

The logo of ETH Zurich, consisting of the letters 'ETH' in a bold, italicized, sans-serif font.

Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich



Novel Strategies for the Synthesis and Use of DNA-Encoded Chemical Libraries

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DCHAB

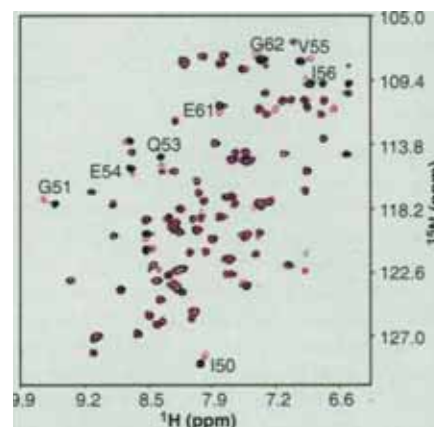
Department of Chemistry and
Applied Biosciences

Small Molecule Ligands – Screening Technologies

High-Throughput Screening

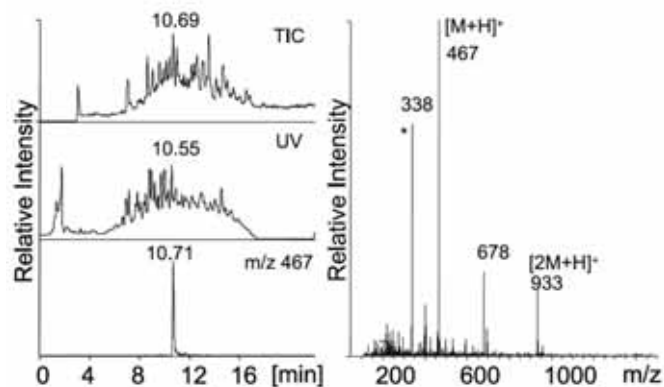


SAR by NMR



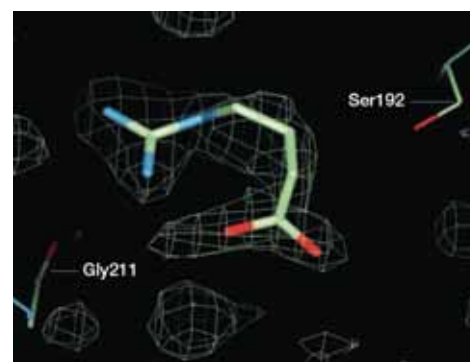
Shuker et al.
Science **1996**, 264, 1531.

SpeedScreen



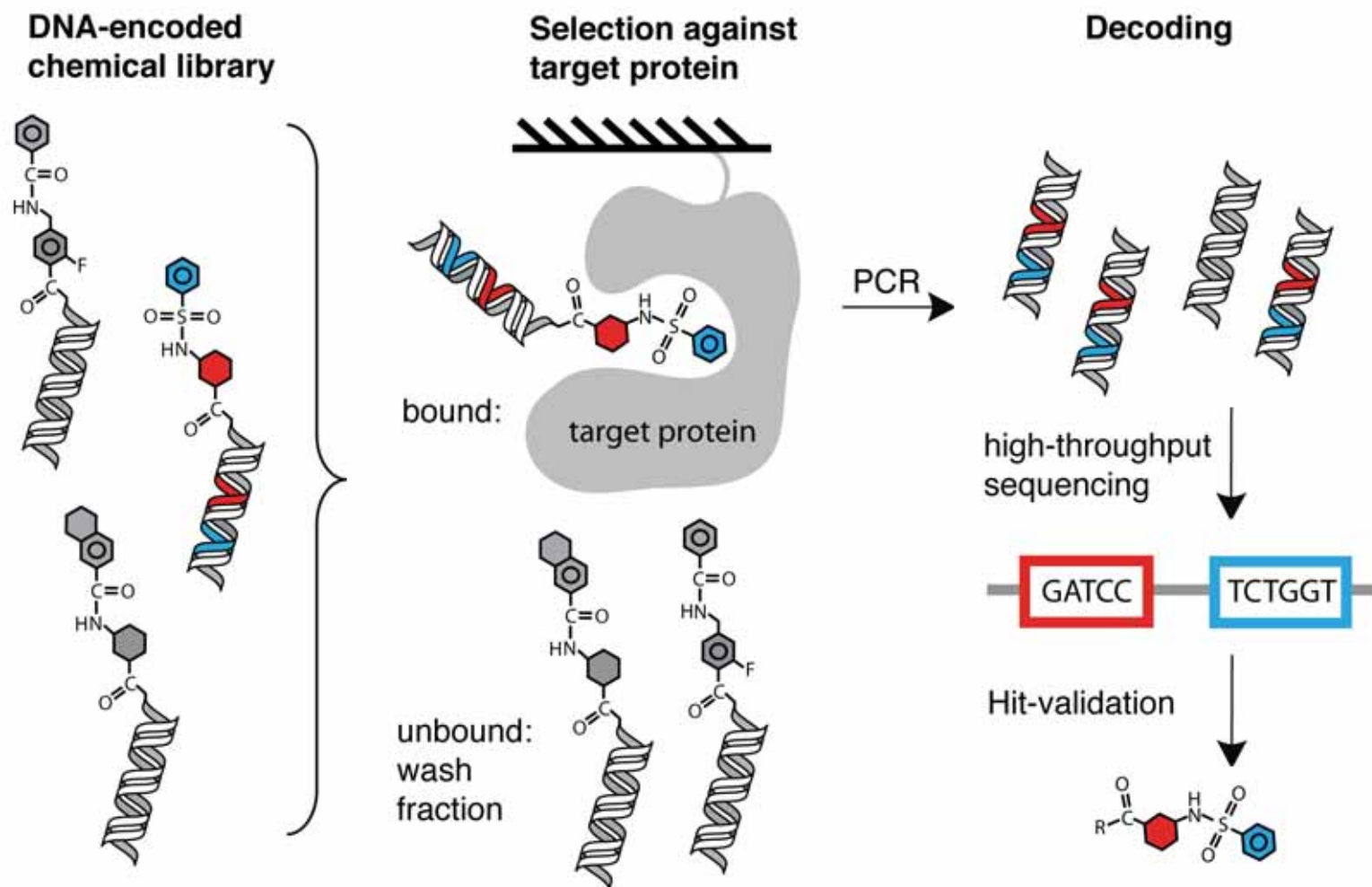
Muckenschnabel et al.
Anal Biochem. **2004**, 324, 241.

