Philochem DEL Technology Platform

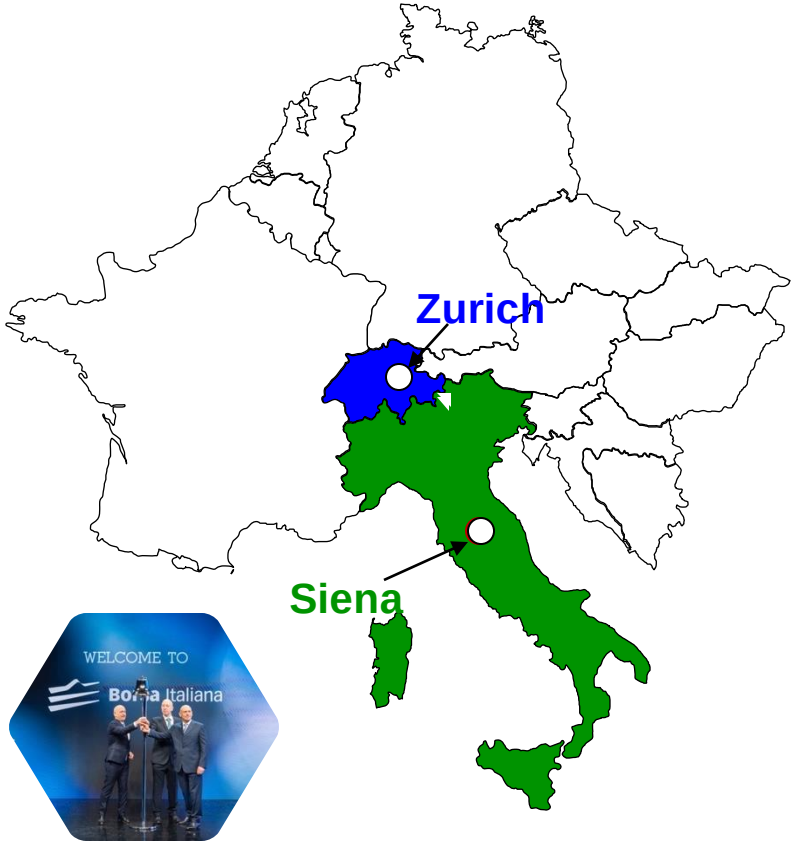
Innovative Solutions for Drug Discovery

Philochem
innovating chemistry

Philochem: a member of the Philogen Group

Philogen
innovating targeting

Headquarters
Antibody Therapeutics



Listed on the Italian Stock Exchange

Philochem
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Discovery Center
Small Molecule Therapeutics

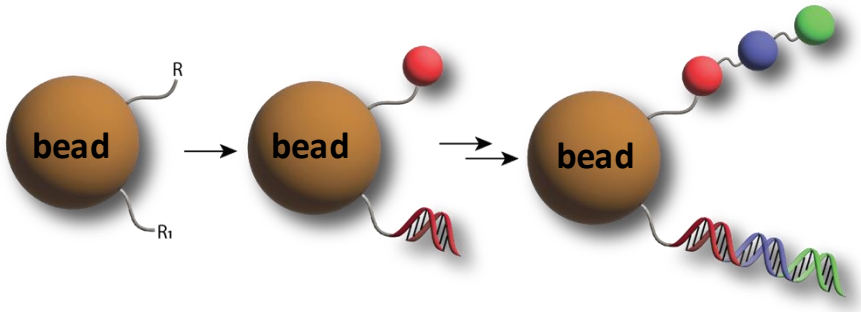
Collaborations with large pharmaceutical companies over the years

Pfizer · NOVARTIS · abbvie · AstraZeneca · Johnson&Johnson · Boehringer Ingelheim · Bristol Myers Squibb · SERVIER · BRACCO · Google · SUN PHARMA · MSD · IBSA

History of DEL Technology

Split & Pool on Beads

Richard Lerner & Sydney Brenner

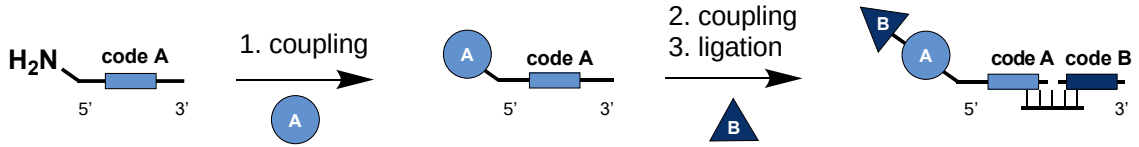


Scripps Research

Lerner and Brenner, *PNAS*, **1992**; 89(12):5381-3

DNA-Recorded Synthesis

Dario Neri's lab



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ETH zürich

Melkko et al., *Nat Biotechnol*, **2004**; 22(5):568-74
Mannocci et al., *PNAS*, **2008**;105(46):17670-5

1992 — 2004 — 2023

White Paper

DNA-Encoded Chemical Libraries

Proc. Natl. Acad. Sci. USA
Vol. 89, pp. 5381–5383, June 1992
Chemistry

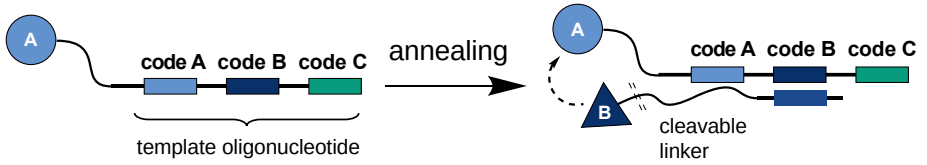
Encoded combinatorial chemistry

(chemical repertoire/encoded libraries/commaless code)

SYDNEY BRENNER AND RICHARD A. LERNER

Departments of Chemistry and Molecular Biology, The Scripps Research Institute, 10666 North Torrey Pines, La Jolla, CA 92037

