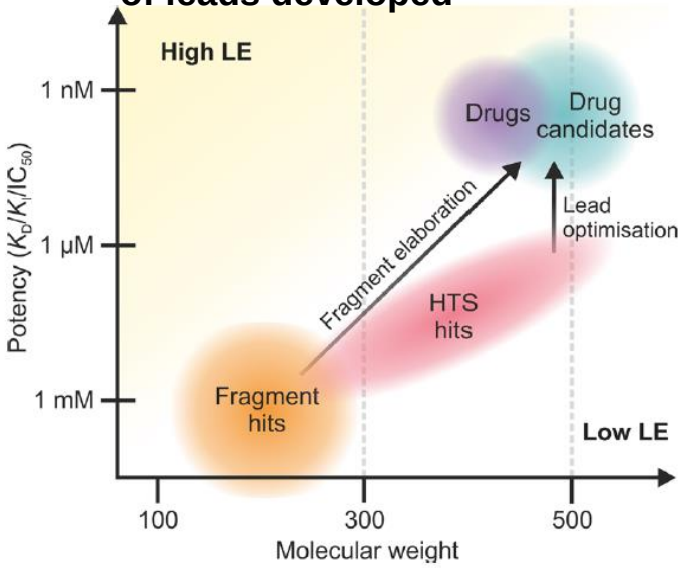




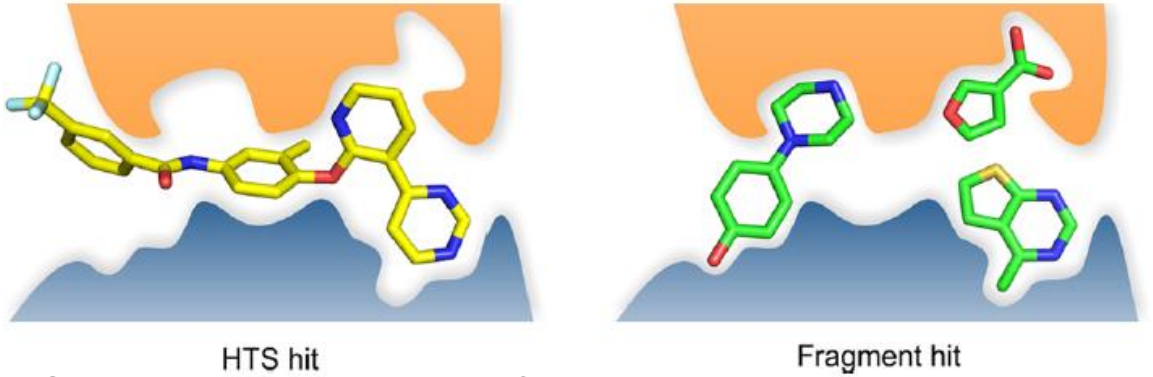
1) Maianti, J. P.; McFedries, A.; Foda, Z. H.; Kleiner, R. E.; Du, X. Q.; Leissring, M. A.; Tang5, W.-J.; Charron, M. J.; Seeliger, M. A.; Saghatelian, A.; Liu, D. R.; *Nature* **2014**, 511, 94.

Dual-pharmacophore type

Comparison of M.W. vs potency of leads developed

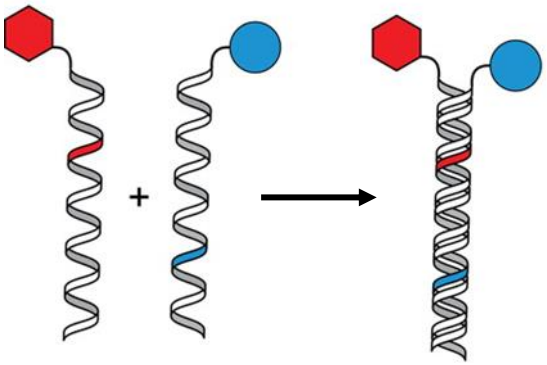


Fragment-based drug discovery(FBDD)

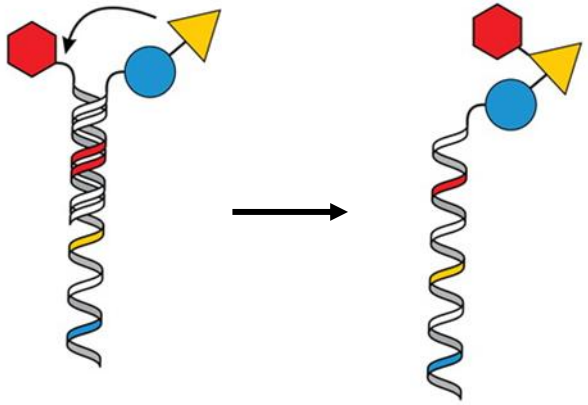


HTS hits may bind by virtue of numerous suboptimal interactions. By contrast, fragment hits are more ligand efficient and involve fewer but more optimized interactions.

Dual-pharmacophore



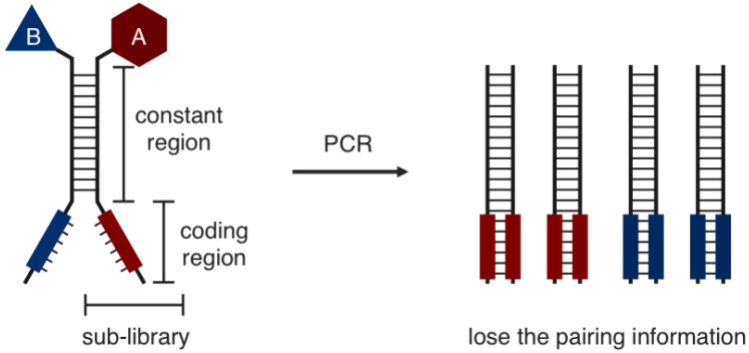
Single-pharmacophore



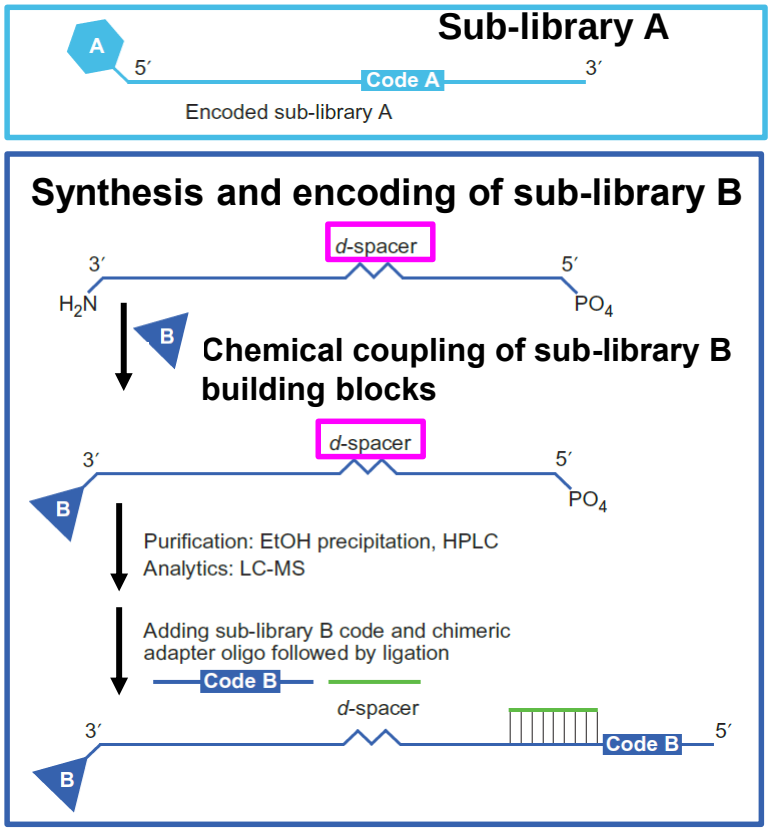
1) Scott, D. E.; Coyne, A. G.; Hudson, S. A.; Abell, C. *Biochemistry* **2012**, *51*, 4990.
2) Wichert, M.; Krall, N.; Decurtins, W.; Franzini, R. M.; Pretto, F.; Schneider, P.; Neri, D.; Scheuermann, J. *Nat. Chem.* **2015**, *7*, 241.

Dual-display DNA-encoded library

Problem



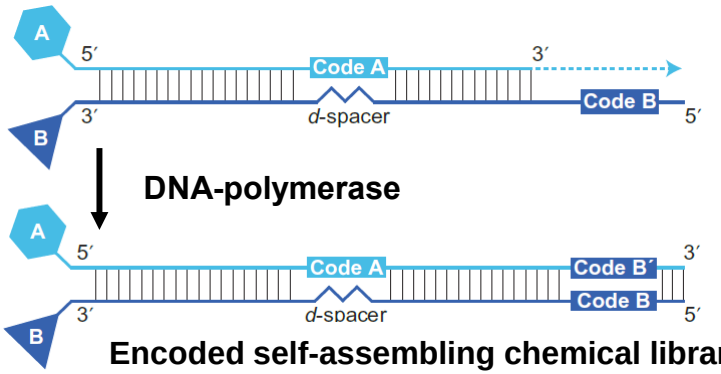
Modified methods (this paper)



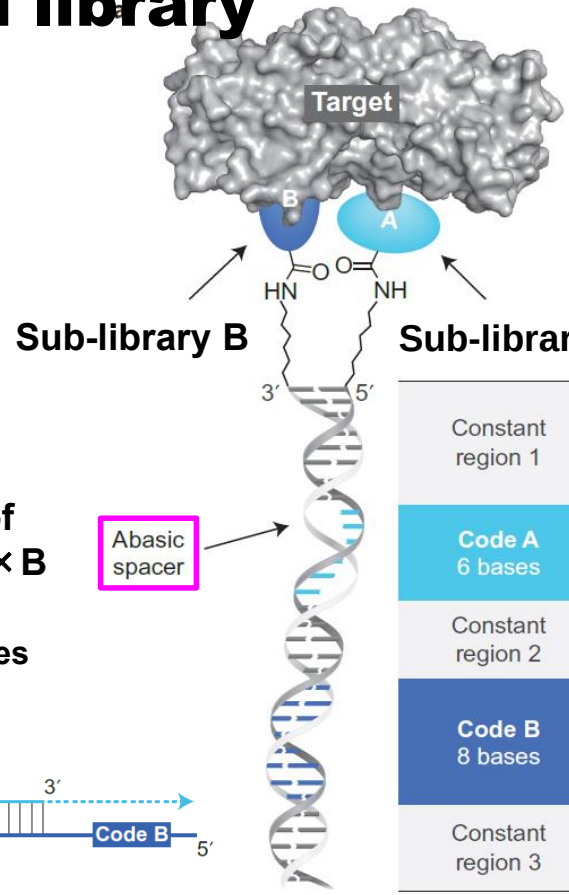
Assembly and encoding of the dual-display library A × B

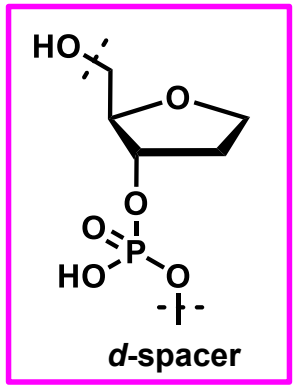
Mixing both sub-libraries

DNA-polymerase



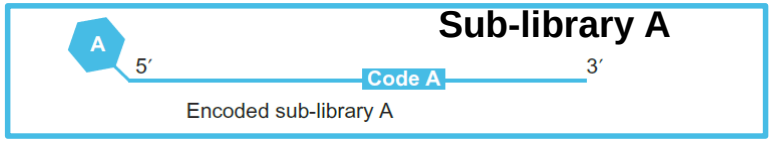
Encoded self-assembling chemical library



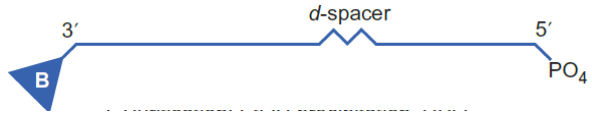


1) Wichert, M.; Krall, N.; Decurtins, W.; Franzini, R. M.; Pretto, F.; Schneider, P.; Neri, D.; Scheuermann, J. *Nat. Chem.* **2015**, *7*, 241.