High-Throughput Crystallography

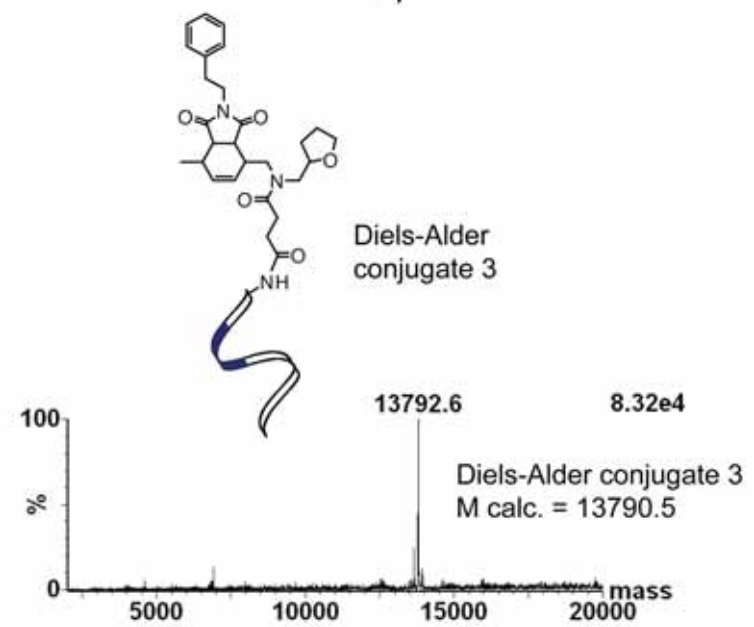
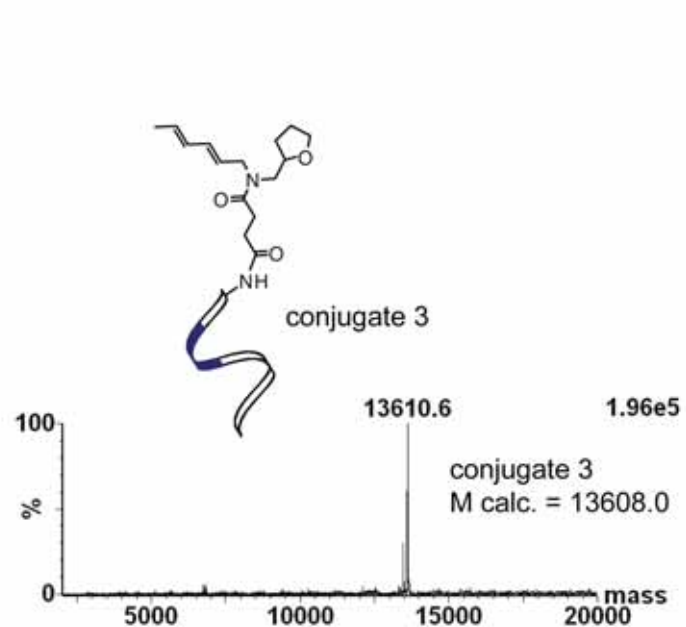
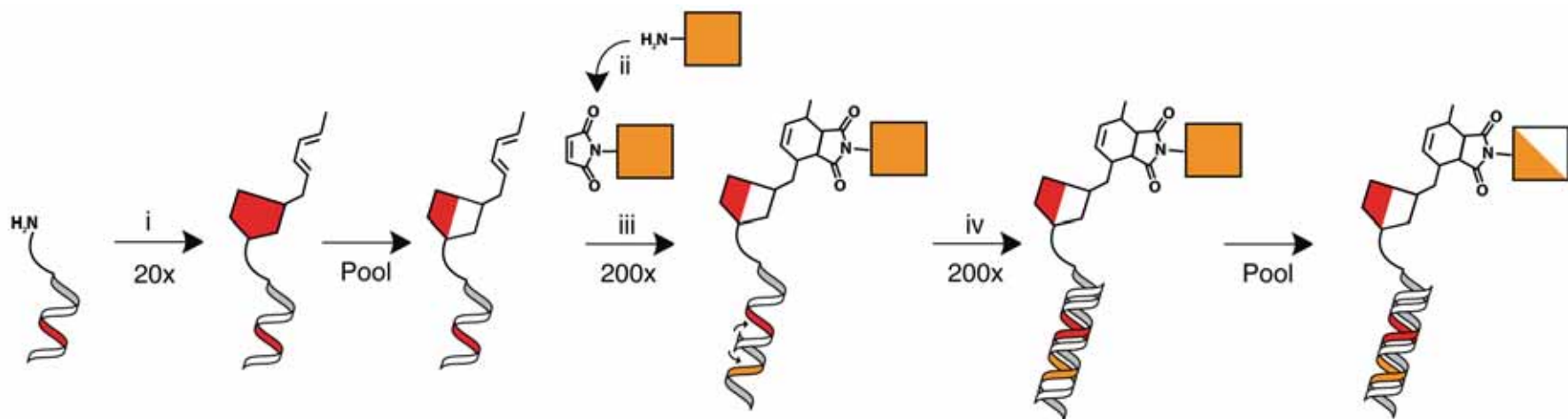


Blundell et al.
Nat Rev Drug Discov. **2002**, 1, 45.