HARVARD UNIVERSITY



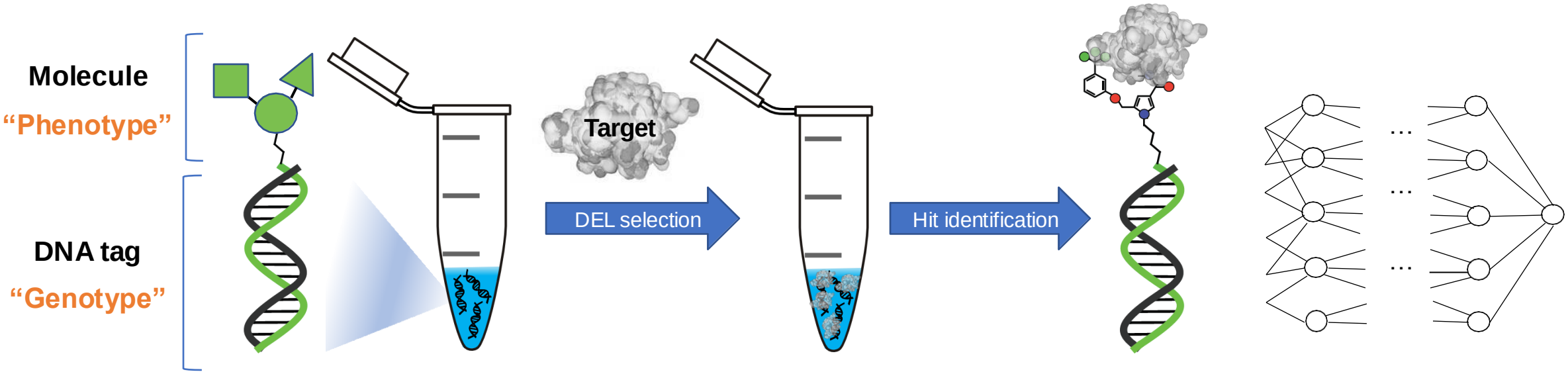
David Liu's lab

Gartner et al., *Science*, **2004**; 305(5690):1601-5

DNA-Templated Synthesis

DEL : DNA-Encoded Chemical Library

Using DEL Technology to discover Small Ligands



Single molecule identified by a **unique barcode**

Efficient and **inexpensive** screening of **billions of compounds**

DNA barcode allows the **identification** of preferential **ligands**

Machine Learning enables identification of **highly potent ligands**

- DELs are continuously used to **discover new targeting moieties** and **mature hit compounds**
- Results of DEL selections are **analysed** and **valorised** through **Machine Learning**

McCloskey et al., *J Med Chem*, **2020**; 63, 16, 8857–8866
Torng et al., *ACS Omega*, **2023**;8(28):25090-25100

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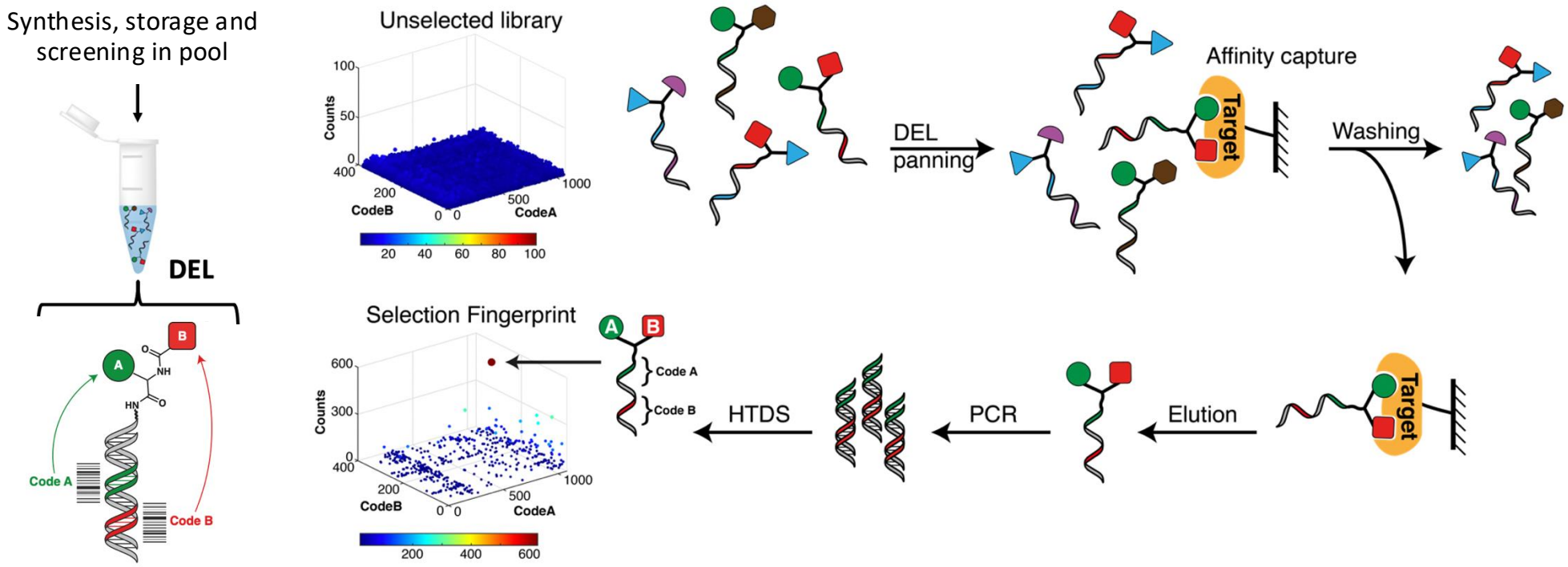
Overview of DEL Selections

Using combinatorial technologies, we can build and screen DELs containing billions of compounds



- DEL technology allows the isolation of small ligands against **virtually any target**
- Philogen has **pioneered** DEL technology (**≥ 20 years of track-record**) and is fully **self-sufficient** in ligand discovery
- We have isolated **ultra-high affinity ligands** (e.g., **OncoACP3**) from our DELs and moved them from the "**bench to the clinic**"

Neri D., Lerner R.A., *Annu Rev Biochem.*, **2018**; 87:479-502
Favalli et al., *FEBS Lett.,* **2018**; 592(12):2168-2180
Decurtins et al., *Nat. Prot.*, **2016**; 11(4):764-80

*HTS = high throughput sequencing

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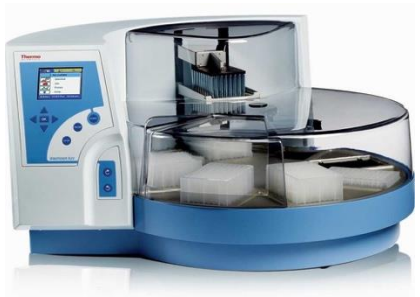
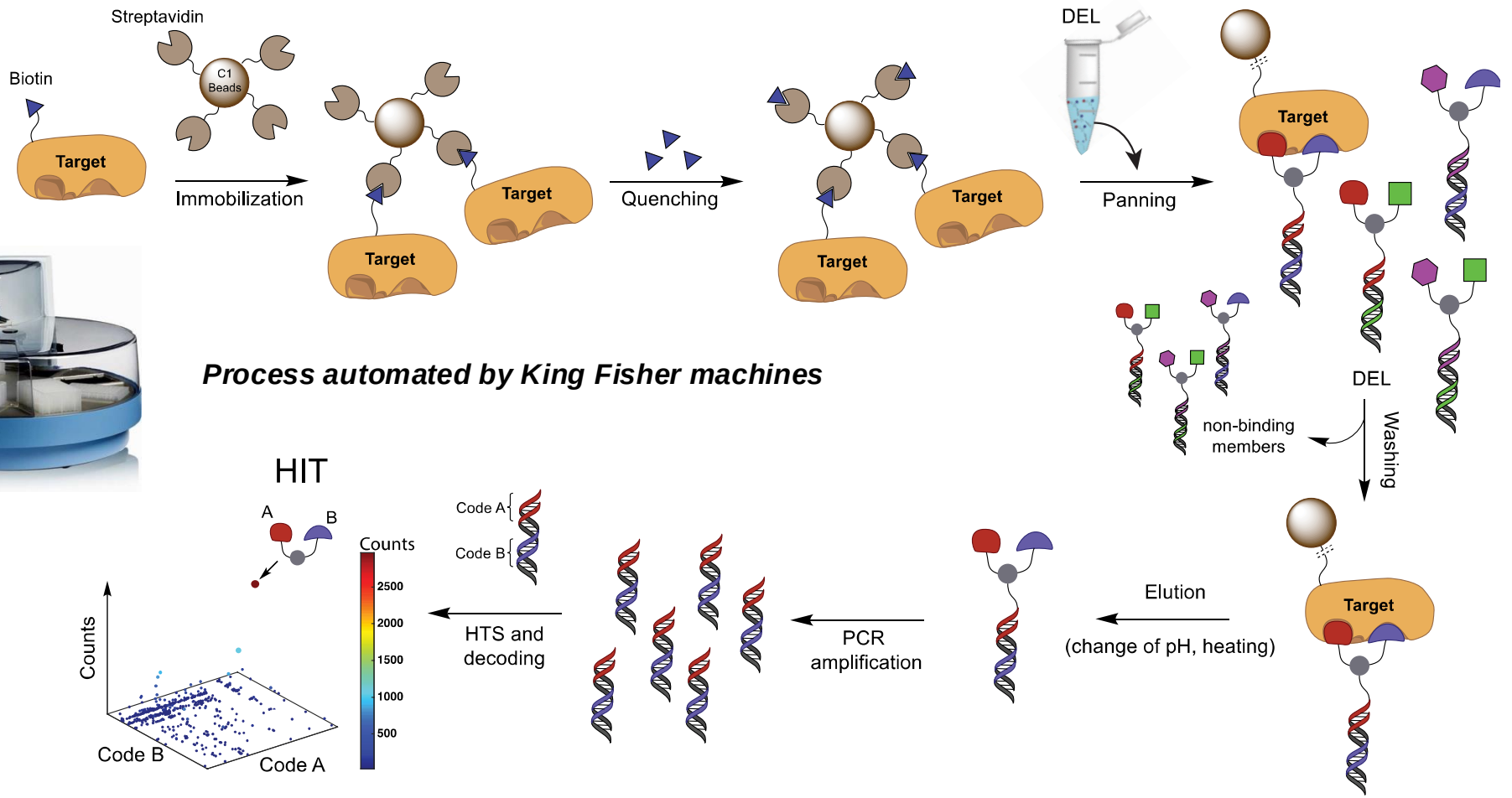
Automated DEL Affinity Selections