Dual-display DNA-encoded library

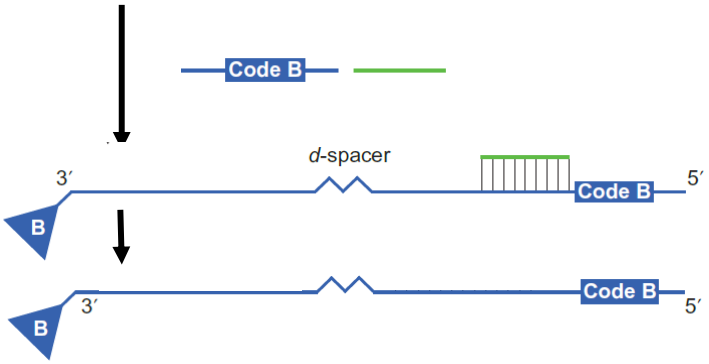


5’ – GGA GCT TCT GAA TTC TGT GTG CTG XXX XXX CGA GTC CCA TGG CGC AGC – 3’



Synthesis and encoding of sub-library B

3’ –CCT CGA AGA CTT AAG ACA CAC GAC ddd ddd GCT CAG GGT AC – 5’

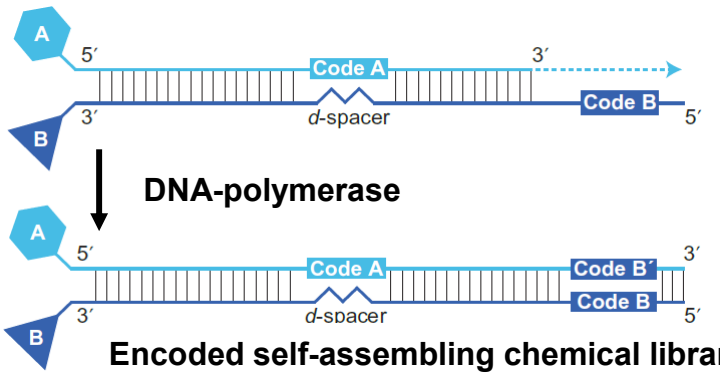


5’ –CGA GTC CCA TGG CGC AGC TGC – 3’

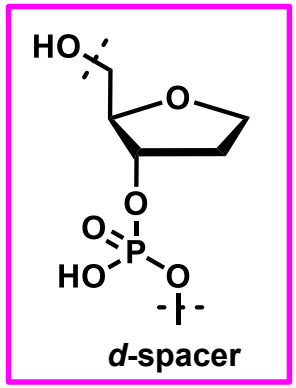
Chimeric adapter

3’ – C GCG TCG ACG XX XXX XXX -

-GTG CCT AGG TAA GCT ACG TCC – 5’



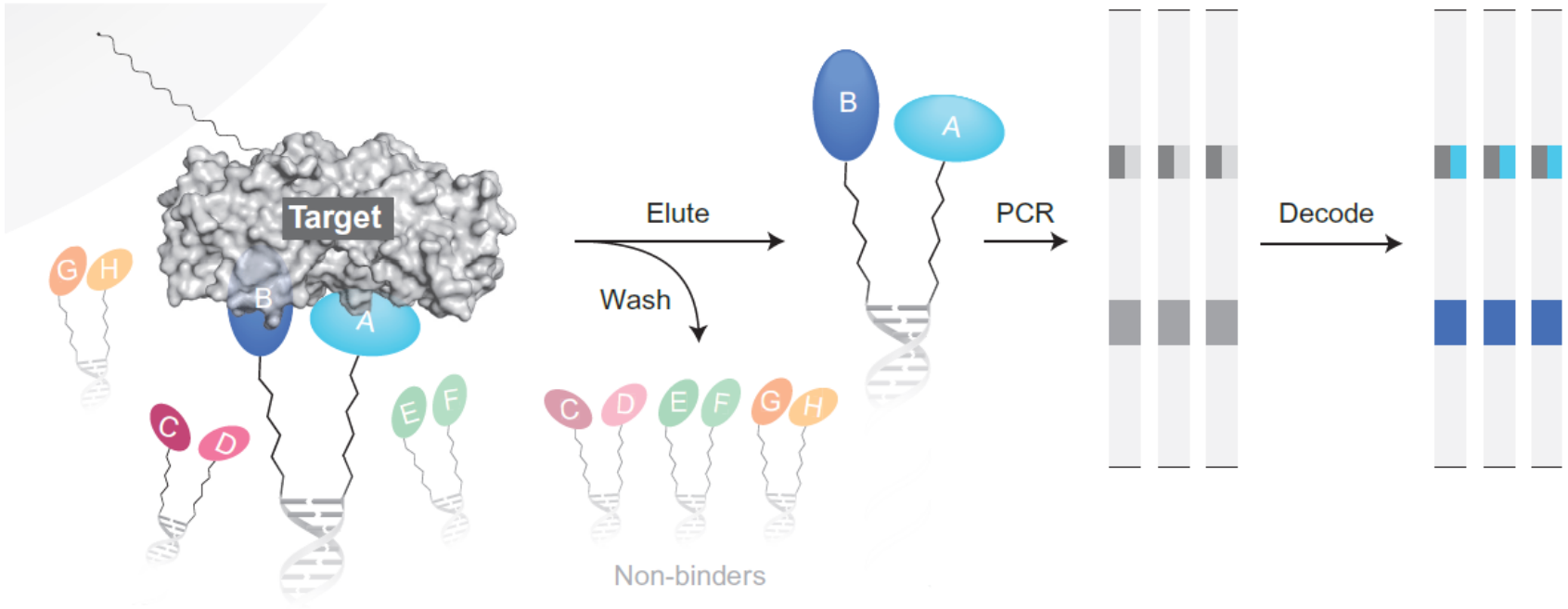
Encoded self-assembling chemical library



1) Wichert, M.; Krall, N.; Decurtins, W.; Franzini, R. M.; Pretto, F.; Schneider, P.; Neri, D.; Scheuermann, J. *Nat. Chem.* **2015**, *7*, 241.

Screening by using Dual-display DNA-encoded library

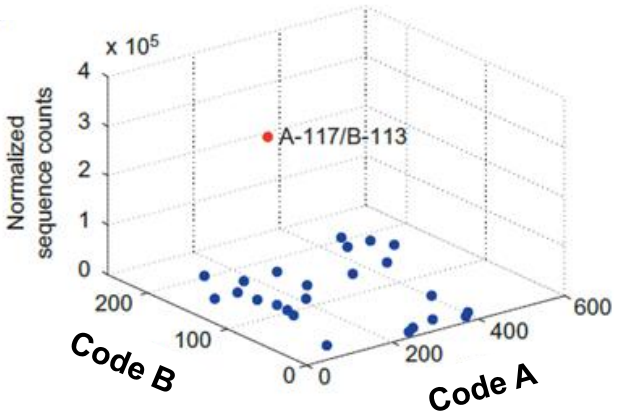
550 × 202 = 111100

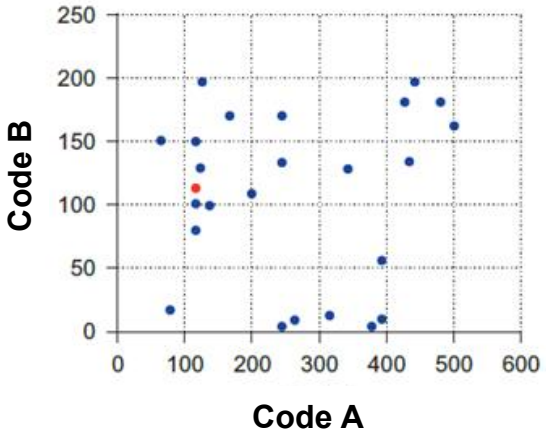


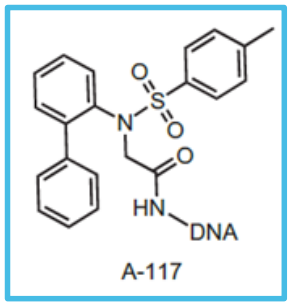
1) Wichert, M.; Krall, N.; Decurtins, W.; Franzini, R. M.; Pretto, F.; Schneider, P.; Neri, D.; Scheuermann, J. *Nat. Chem.* **2015**, *7*, 241.