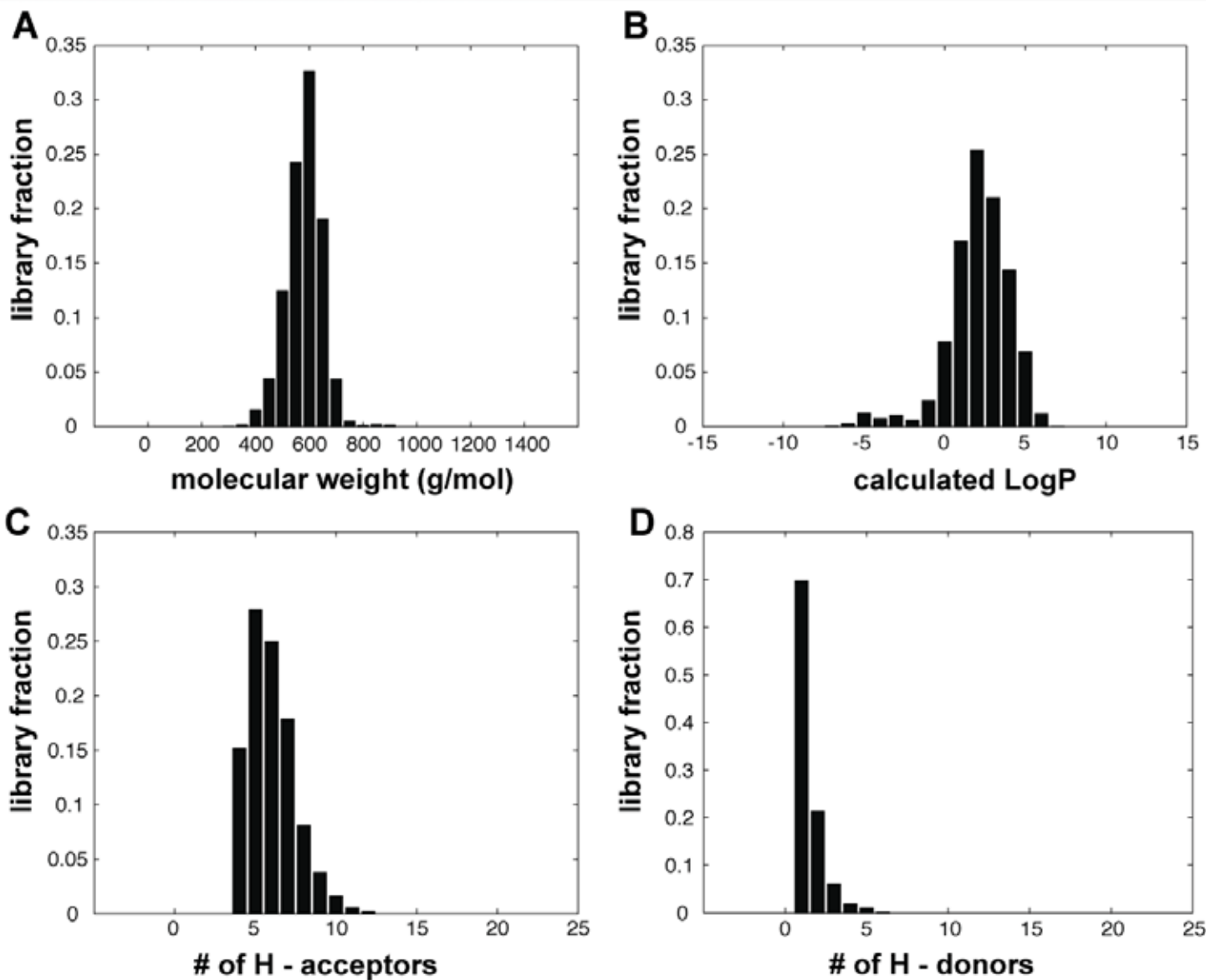
Small Molecule Selection with a DNA-Encoded Library



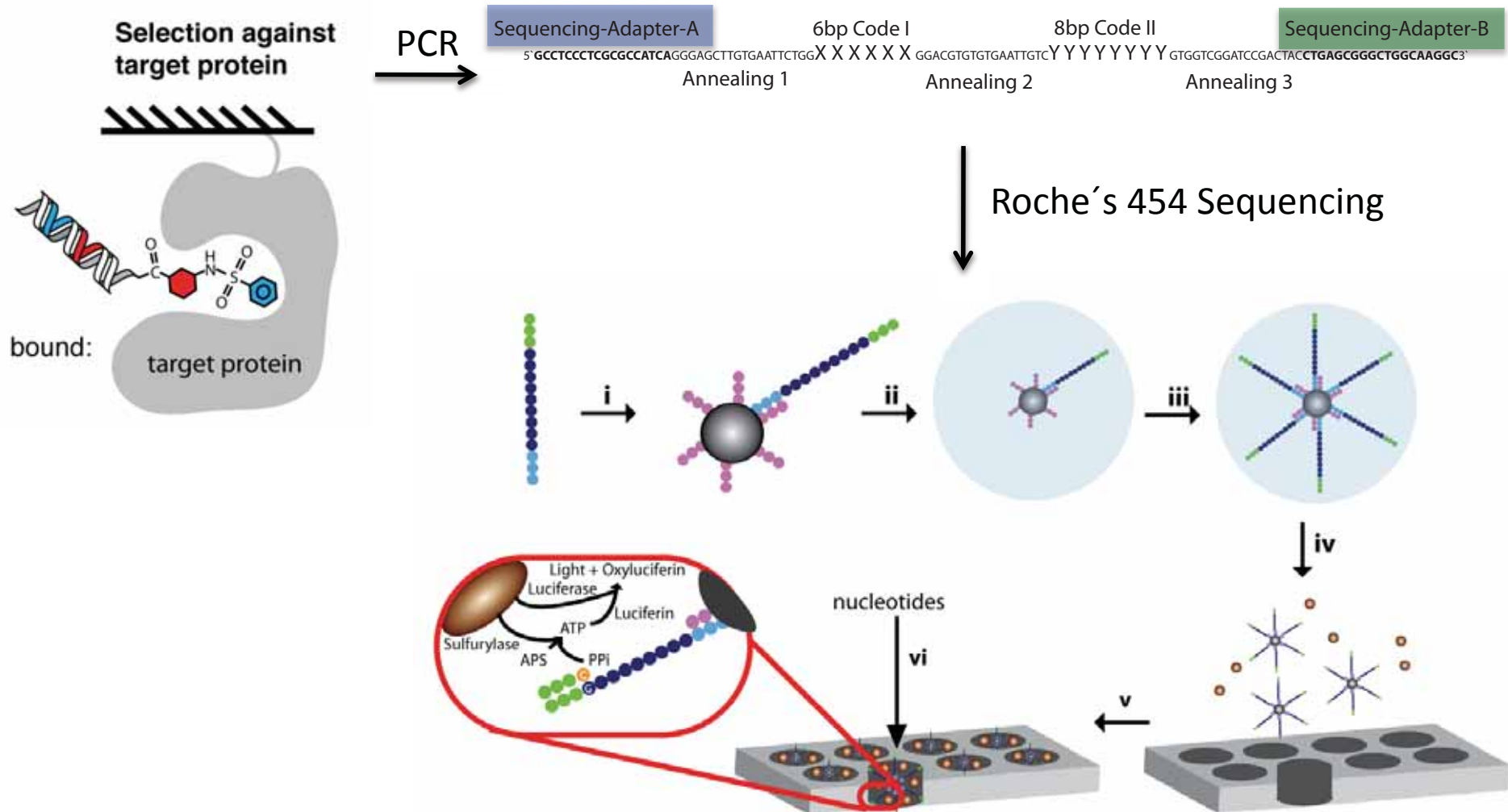
Library Synthesis Using Diels-Alder Cycloadditions