We have automated DEL affinity selections using King Fisher machines



Process automated by King Fisher machines



Decurtins et al., *Nat. Prot.*, **2016**; 11(4):764-80

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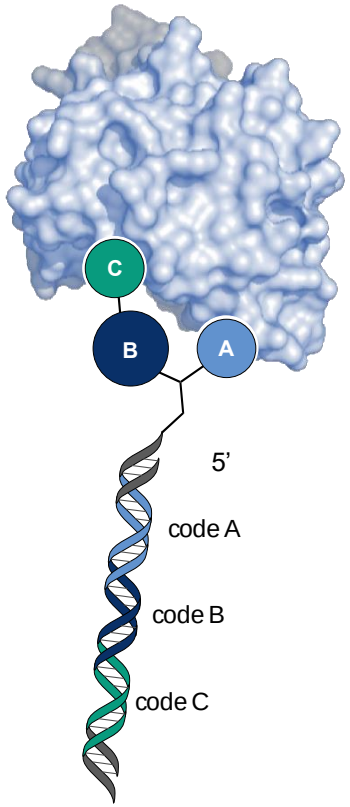
Single and Dual Pharmacophore DELs

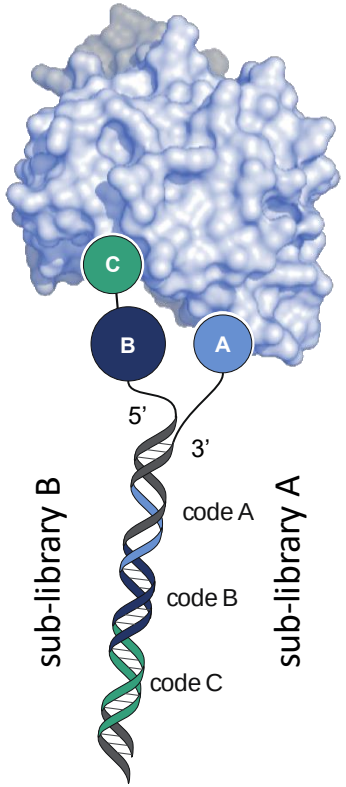
We have constructed innovative DELs in both single- and dual-pharmacophore format

Single-pharmacophore DELs [1-4]



- DNA can be either single or double stranded
- Different formats available: two or three sets of building blocks, with or without scaffold
- Display of rigid and compact structures
- High purity achieved by HPLC purification of individual conjugate

Dual-pharmacophore DELs (ESAC) [5,6]



- Double stranded DNA (obtained from the combinatorial assembly of two sub-libraries)
- Different formats available:1+1; 1+2 or 2+2 ESAC
- Display of flexible structures
- High purity achieved by HPLC purification of individual conjugate for each sub-library

[1] Mannocci et al., *PNAS*, **2008**;105(46):17670-5
[2] Favalli et al., *Nat. Chem*., **2021**; 13(6):540-548
[3] Bassi, et. al., *BBRC*., **2020**; 533(2):223-229
[4] Oehler et al., *Nat. Chem*., **2023**; 15(10):1431-1443
[5] Melkko et al., *Nat Biotechnol*, **2004**; 22(5):568-74
[6] Wichert et al., *Nat. Chem*., **2015**; 7(3):241-9

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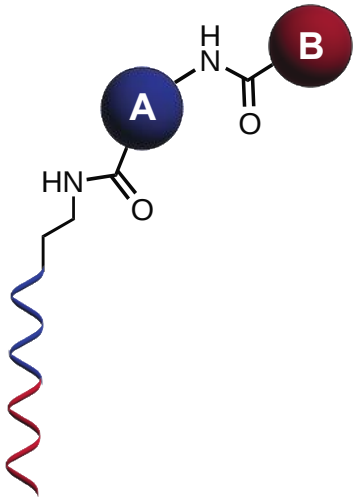
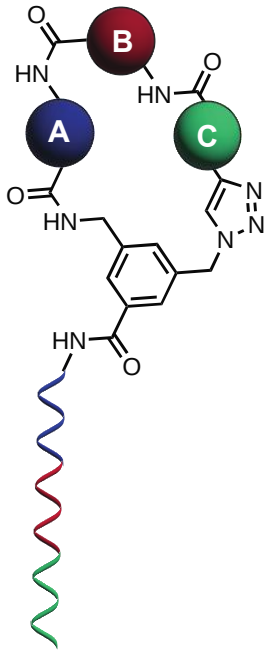
Examples of Philochem DELs in the Literature

We have published the construction and validation of many innovative DELs over the last 20 years