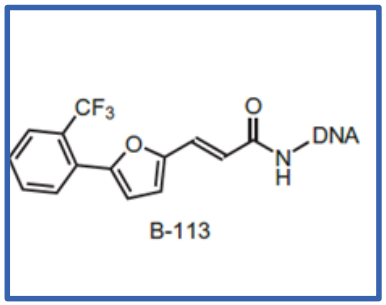
Screening by using Dual-display DNA-encoded library

alpha-1-acid glycoprotein (AGP)

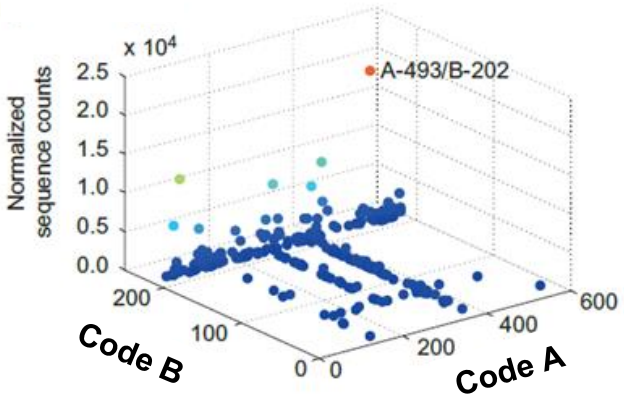




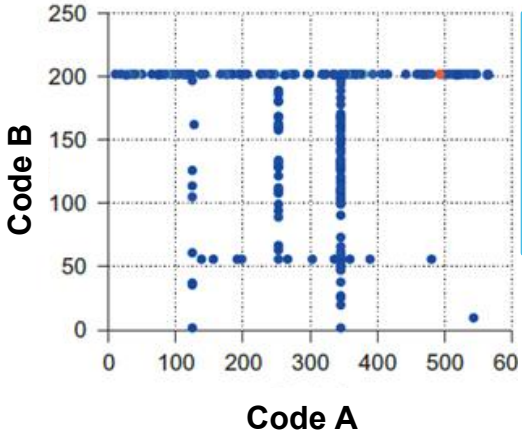


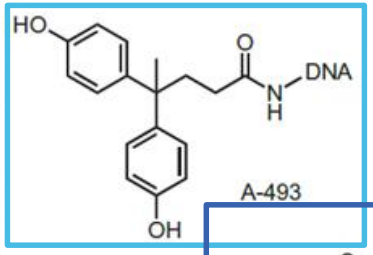


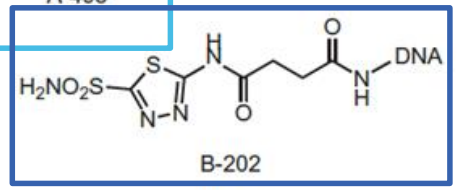
carbonic anhydrase IX (CAIX)



Code B





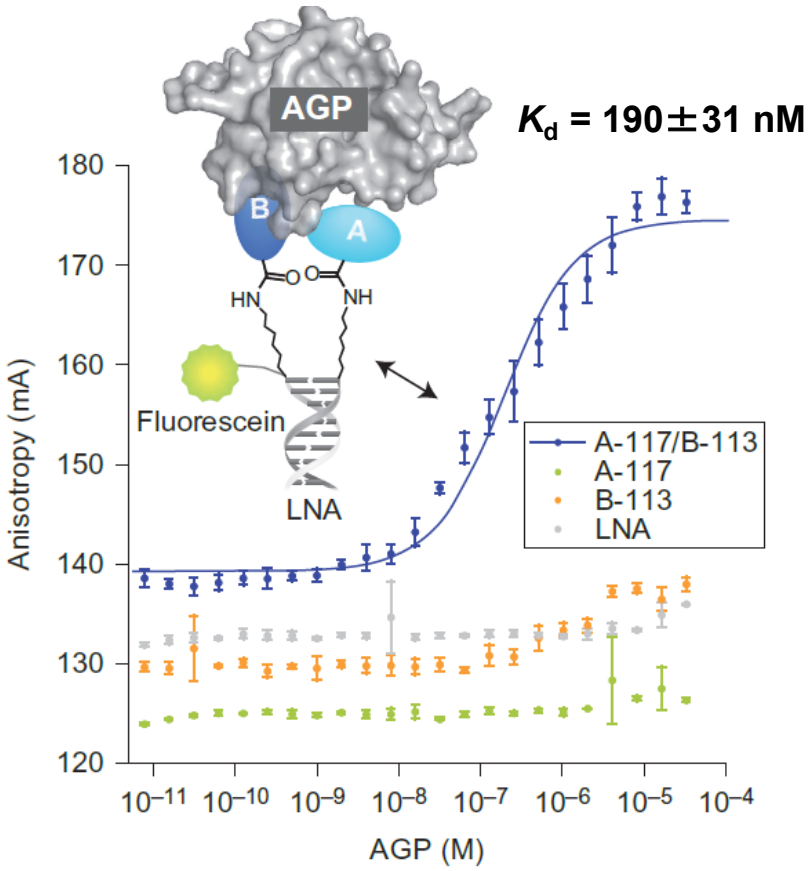


1) Wichert, M.; Krall, N.; Decurtins, W.; Franzini, R. M.; Pretto, F.; Schneider, P.; Neri, D.; Scheuermann, J. *Nat. Chem.* **2015**, *7*, 241.

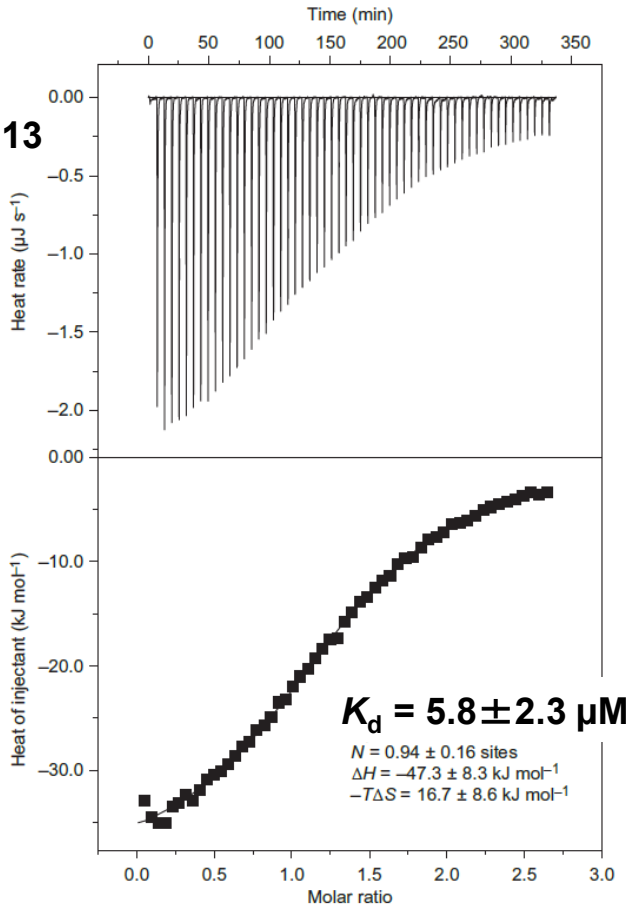
Hit validation of pharmacophore pair A-117/B-113

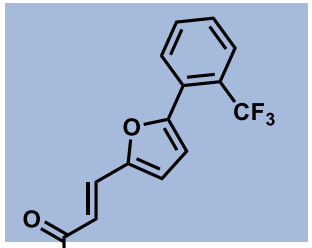
Against alpha-1-acid glycoprotein (AGP)

FP ‘on-DNA’

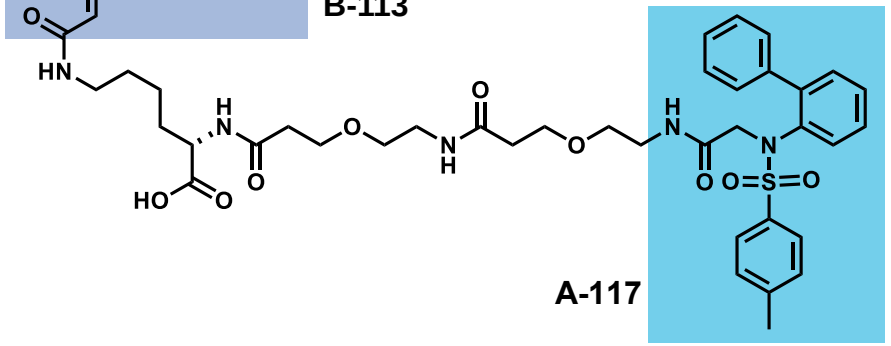


‘off-DNA’ A-117/B-113





B-113



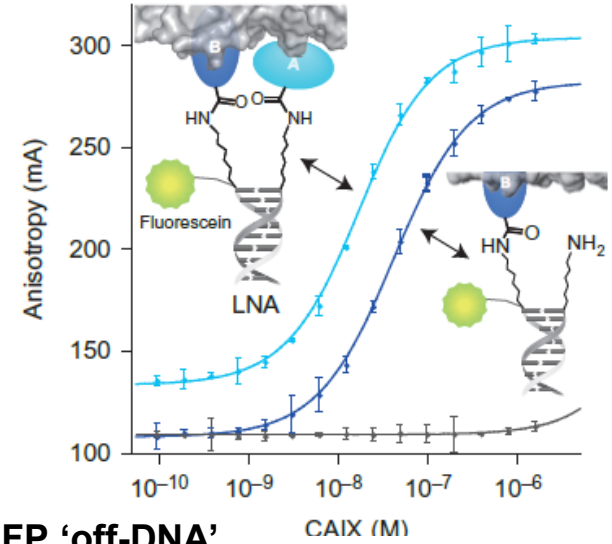
A-117

1) Wichert, M.; Krall, N.; Decurtins, W.; Franzini, R. M.; Pretto, F.; Schneider, P.; Neri, D.; Scheuermann, J. *Nat. Chem.* **2015**, *7*, 241.

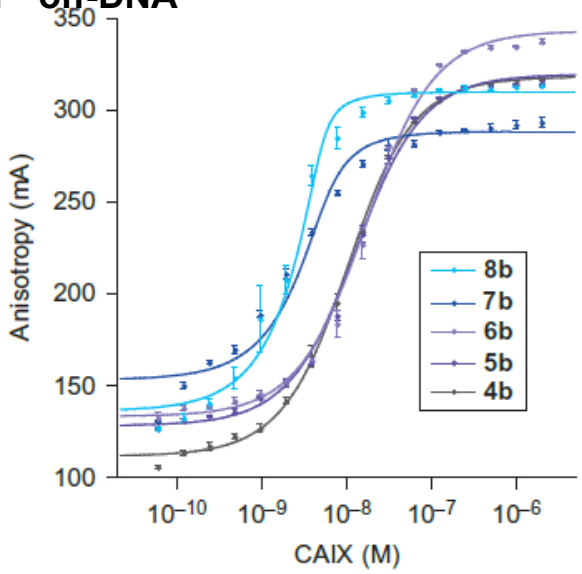
Hit validation of pharmacophore pair A-493/B-202

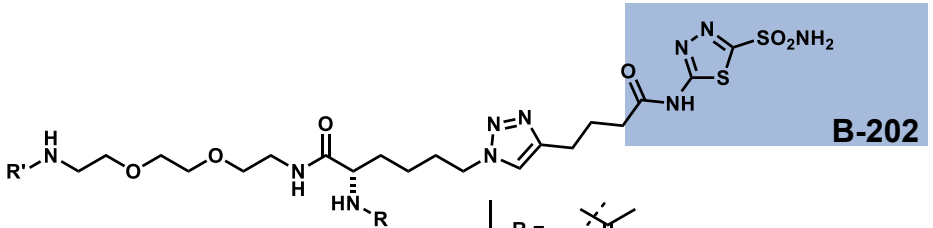
Against CAIX

FP ‘on-DNA’



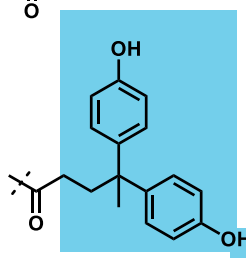
FP ‘off-DNA’