Library Characteristics of the 4'000 Member Library

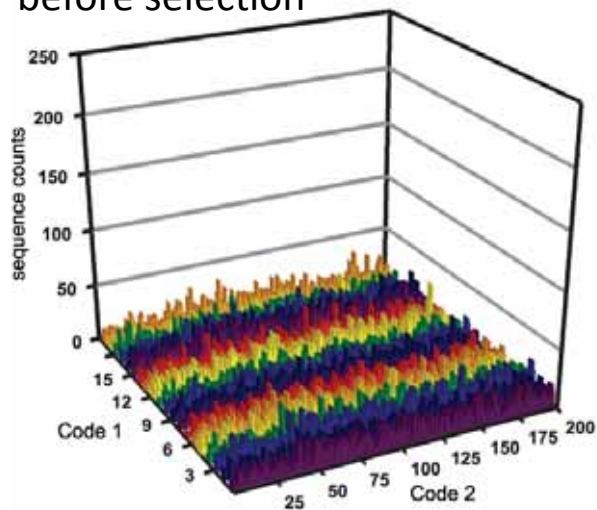


Library Decoding by 454 High-Throughput Sequencing

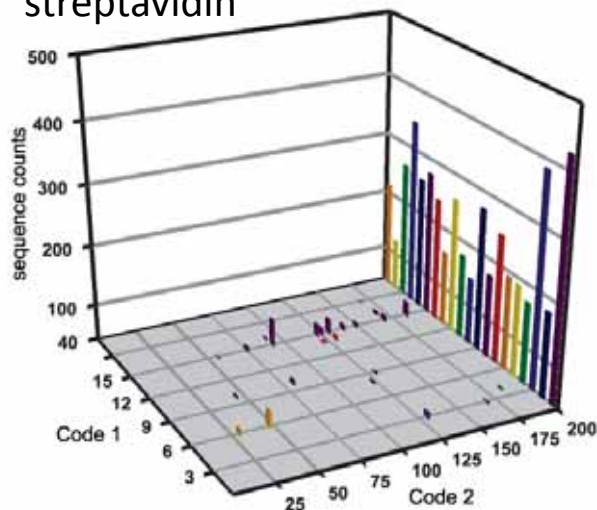


Library Decoding after Affinity-Based Selections

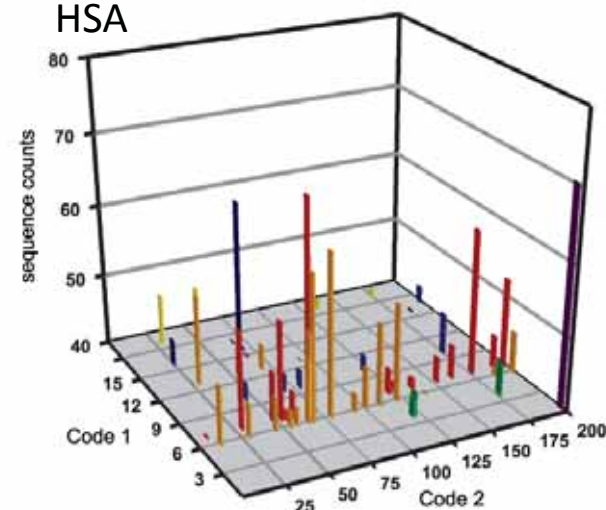
before selection



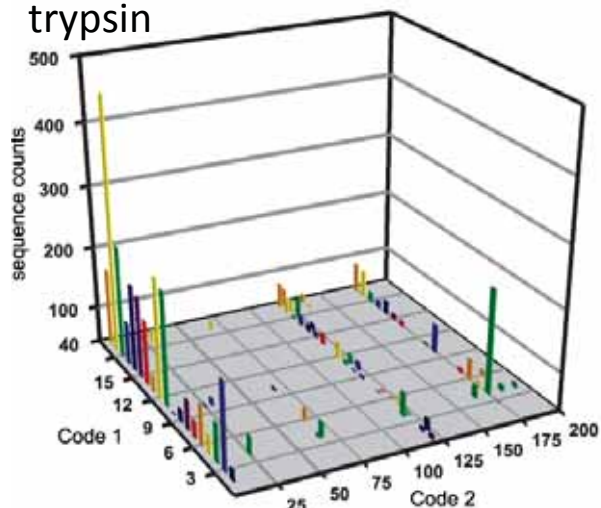
streptavidin



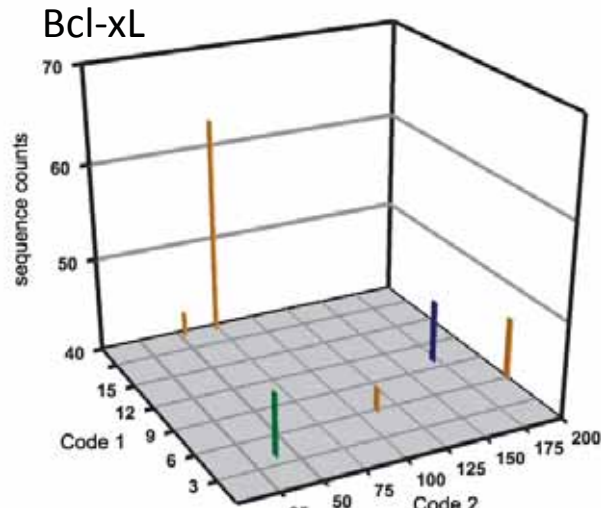
HSA



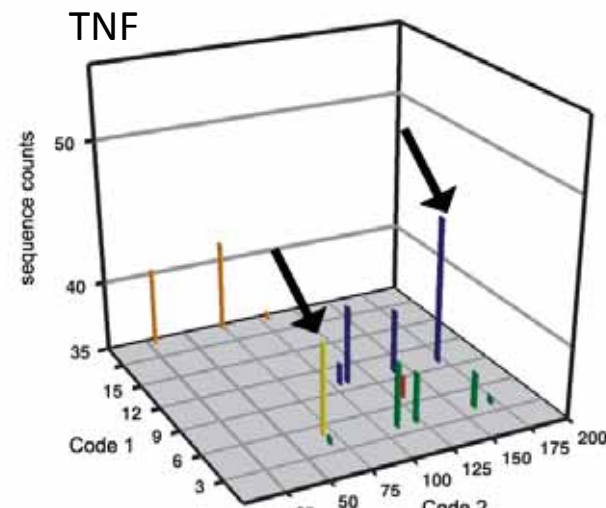
trypsin



Bcl-xL



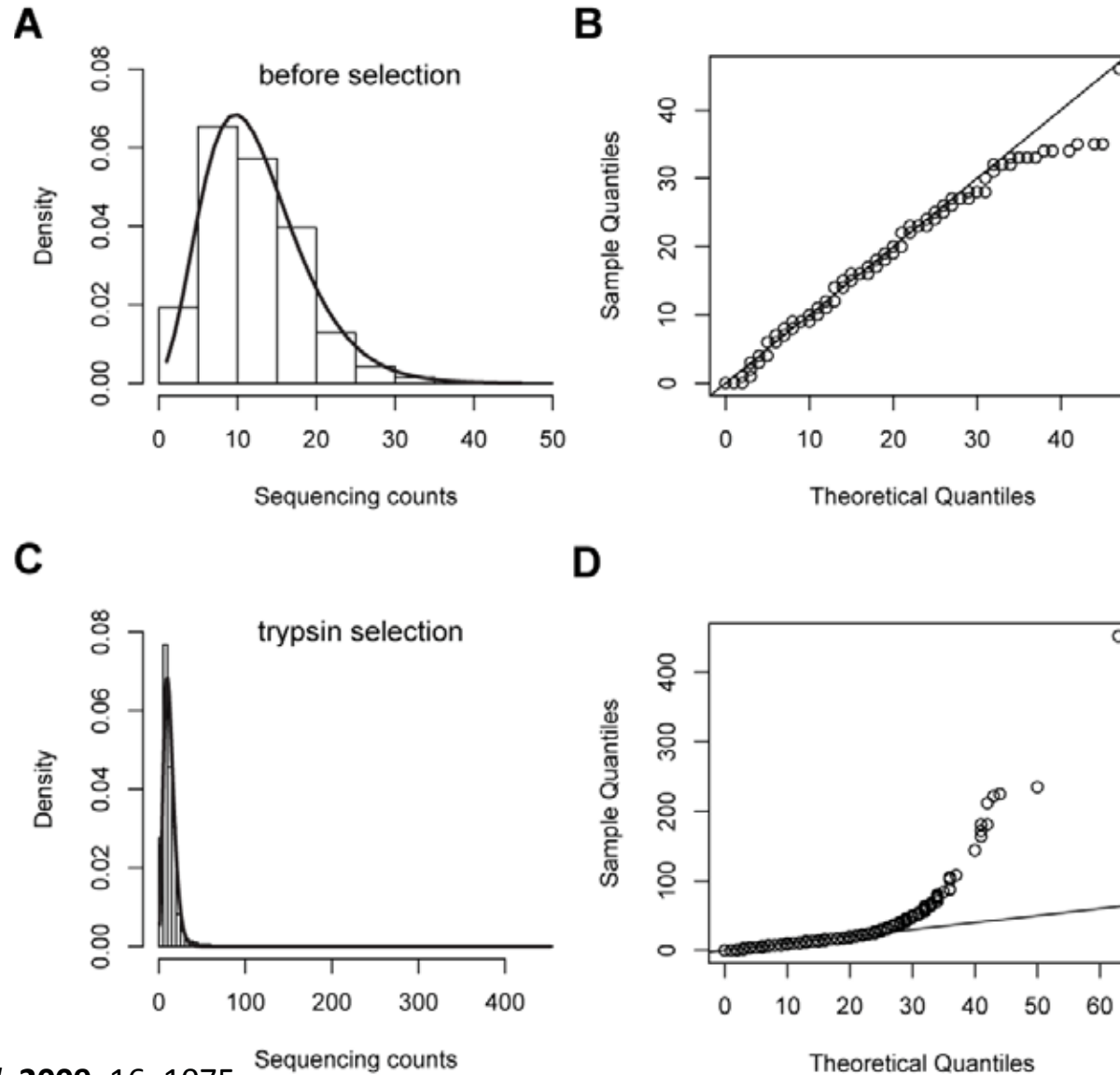
TNF