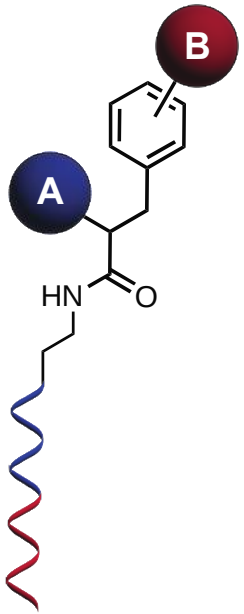


Leimbacher et al., Chemistry **2012**; 18(25):7729-37

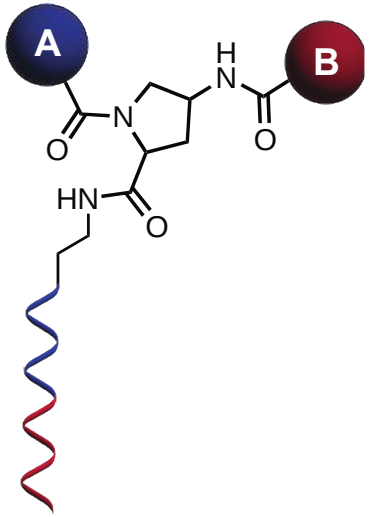
Gironda et al., *J. Med. Chem*. **2021**; 64(23):17496-17510



Onda et al., Chem. Eur. J. **2021**; 27(24):7160-7167



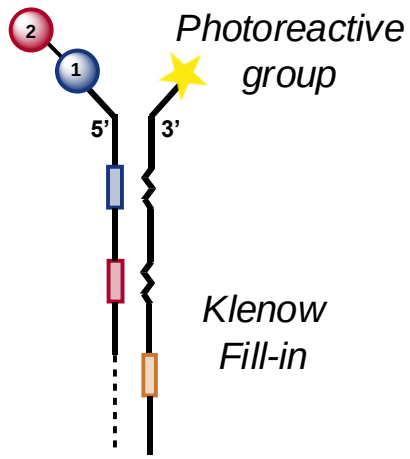
Favalli et. al., Nat. Chem. **2021**; 13(6):540-548



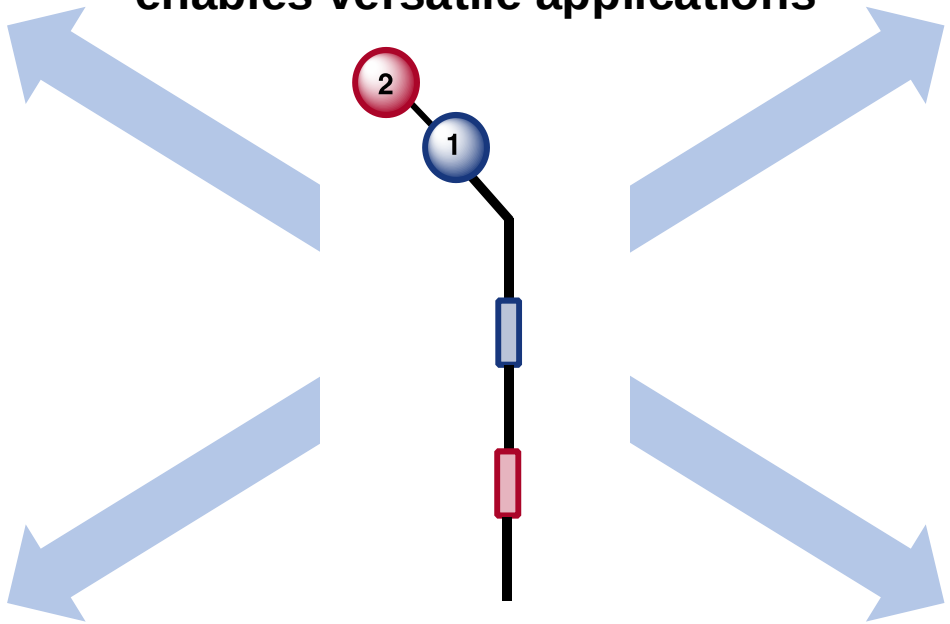
Oehler et al., Nat. Chem. **2023**; 15(10):1431-1443

Advantages of the single-stranded DEL format

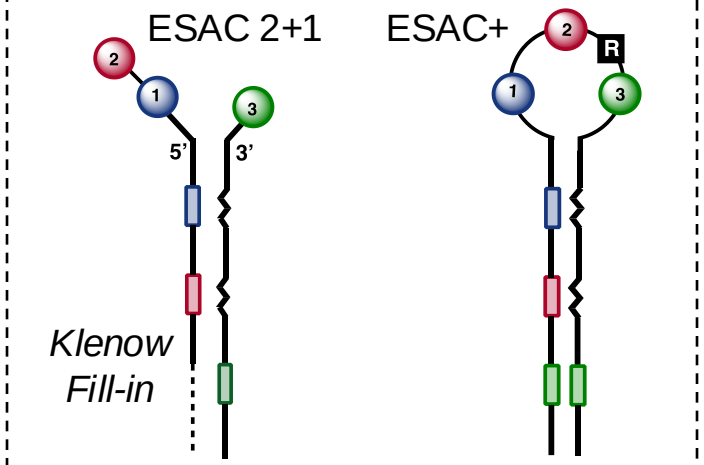
Photocrosslinking Strategy



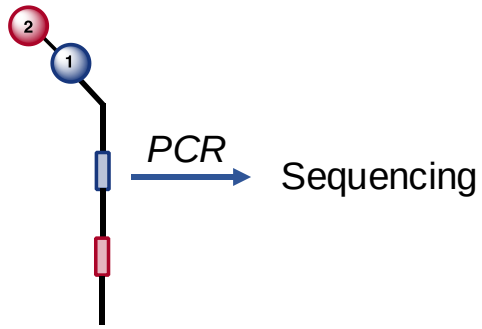
Single-stranded format enables versatile applications



Patented ESAC Libraries



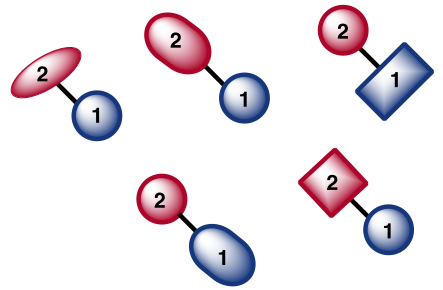
Single Strand Screenings



Advantages of the Philochem format

1. Modular combinatorial strategies
2. Superior chemical space coverage
3. High purity leading to superior success rate

New DNA-Compatible Reactions



Sannino et al., ACS Comb Sci. 2020;22(4):204-212
Melkko et al., Nat Biotechnol. 2004;22(5):568-74
Bassi et al., Adv Sci (Weihnh) 2020;7(22):2001970
Bassi et al., Biochem Biophys Res Commun. 2020;533(2)223-229
Puglioli et al., Bioconjug Chem. 2024;35(7):1033-1043
Onda et al., Chem 2021;27(24):7160-7167