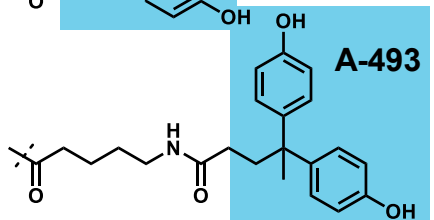
4a	R' = H	K_d (SPR) 16.7 nM	R =
4b	R' = FITC	K_d (FP) 8.0±0.4 nM	

5a	R' = H	K_d (SPR) 4.6 nM	R =
5b	R' = FITC	K_d (FP) 10.6±0.9 nM	

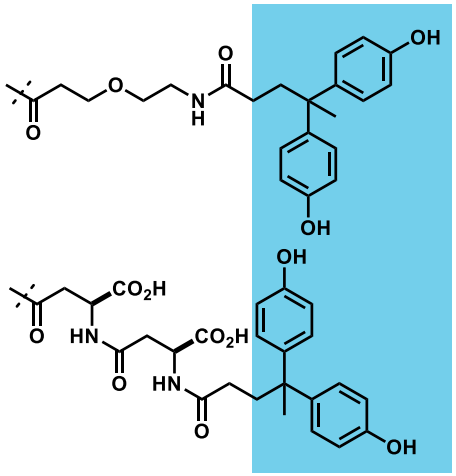


A-493

6a	R' = H	K_d (SPR) 4.8 nM	R =
6b	R' = FITC	K_d (FP) 14.8±1.3 nM	



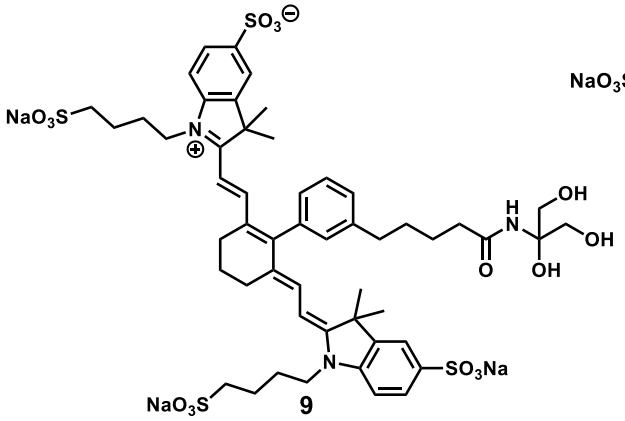
7a	R' = H	K_d (SPR) 4.6 nM	R =
7b	R' = FITC	K_d (FP) 10.6±0.9 nM	

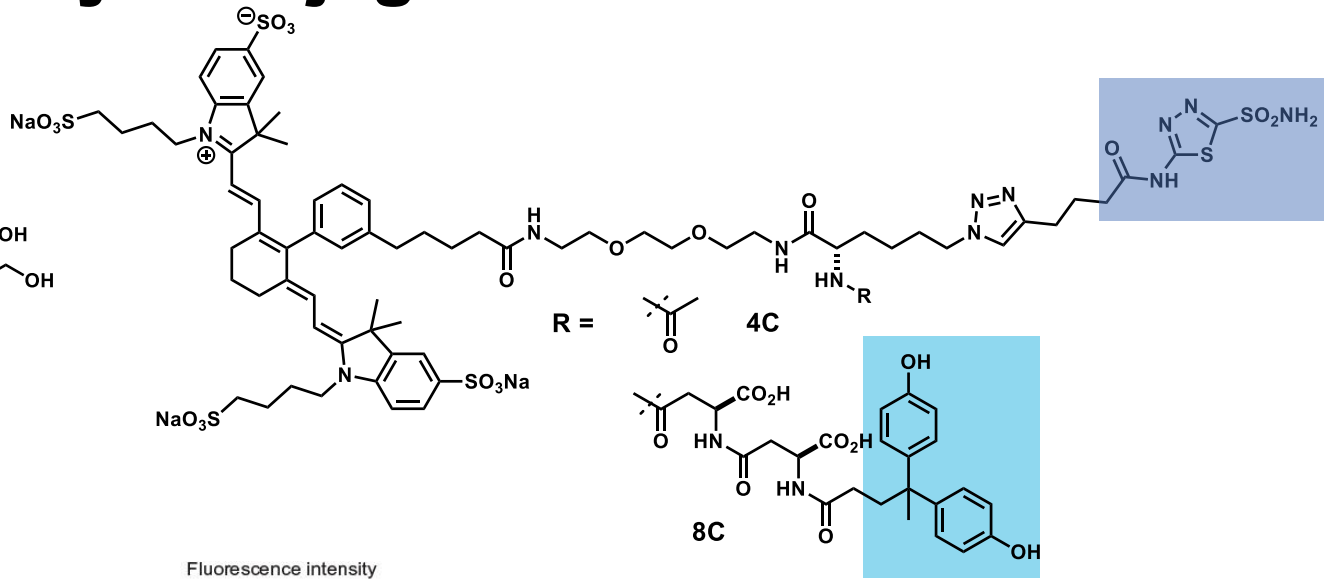


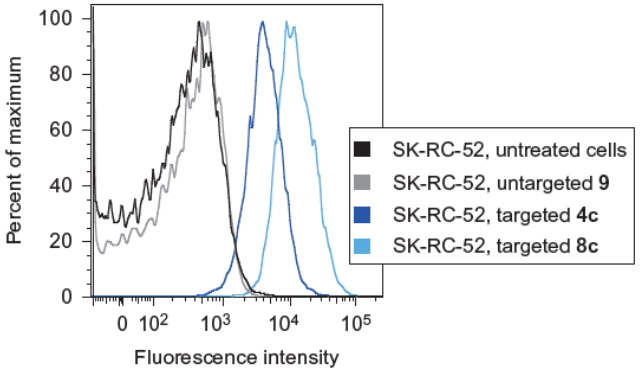
8a	R' = H	K_d (SPR) 4.8 nM	R =
8b	R' = FITC	K_d (FP) 14.8±1.3 nM	

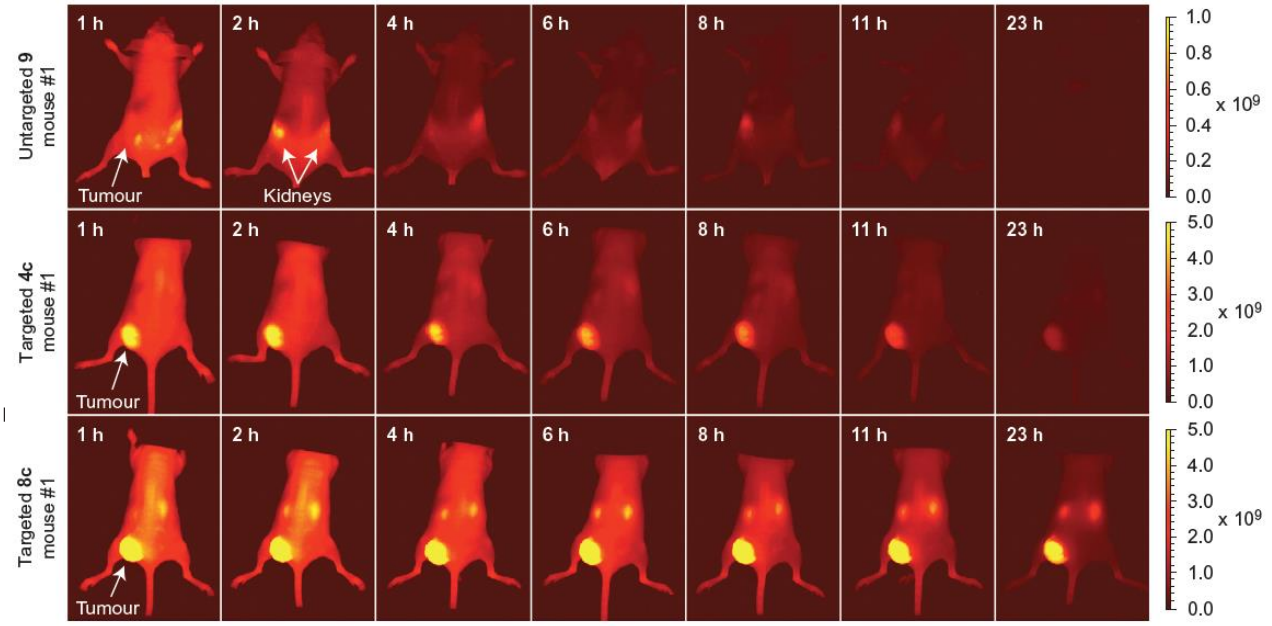
1) Wichert, M.; Krall, N.; Decurtins, W.; Franzini, R. M.; Pretto, F.; Schneider, P.; Neri, D.; Scheuermann, J. *Nat. Chem.* **2015**, *7*, 241.

compound–dye conjugate at the tumor site







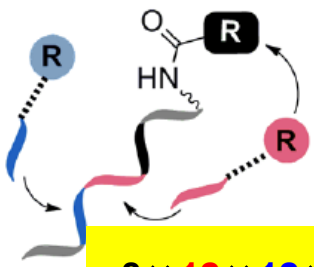


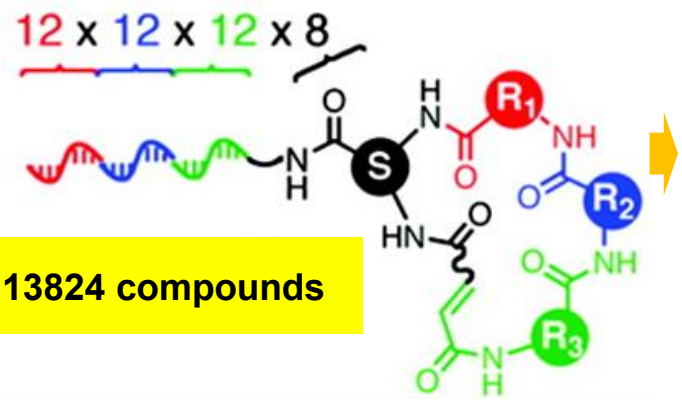
1) Wichert, M.; Krall, N.; Decurtins, W.; Franzini, R. M.; Pretto, F.; Schneider, P.; Neri, D.; Scheuermann, J. *Nat. Chem.* **2015**, *7*, 241.