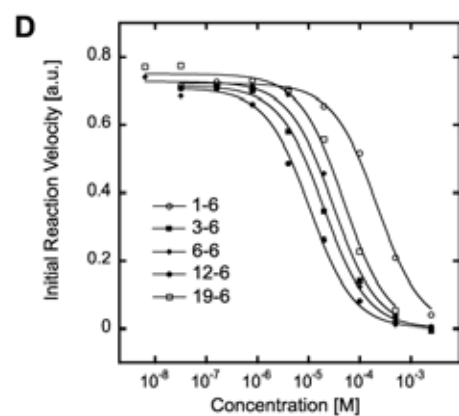
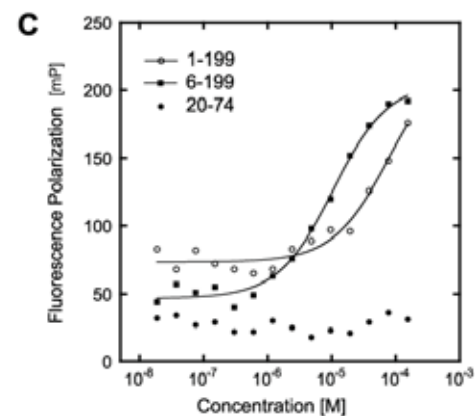
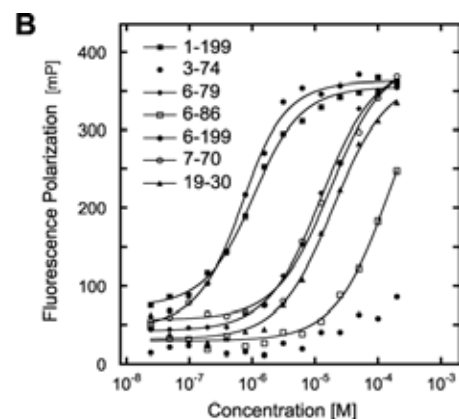
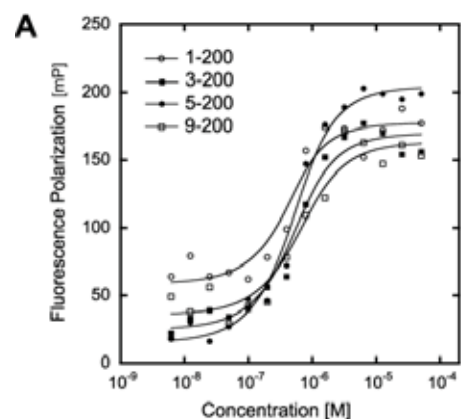
Buller et al. *Chem Biol*, 2009, 16, 1075.

50'000 sequences evaluated / selection

Statistical Analysis of the Library Decoding



Hit-Validation of Selected Small Molecules



A

streptavidin

Compound	R ₁	K _d ^a [nM]	counts ^b	p ^c
1-200		185	426	<0.001
5-200		278	191	<0.001
3-200		284	388	<0.001
9-200		422	274	<0.001

D

trypsin

Compound	R ₁	K _i ^d [μM]	counts ^b	p ^c