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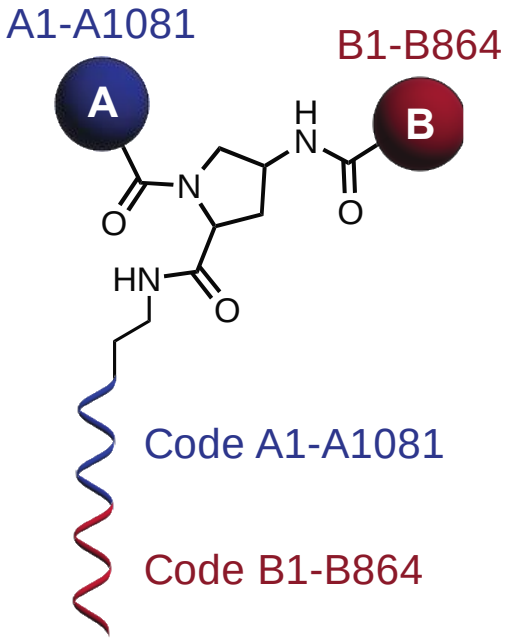
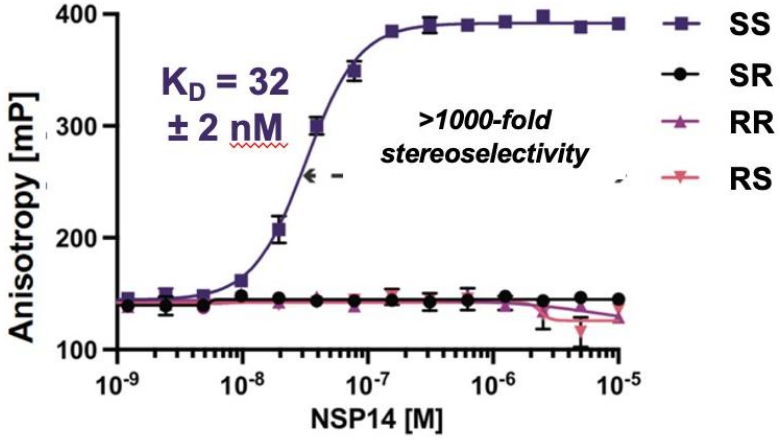
Stereoselectivity of Philochem DELs

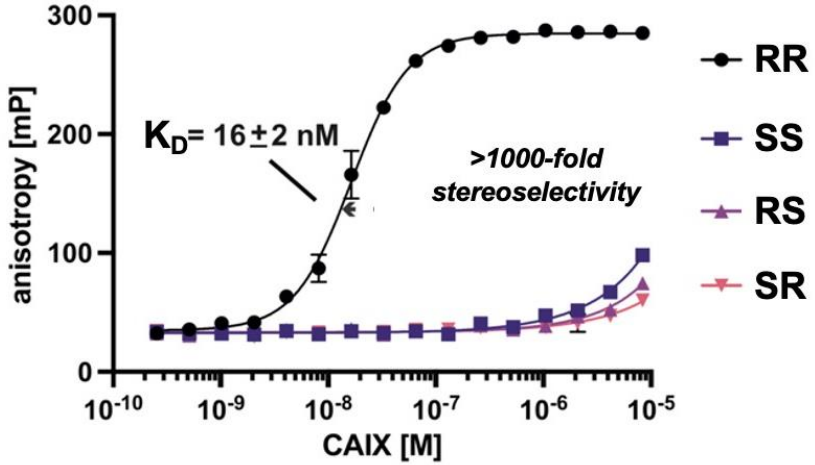
Ligands isolated from our stereo-defined DELs show big differences in binding affinity between stereoisomers



1081 x 864 x 4
= 3´735´936

The binding affinity of stereoisomers against various pharmaceutical targets shows a >1000-fold stereoselectivity, as measured by Fluorescence Polarization





Oehler et al., *Nat. Chem.*, **2023**; 15(10):1431-1443

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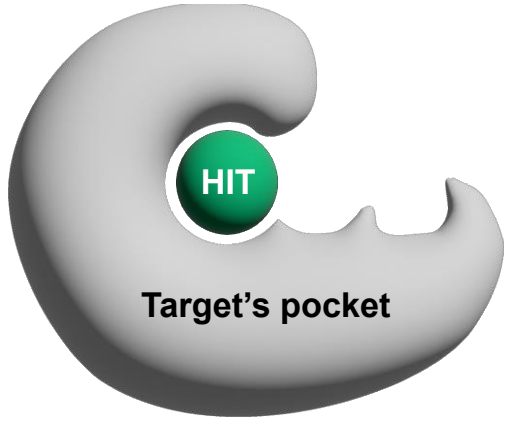
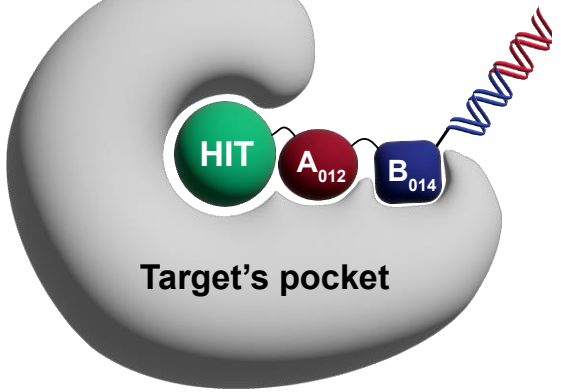
Strategies for Lead Expansion: Affinity Maturation DELs

We use DEL technology to affinity mature hits of even very low affinity

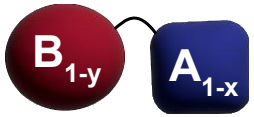


A: Affinity Maturation

Customized DEL Libraries

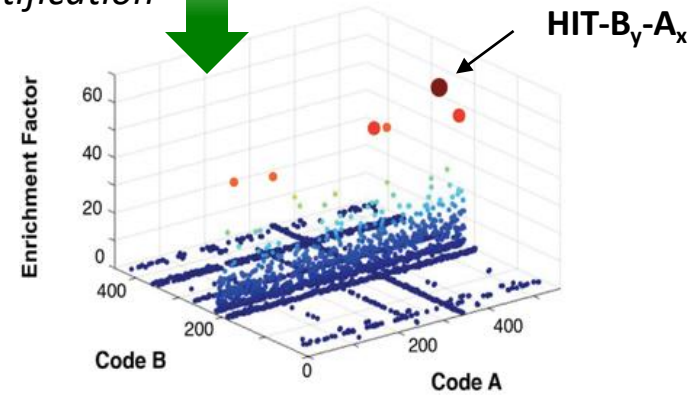


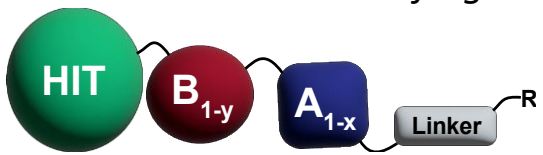
HIT potency in the high nM to low µM range



$y \cdot x = 10^6$ to 10^9 combinations of high purity & chemical diverse fragments

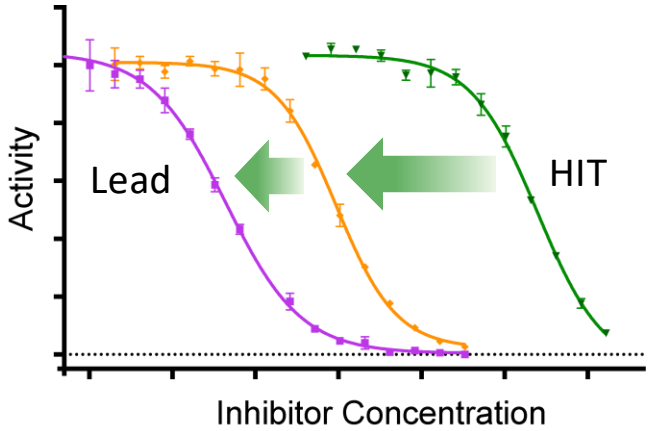
DEL selection
A-B fragment identification