Summary

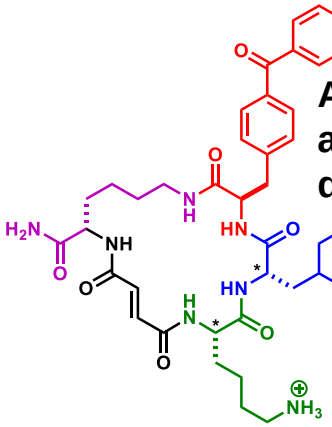
DNA-encoded library

Application for small macrocyclic peptide (by Prof. David R. Liu)





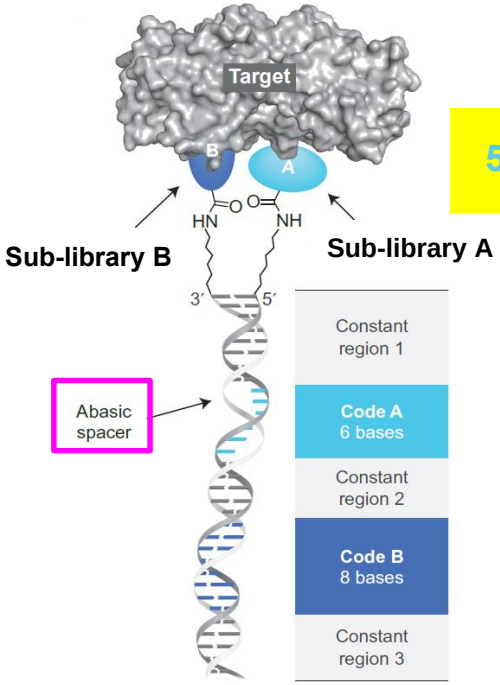
8 × 12 × 12 × 12 = 13824 compounds



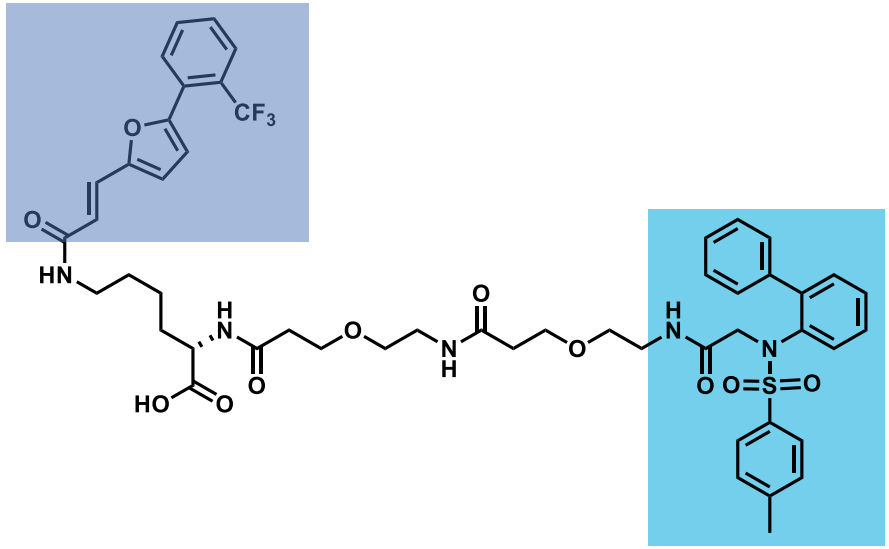
Anti-diabetic activity of insulin-degrading enzyme

IC_{50} = 50 nM

Dual-display libraries (by Prof. Dario Neri and Jörg Scheuermann)



550 × 202 = 111100 pairs



- ✓ Low micromolar binder to AGP
- ✓ The newly discovered subnanomolar CAIX binder dramatically improved tumour targeting performance *in vivo*.

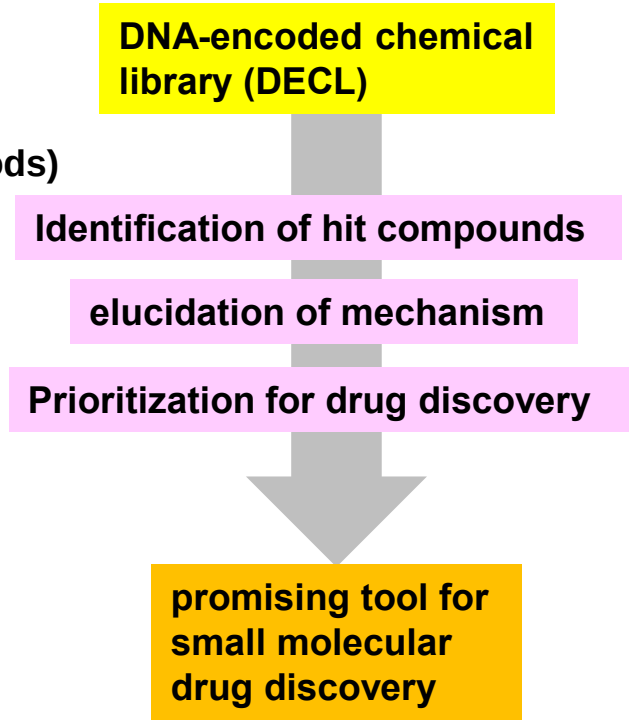
DNA-encoded chemistry: enabling the deeper sampling of chemical space

DNA-encoded chemical library (DECL) technologies are increasingly being adopted in drug discovery for hit and lead generation

Advantage

- ➢ exploration of chemical spaces (more deeply than traditional high-throughput screening methods)
- ➢ compound information is available as coded information
- ➢ available ranking information about binding affinity
- ➢ further application is abailable

- ✓ simplified methods
  - no need man power
  - no long time
  - low cost
- ✓ no need stock space
- ✓ automated system

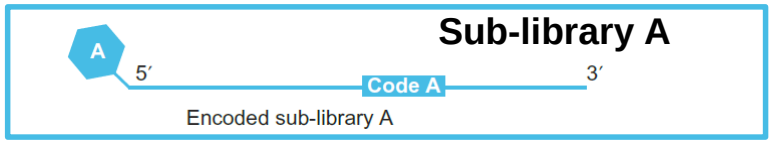


Requested improvement

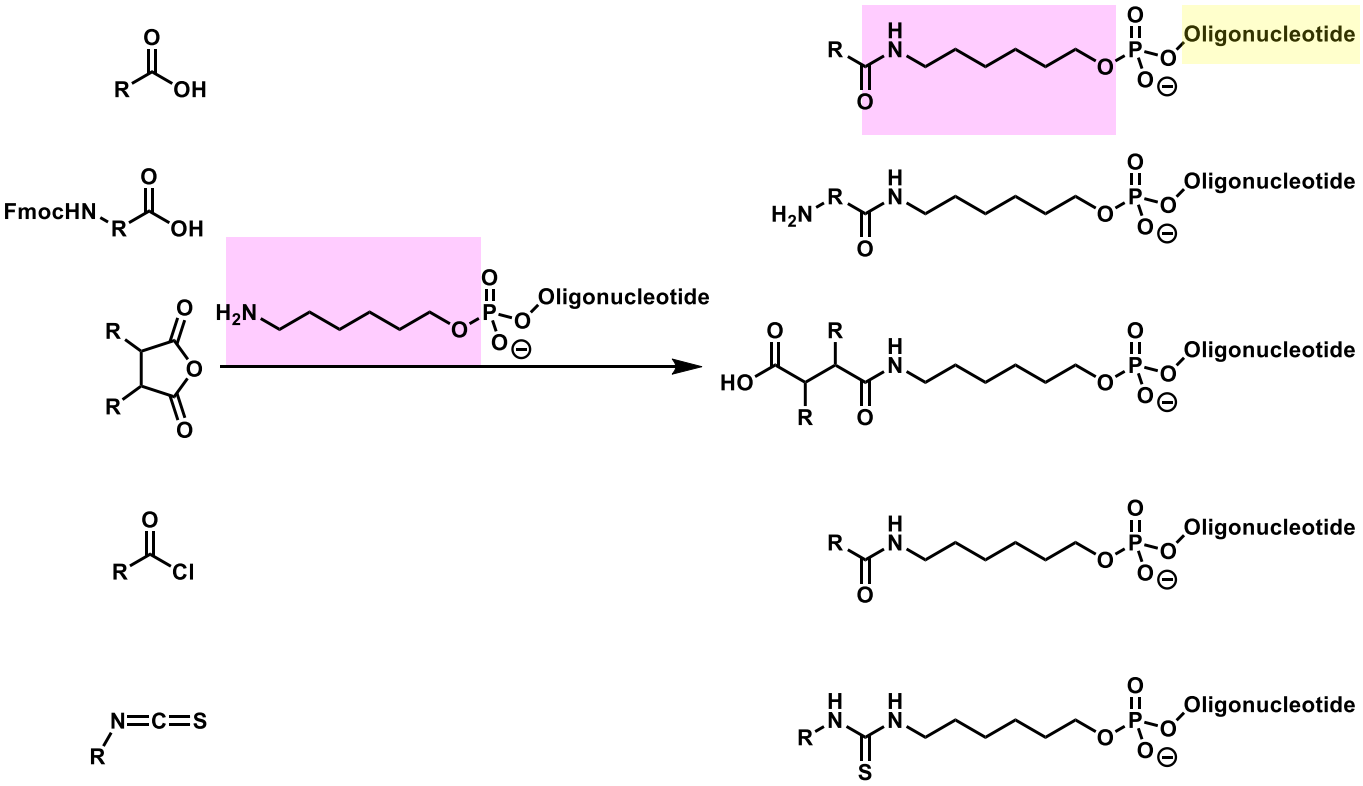
- ✓ application for medium molecular and complicated compounds
- ✓ application of target library
- ✓ application for triple or more displayed libraries
- ✓ application for harsh reaction conditions

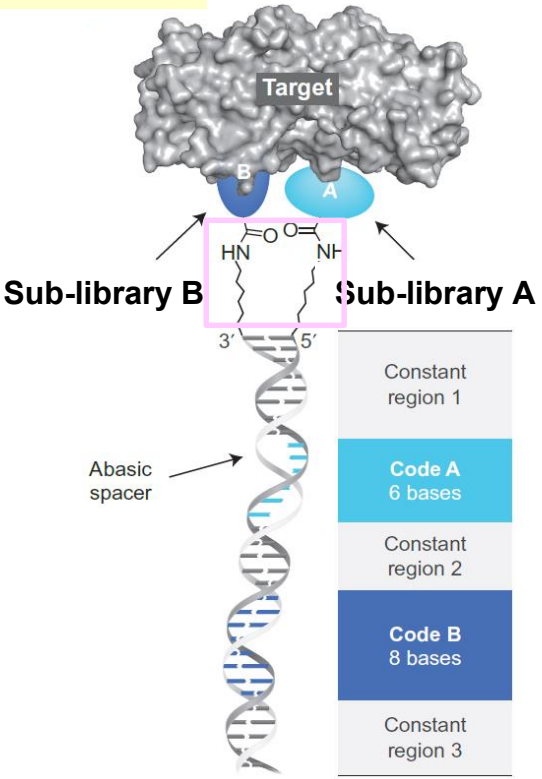
Appendix

Linker of DNA-encoded library



5’ – GGA GCT TCT GAA TTC TGT GTG CTG XXX XXX CGA GTC CCA TGG CGC AGC – 3’