12-6		11	235	<0.001
3-6		20	181	<0.001
6-6		30	105	<0.001
19-6		49	425	<0.001
1-6		220	34	n.s.

B

human serum albumin

Compound	R ₁	R ₂	K _d ^a [μM]	counts ^b	p ^c
6-199			0.44	46	0.039
1-199			0.79	70	<0.001
6-79			12	63	0.002
7-70			17	69	<0.001
19-30			19	47	0.034
6-86			155	29	n.s.
3-74			n.a.	12	n.s.

C

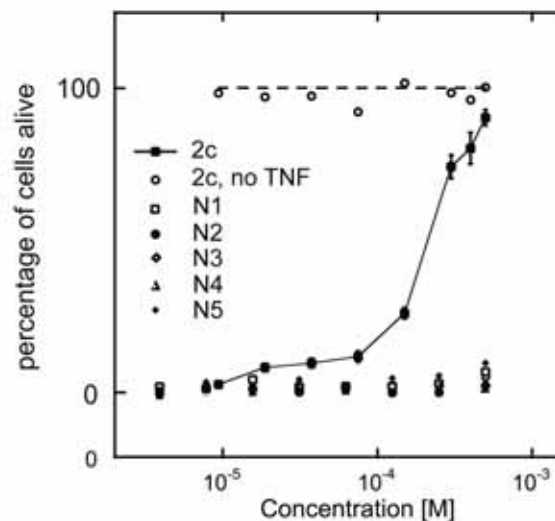
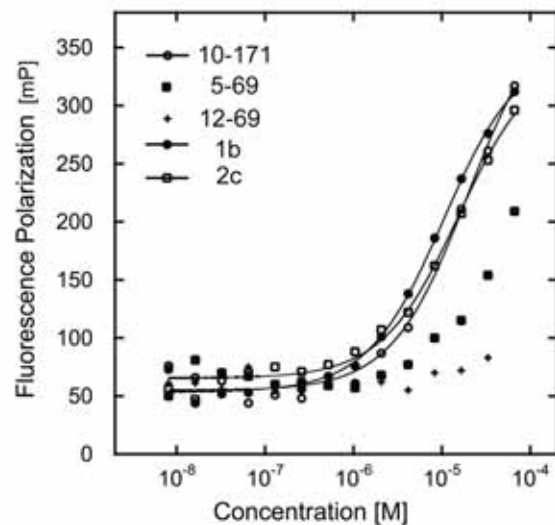
Bcl-xL

Compound	R ₁	R ₂	K _d ^a [μM]	counts ^b	p ^c
6-199			10	47	0.025
1-199			78	10	n.s.
20-74			n.a.	63	0.001