Off-DNA validation and HIT to Lead Optimization

Higher Potency & Selectivity



Bigatti et al., *ChemMedChem*, **2017**; 12(21):1748-1752
Puglioli et al., *Chem*, **2023**; 9(2):411-429

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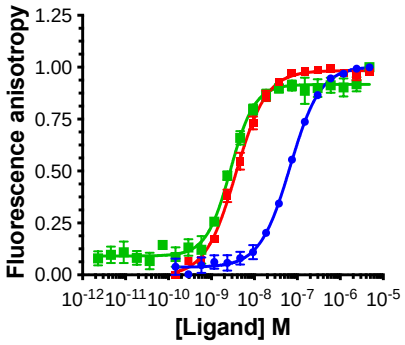
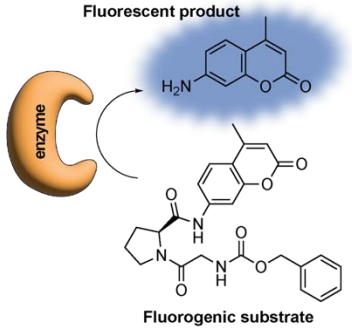
Hit Validation

We use multiple orthogonal methodologies to validate our Hits

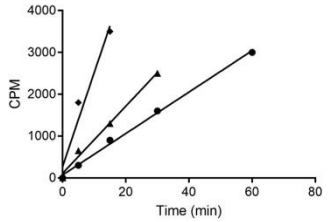
Fluorescence Polarization



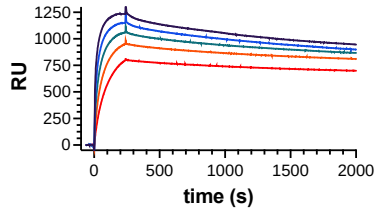
Enzymatic assay



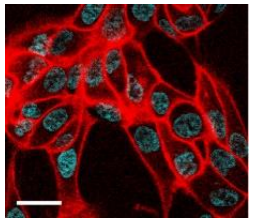
Radiometric assays



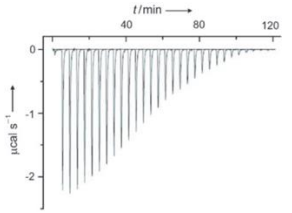
Surface Plasmon Resonance



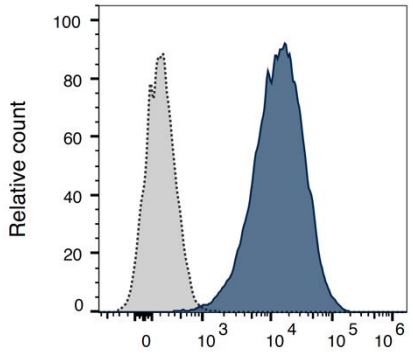
Confocal Microscopy



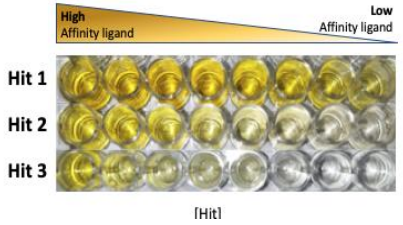
Isothermal Titration Calorimetry



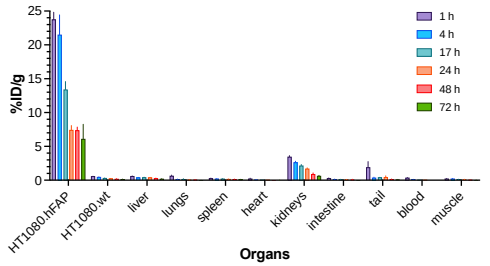
Flow Cytometry



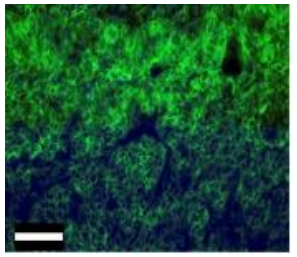
ELISA



Biodistribution (BD) in mice



Ex vivo BD in mice



Dumelin et al., *Angew Chem Int Ed*, **2008**; 47(17):3196-201
Catalano et al., *Anal Chem*, **2020**; 92(15):10822-10829
Prati et al., *BBRC*, **2020**; 533(2):235-240
Millul et al., *Proc Natl Acad Sci USA*, **2021**; 118(16):e2101852118
Puglioli et al., *Chem*, **2023**; 9(2):411-429

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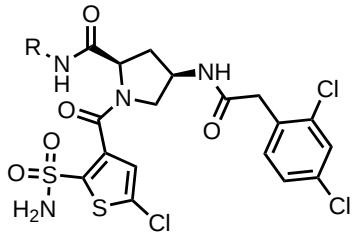
Success Stories of the Philochem DEL Platform

Tumor Associated Antigens (TAAs)

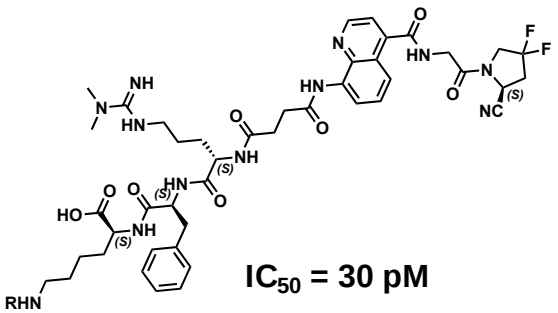
CAIX



K_D = 16 nM (isoform-specific)

Oehler et al., *Nat. Chem.*, **2023**; 15(10):1431-1443

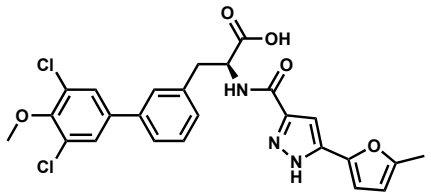
FAP



IC_{50} = 30 pM

Puglioli et al., *Chem*, **2023**

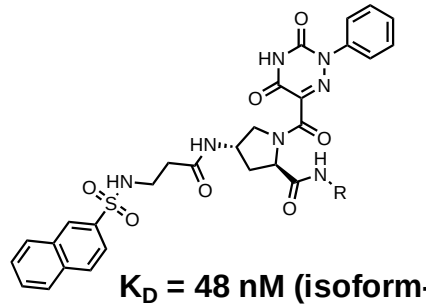
PLAP



IC_{50} = 32 nM

Bassi et al., *J Med Chem, **2021;*** 64(21):15799-15809

PSMA

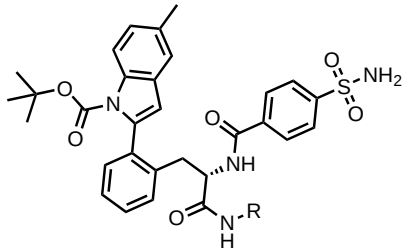


K_D = 48 nM (isoform-specific)