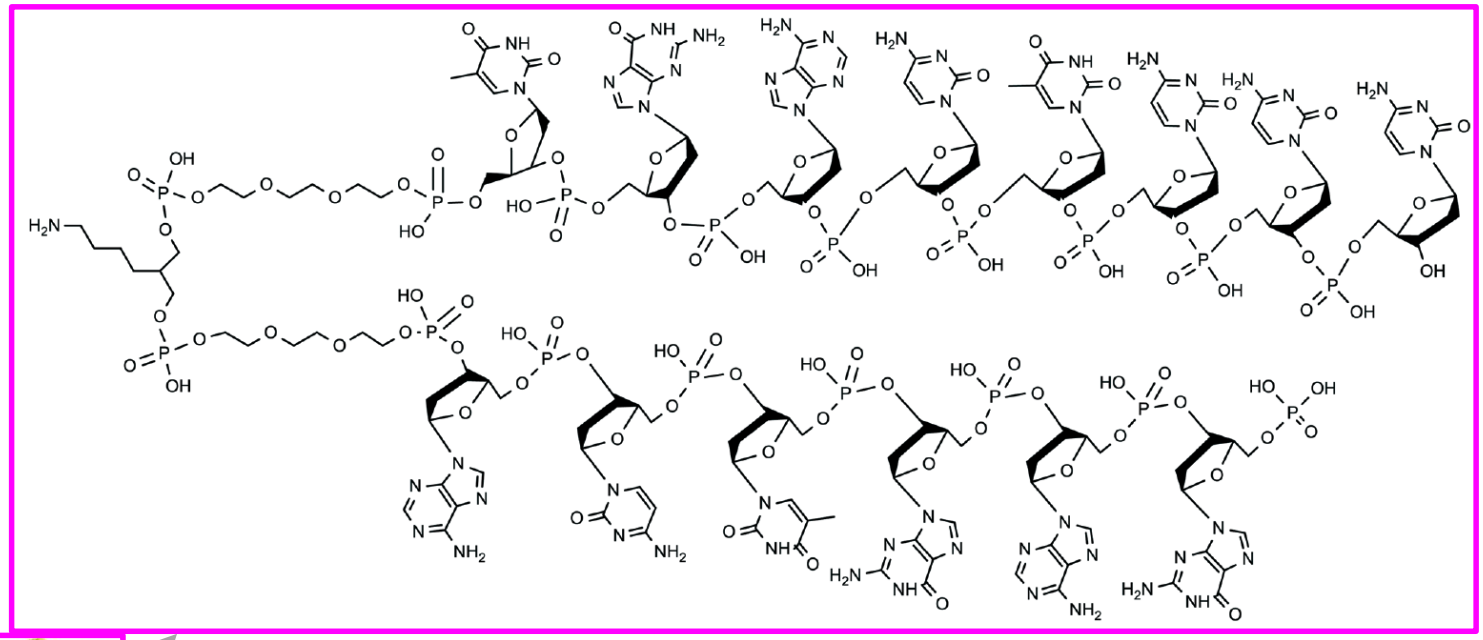


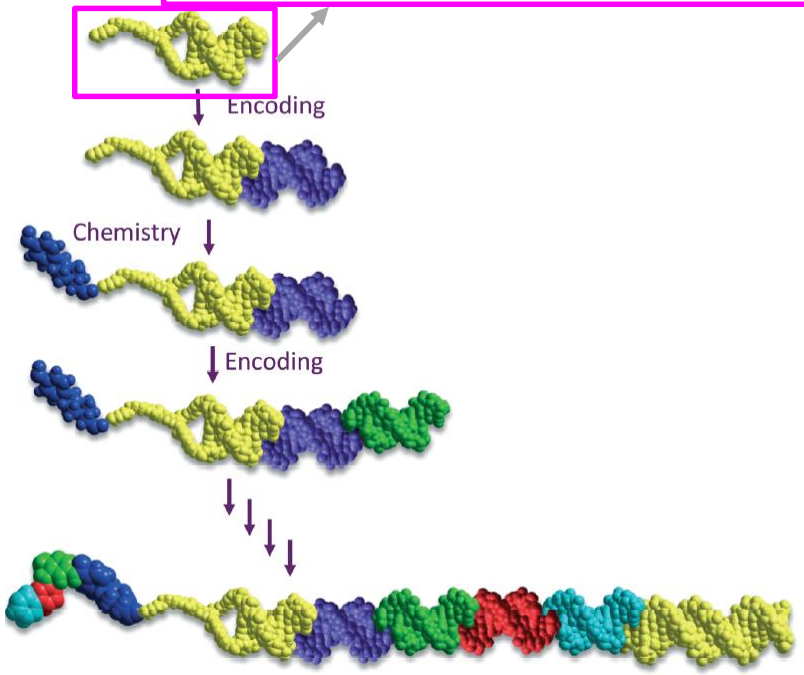


48-mer oligonucleotides carrying a free amino group at the 5’-end (ω-aminohexyl phosphate diester) were reacted.

1) Wichert, M.; Krall, N.; Decurtins, W.; Franzini, R. M.; Pretto, F.; Schneider, P.; Neri, D.; Scheuermann, J. *Nat. Chem.* **2015**, *7*, 241.
2) Dumelin, C. E.; Scheuermann, J.; Melkko, S.; Neri, D. *Bioconjugate Chem.* **2006**, *17*, 366.

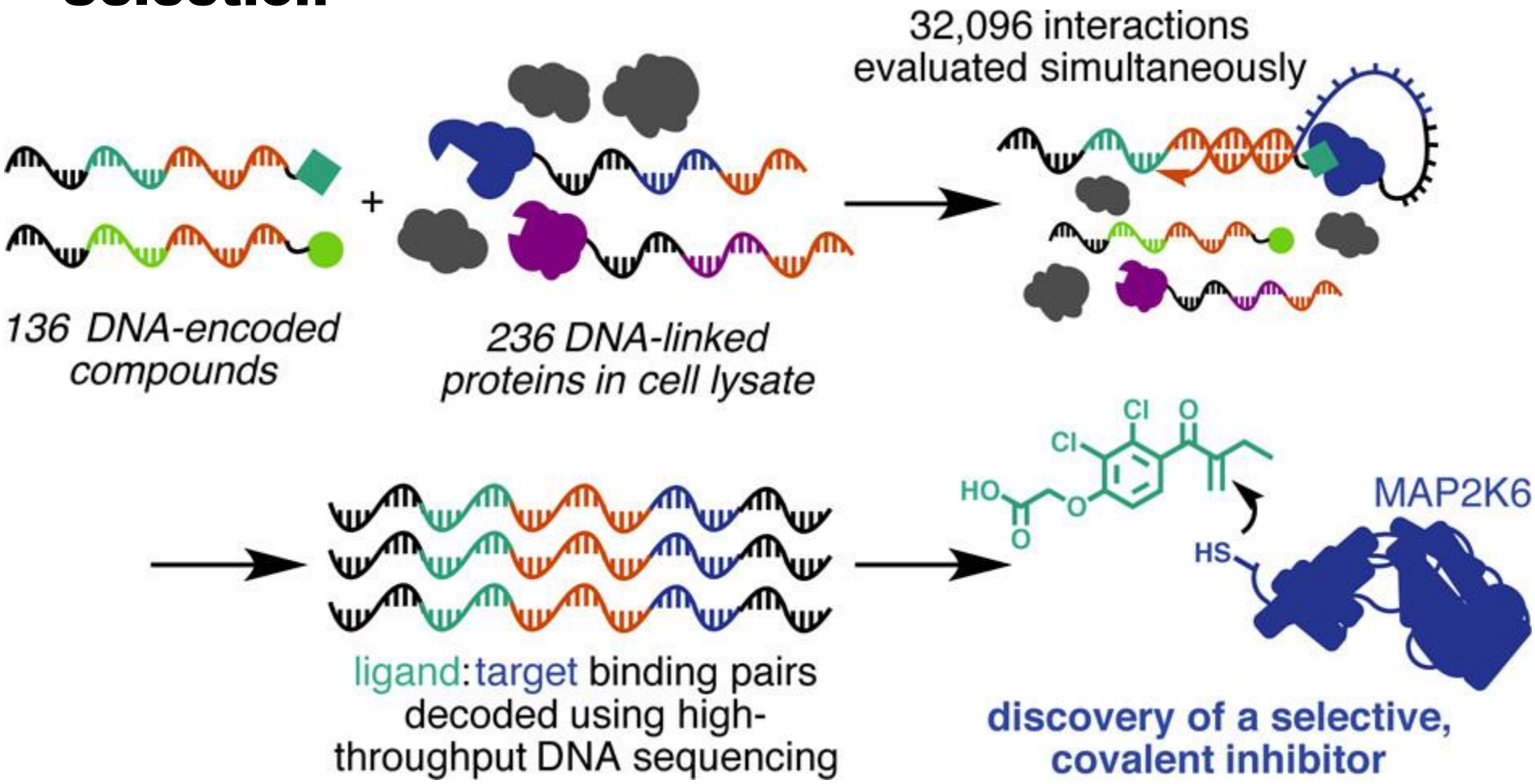
Structure of the DEL headpiece





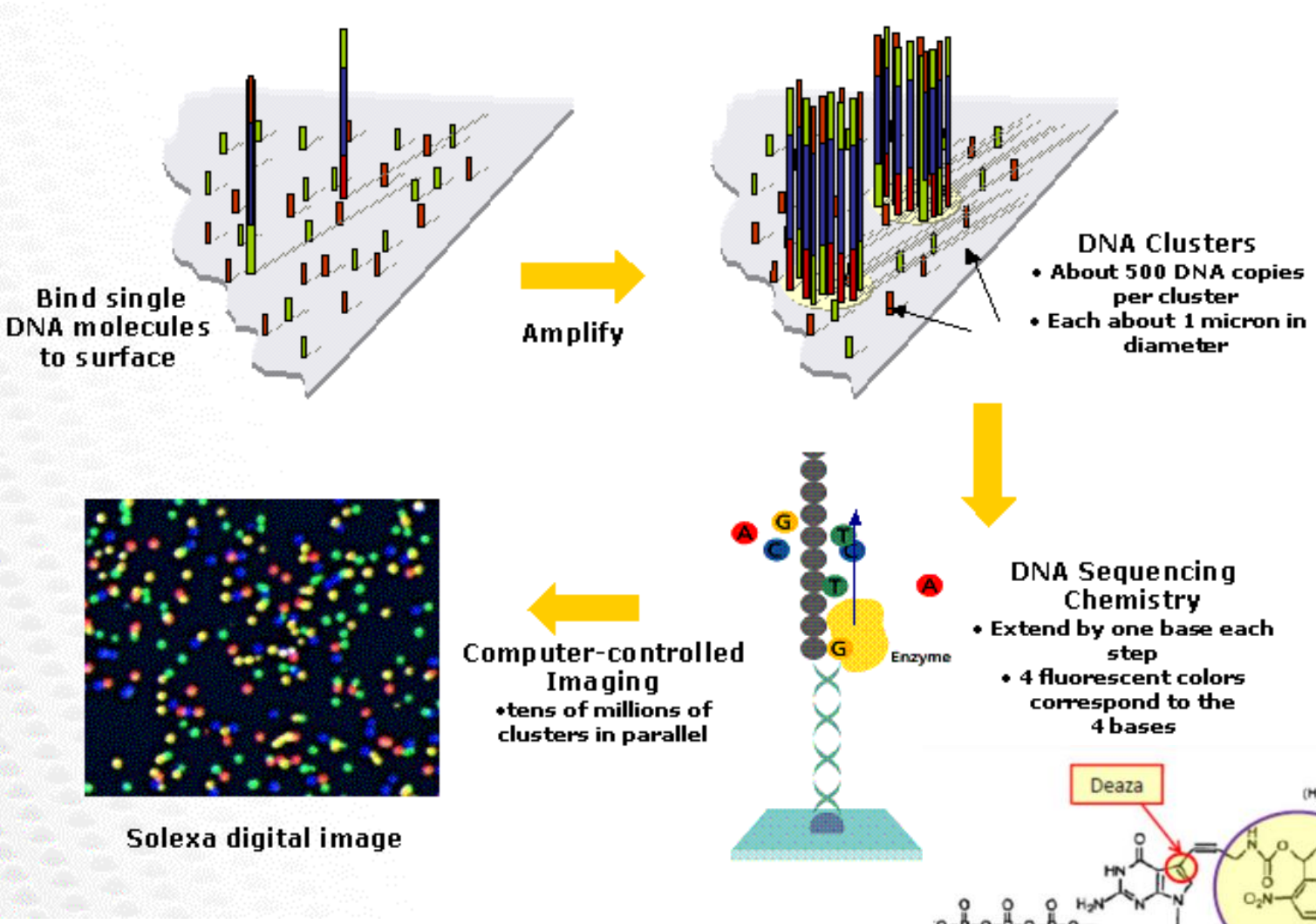
1) Arico-Muendel, C. C. *Med. Chem. Commun.* **2016**,*7,* 1898.