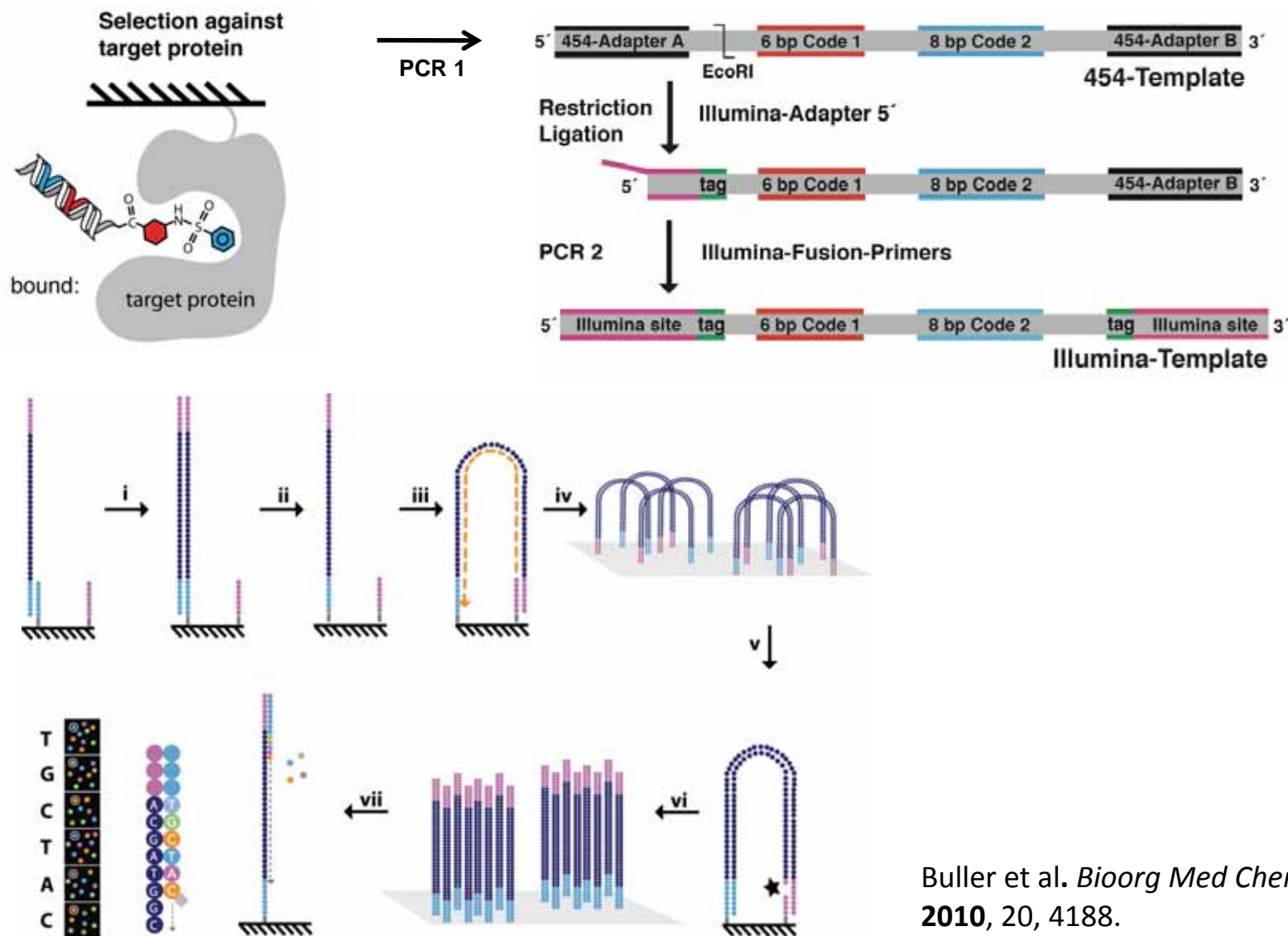
^a Measured by fluorescence polarization.
^b Sequence counts of the DNA-conjugate after selection.
^c adjusted p-value for the Benjamini & Hochberg (1995) FDR controlling procedure
^d Measured by trypsin-inhibition of the carboxylic acid.

Ligands Selected Against Tumor Necrosis Factor (TNF)

library compounds	(1a-b)		(2a-c)		
	R ₁	R ₂	K _d ^a [μM]	counts ^b	ρ ^c
10-171			20	45	0.047
5-69			>50	41	0.065
1a			50		
1b			10		
2a			>50		
2b			>70		
2c			15		