Oehler et al., *Nat. Chem.*, **2023**; 15(10):1431-1443

Immunological targets

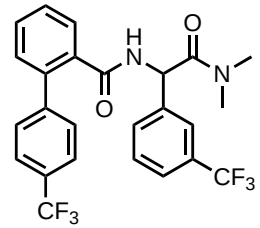
NKG2D



K_D = 410 nM

Dakhel et al., *Chem.Med.Chem.*, **2022**

Collaboration with Janssen



IC_{50} = 1 µM

Thompson et al., *PNAS*, **2023**

Phosphatases

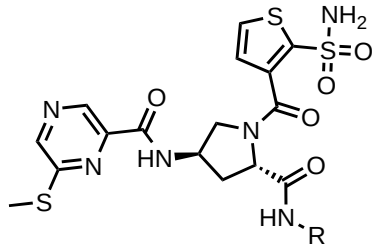
TC-PTP

- Undisclosed Structure -

K_D = 65 nM

Partnered Project

TNAP



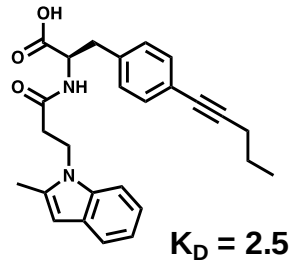
IC_{50} = 39 nM (isoform-specific)

Oehler et al., *Nat. Chem.*, **2023**; 15(10):1431-1443

Success Stories of the Philochem DEL Platform

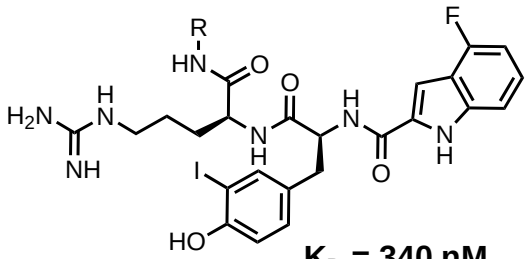
Cytokines

IL2



K_D = 2.5 µM

Leimbacher et al., *Chem Eur J,* **2012**; 18(25):7729-37

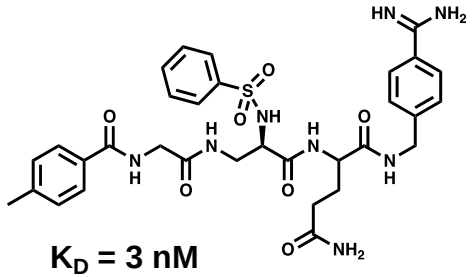


K_D = 340 nM

Gironda-Martinez et al., *J Med Chem.,* **2021**; 64(23):17496-17510

Proteases

Trypsin

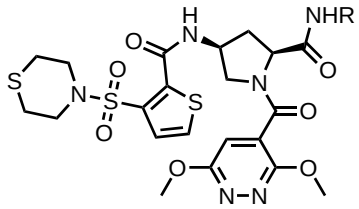


K_D = 3 nM

Mannocci et al., *Bioconj Chem*, **2010**; 21, 10, 1836–1841

Viral methyltransferases

NSP-14

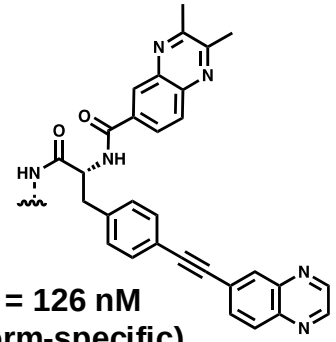


IC_{50} = 25 nM

Oehler et al., *Nat. Chem.*, **2023**; 15(10):1431-1443

Kinases

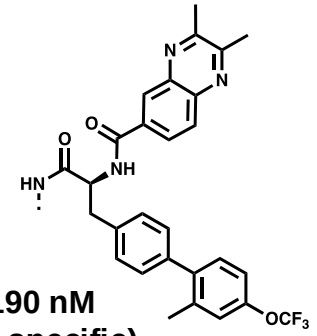
PI3K (WT)



K_D = 126 nM
(isoform-specific)

Favalli et al., *Nat Chem,* **2021**; 13(6):540-548

PI3K (H1047R)

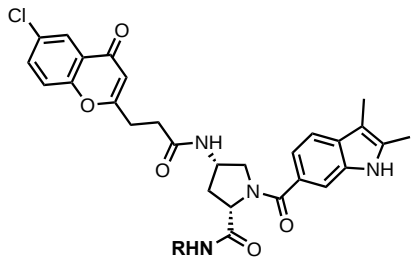


K_D = 190 nM
(isoform-specific)

Favalli et al., *Nat Chem,* **2021**; 13(6):540-548

Others

HSA



IC_{50} = 3 nM

Oehler et al., *Nat. Chem.*, **2023**; 15(10):1431-1443

TAA

OncoACP3

- Undisclosed Structure -

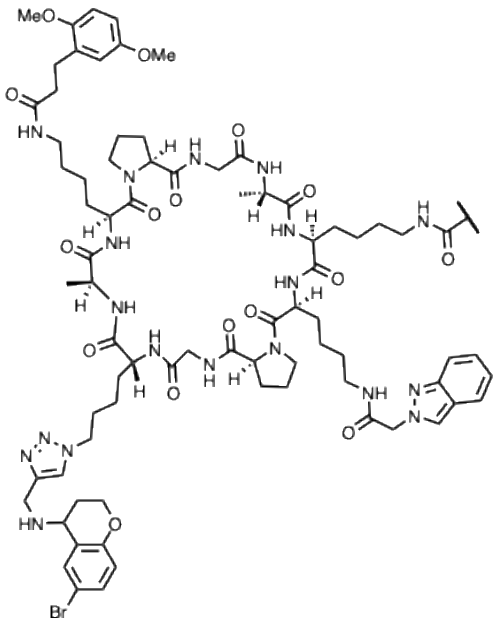
$K_D = \sim 10^{-10}$ M

Manuscript accepted

Success Stories of the Philochem DEL Platform (macrocycles)

Immunological and serum targets

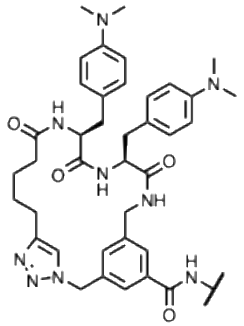
TNF



K_D = 15 µM

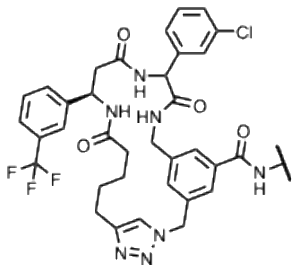
Li et al., *Nat Chem,* **2018**; 10:441-448