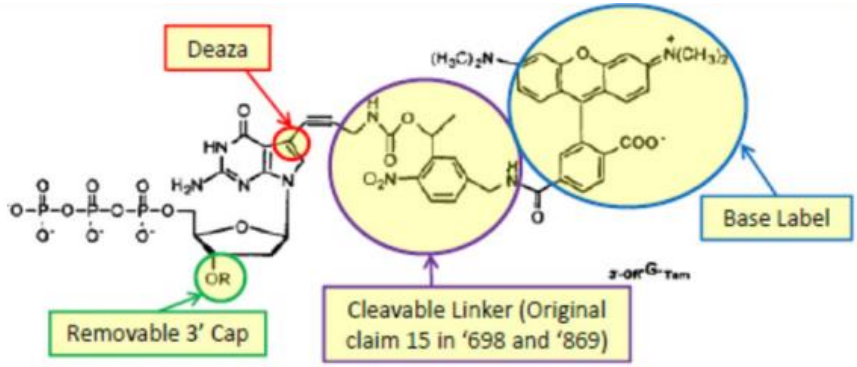
Discovery of a Covalent Kinase Inhibitor from a DNA-Encoded Small-Molecule Library × Protein Library Selection



1) Chan, A. I.; McGregor, L. M.; Jain, T.; Liu., D. R. *J. Am. Chem. Soc.* **2017**, 139, 10192.

Solexa (Illumina) DNA sequencing technology



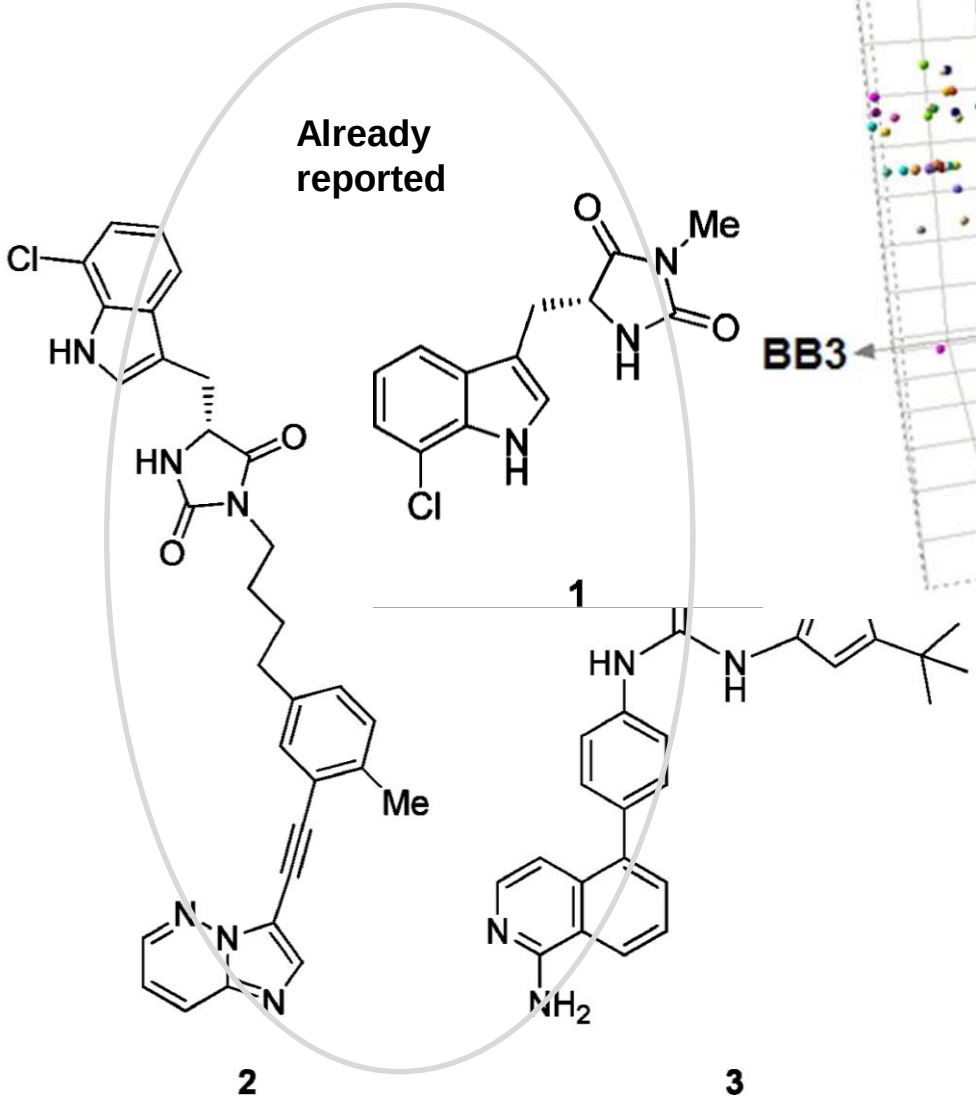


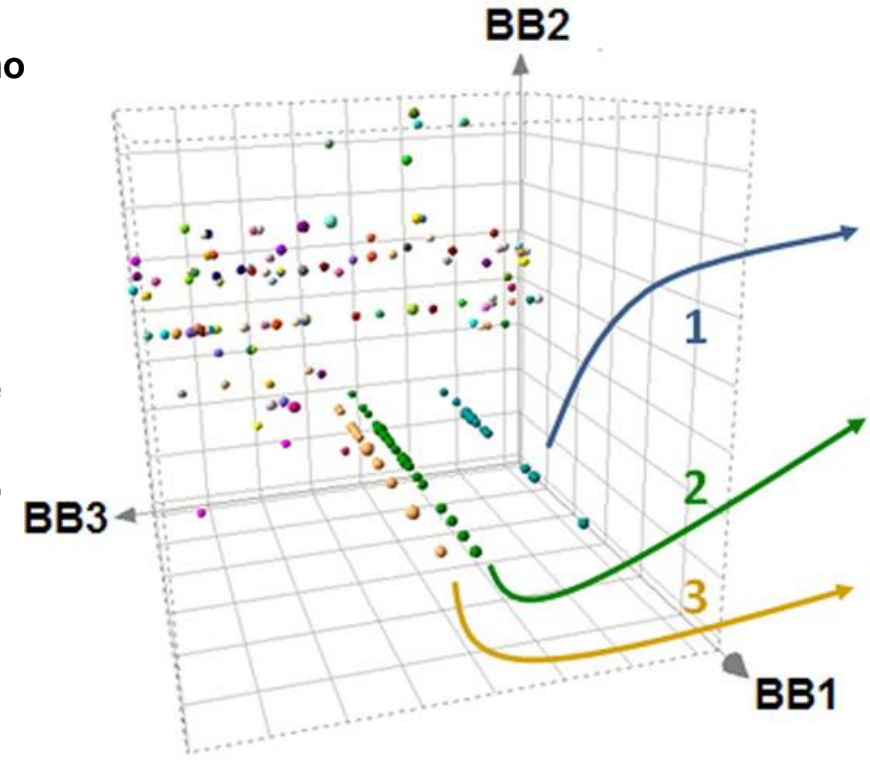
1) Bentley, D. R.; Balasubramanian, S.; Swerdlow, H. P.; Smith, G. P.; Milton, J.; Brown, C. G.; Hall, K. P.; Evers, D. J.; Barnes, C. L.; Bignell, H. R. *Nature* **2008**, *456*, 53.

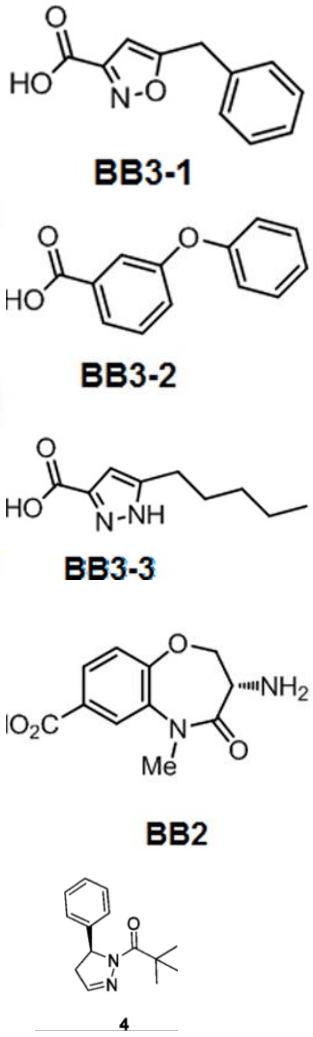
“success stories” DNA-encoded libraries hits

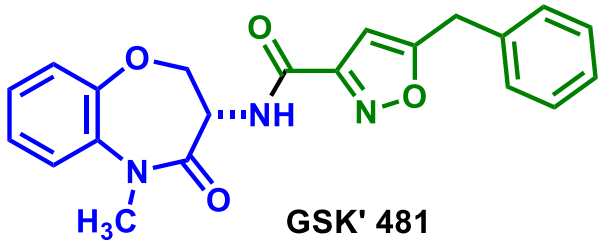
By GlaxoSmith-Kline (GSK)