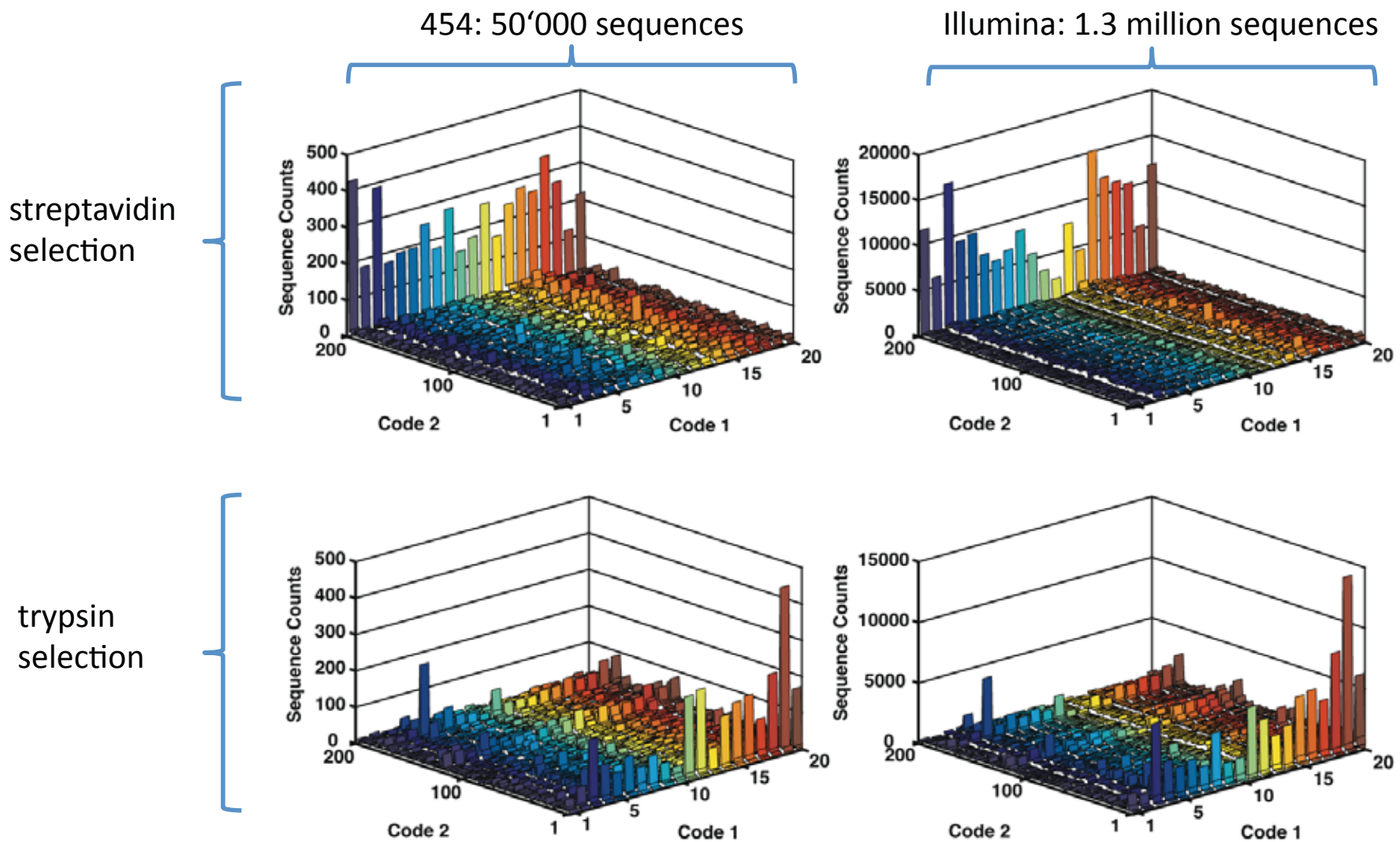


Library Decoding by Illumina Sequencing



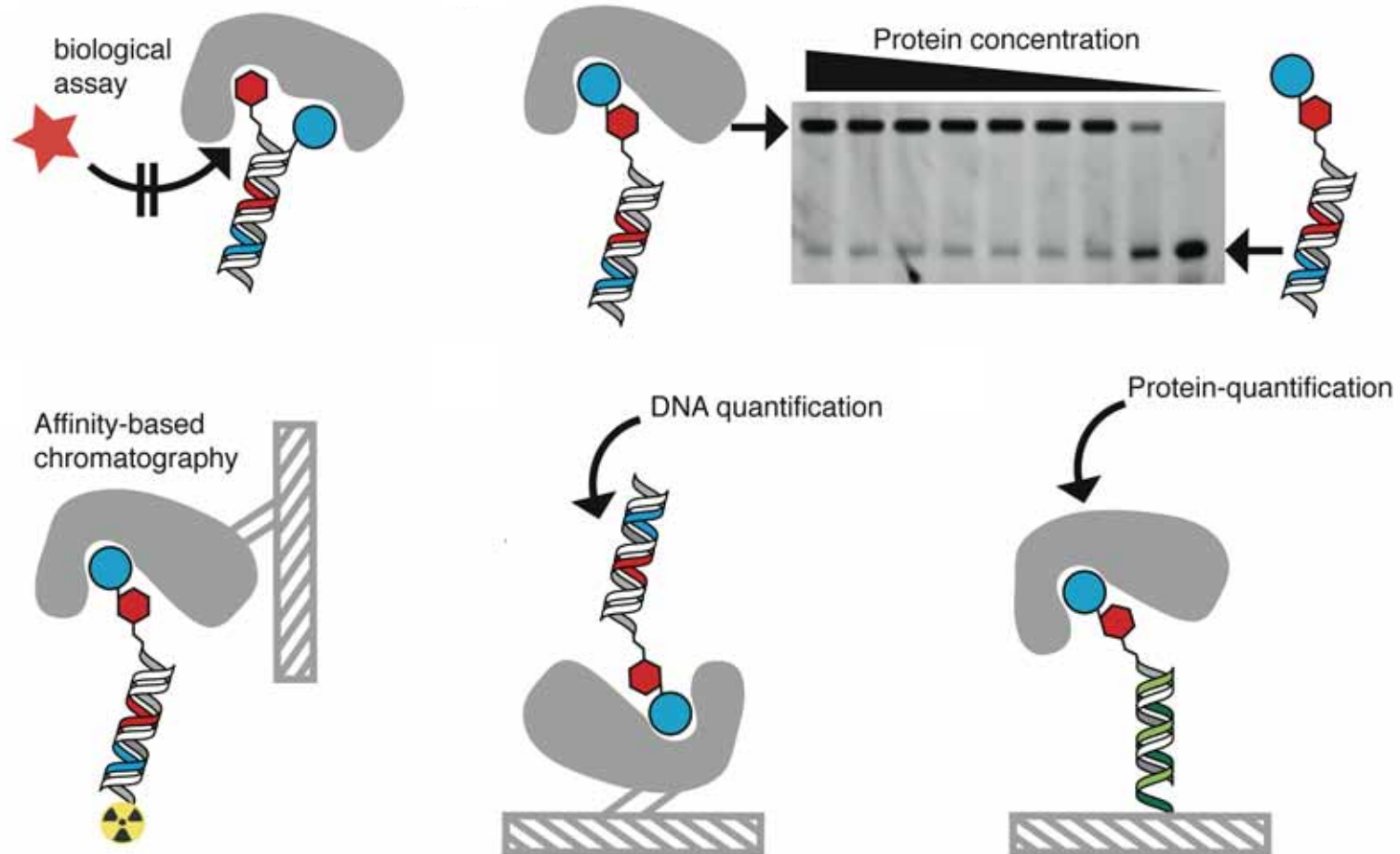
Buller et al. *Bioorg Med Chem Lett*, 2010, 20, 4188.

Comparison of 454 and Illumina Library Decoding



Buller et al. *Bioorg Med Chem Lett*,
2010, 20, 4188.

DNA-Based Hit-Validation of Selected Compounds



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