Development of highly potent and mono Interacting protein 1 kinase inhibitors



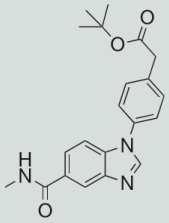
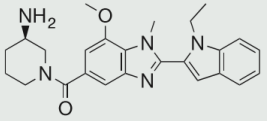
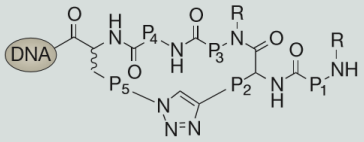
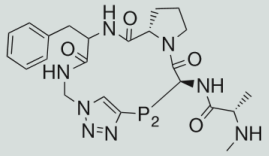
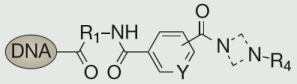
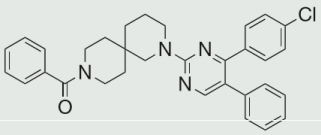
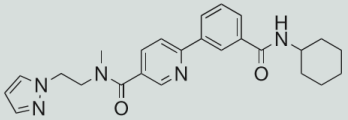
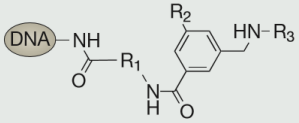
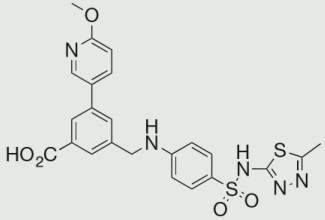






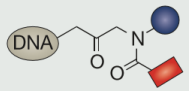
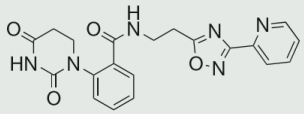
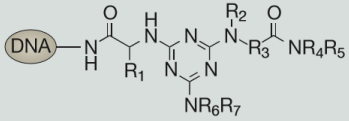
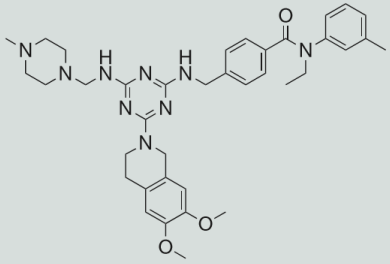
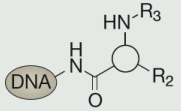
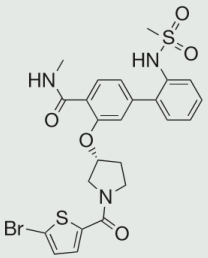
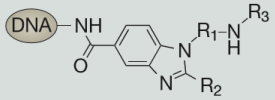
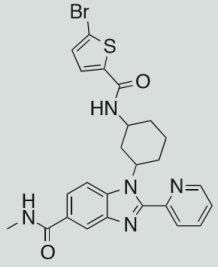
1) Harris, P. A. *et al. J. Med. Chem.* **2016**, 59, 2163.

“success stories” DNA-encoded libraries hits

Target	Institution	Library structure and size	Exemplar compound	Activity	Status
Receptor-interacting protein kinase 3 (RIP3; also known as RIPK3)	• Emory University • GlaxoSmith-Kline	Not disclosed		0.3 nM IC_{50} in biochemical assays	Active in cell assays
Protein-arginine deiminase type 4 (PAD4)	GlaxoSmith-Kline	Not disclosed		200 nM IC_{50} in biochemical assays	Cell active in *in vitro* assay, crystal structure available
X-chromosome-linked inhibitor of apoptosis protein (XIAP)	Ensemble	160,000 chemical compounds 		140 nM IC_{50} in BIR2 biochemical assays, dimer more active	Active in mouse xenograft model
Hepatitis C virus NS4B protein	GlaxoSmith-Kline	Not disclosed 		20 nM IC_{50} antiviral activity *in vitro*	Has antiviral activity but unattractive resistance profile
Soluble epoxide hydrolase	X-Chem	334 million compounds		2 nM IC_{50} in biochemical assay	Biochemical activity *in vitro*
Phosphoinositide 3-kinase-α (PI3Kα)	GlaxoSmith-Kline	3.5 million chemical compounds 		10 nM IC_{50} in biochemical assays	Crystal structure available

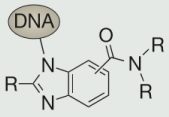
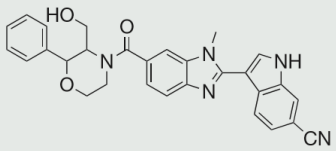
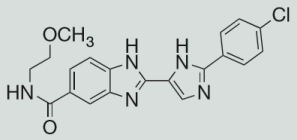
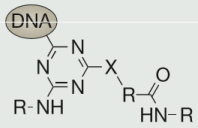
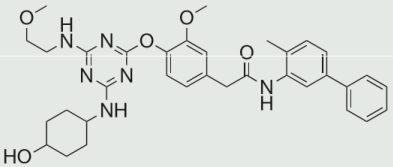
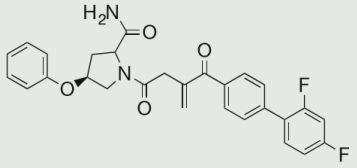
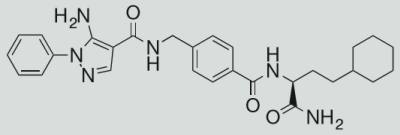
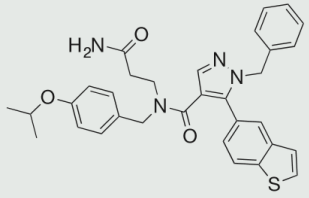
1) Goodnow Jr, R. A.; Dumelin, C. E.; Keefe, A. D. *Nature* **2017**, *16*, 131.

“success stories” DNA-encoded libraries hits

Target	Institution	Library structure and size	Exemplar compound	Activity	Status
Tankyrase 1 (TNKS)	ETH Zurich	76,000 chemical compounds 		250 nM IC_{50} in biochemical assay	Biochemical activity
A disintegrin and metalloproteinase with thrombospondin motifs 4 (ADAMTS4)	GlaxoSmith-Kline	802 million chemical compounds 		10 nM IC_{50} in biochemical assay	>1,000-fold selectivity over related targets
Branched chain aminotransferase, mitochondrial (BCATm)	GlaxoSmith-Kline	34.7 million compounds 		2.0 µM IC_{50} in biochemical assay	Crystal structure available
BCATm	GlaxoSmith-Kline	117 million compounds 		1 µM IC_{50} in *in vitro* cell-assay	Active in orally dosed mouse model

1) Goodnow Jr, R. A.; Dumelin, C. E.; Keefe, A. D. *Nature* **2017**, *16*, 131.

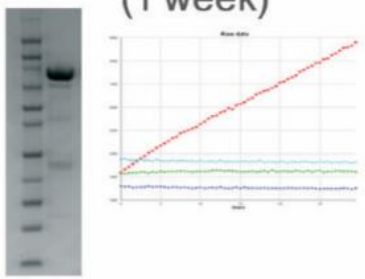
“success stories” DNA-encoded libraries hits

Target	Institution	Library structure and size	Exemplar compound	Activity	Status
Phosphodiesterase 12 (PDE12)	GlaxoSmith-Kline	9.2 million chemical compounds 		8 nM IC_{50} in biochemical assay	Antiviral activity, crystal structure available
Receptor-interacting protein 2 (RIP2)	GlaxoSmith-Kline	Not disclosed		500 nM IC_{50} in biochemical assays	Crystal structure available
Neurokinin 3 (NK3)	GlaxoSmith-Kline	41 million chemical compounds 		2 nM IC_{50} in *in vitro* cell assays	Active in cell assays
Dual specificity mitogen-activated protein kinase kinase 2 (MEK2; also known as MAP2K2)	University of Geneva	10,000 electrophile-containing dipeptides		Irreversible covalent inhibitor	Competitive with active-site binder
p38α (also known as MAPK14)	Vipergen	12.6 million chemical compounds, linear 3-cycle library assembled using acylation, reductive amination and urea formation		7 nM IC_{50} in cell assays	Active in cell assays, selective, crystal structure available
Undecaprenyl pyrophosphate synthase (UppS)	GlaxoSmith-Kline	1.6 million compounds, 3-cycle diversity library		8 µg per ml MIC in cellular assays	Active in antibacterial assays, crystal structure available

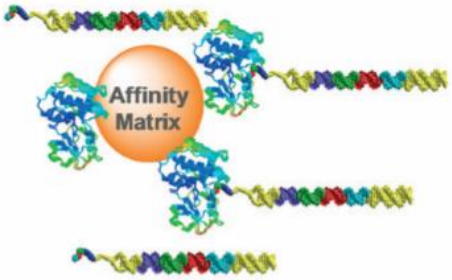
1) Goodnow Jr, R. A.; Dumelin, C. E.; Keefe, A. D. *Nature* **2017**, *16*, 131.

DEL screening cycle: time scale

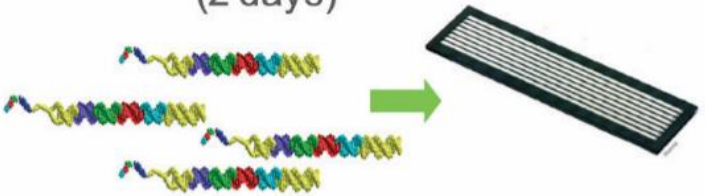
Step 1:
Target immobilization and activity confirmation
(1 week)



Step 2:
Affinity Selections
(1 week)

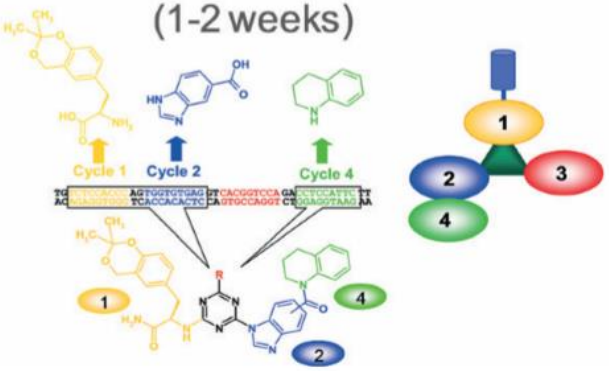


Step 3:
Sample preparation/ amplification for sequencing
(2 days)

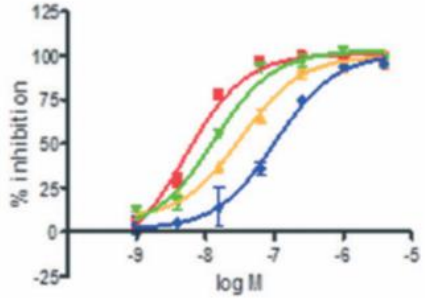


Step 4:
Sequencing by Illumina HiSeq
(1-2 weeks)

Step 5:
Translation of sequences into structures
(1-2 weeks)



Step 6:
Off-DNA synthesis and hit evaluation
(2-3 weeks per chemotype)



1) Arico-Muendel, C. C. *Med. Chem. Commun.* **2016**,*7*, 1898.