NKp46



K_D = 7.4 µM

HSA

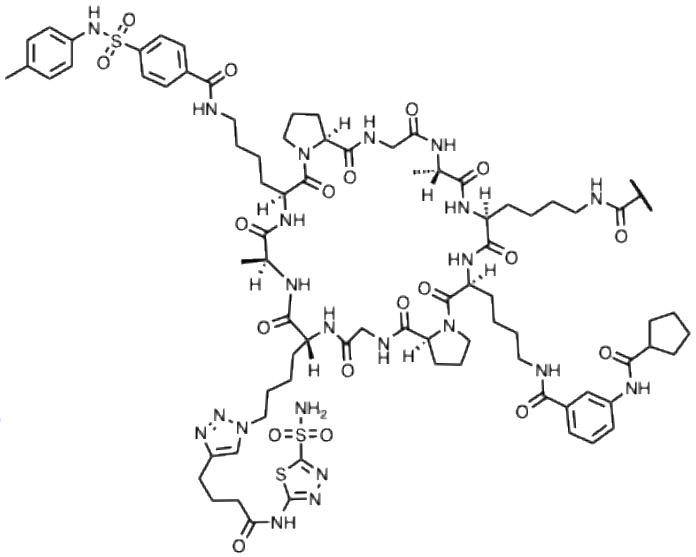


K_D = 1.9 µM

Onda et al., *Chem,* **2021**; 27(24):7160-7167

Tumor marker

PSA

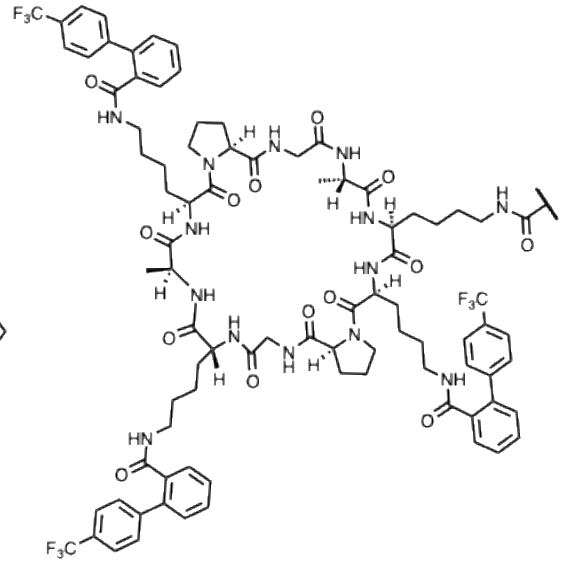


K_D = 13 µM

Li et al., *Nat Chem,* **2018**; 10:441-448

Others

CaM



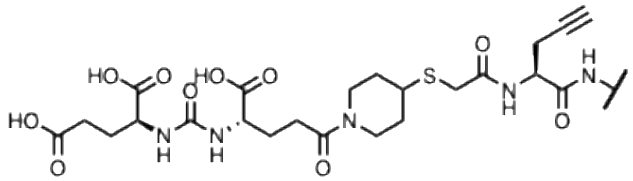
K_D = 0.16 µM

Li et al., *Nat Chem,* **2018**; 10:441-448

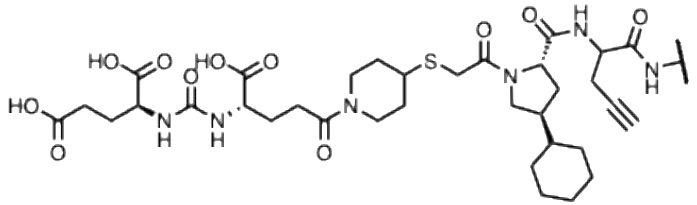
Success Stories of the Philochem DEL Platform

Peptidases

GCPII (PSMA)



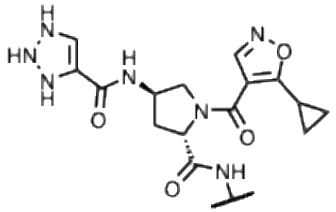
K_D = 0.9 nM
(isoform-selective)



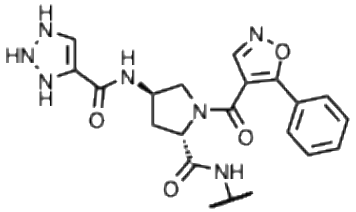
K_D = 2.2 nM
(isoform-selective)

Lucaroni et al., *Chem Sci*, **2024**; 15:6789-6799

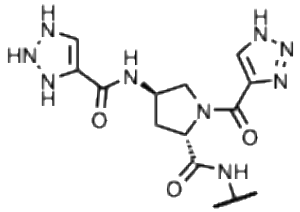
GCPIII (~70% sequence identity with PSMA)



K_D = 1.8 nM
(isoform-specific)



K_D = 6.4 nM
(cross-reactive)

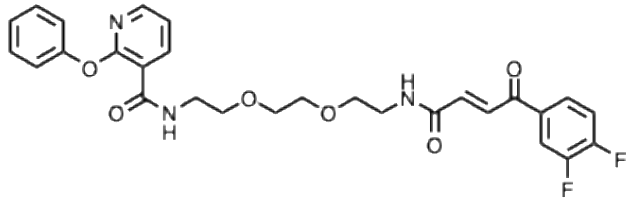


K_D = 1.7 nM
(isoform-specific)

Müller et al., *J Med Chem,* **2024**; 67:8247-8260

Kinases

JNK-1

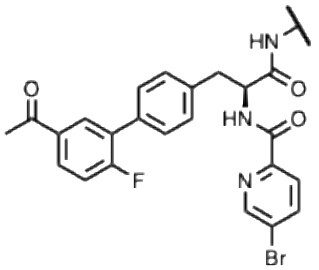


K_D = 1 µM
(selective covalent binder)

Zimmermann et al., *Chem Eur J*, **2017**; 23:8152-8155

Others

CREBBP

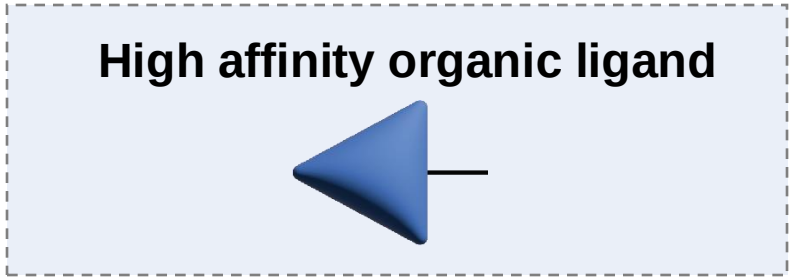


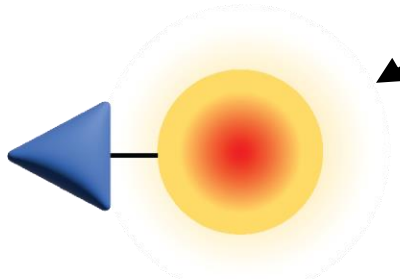
K_D = 0.9 µM
(stereo-selective)

Favalli et al., *Nat Chem,* **2021**; 13(6):540-548

DEL inspired Product Development Activity at Philochem

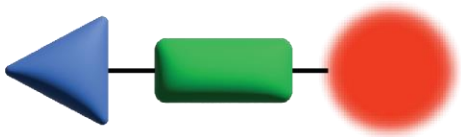
We use high affinity organic ligands to deliver therapeutic and diagnostic payloads





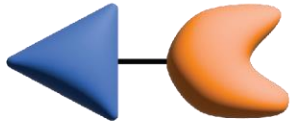
Radio Conjugates

Kulterer *et al., J Nucl Med,* **2021**, 62, 360
Millul *et al., PNAS,* **2021**, 118, e2101852118
Bartoli *et al., Pharmaceuticals (Basel),* **2022**, 15(8), 958
Galbiati *et al., J Nucl Med.,* **2022**, 63(12), 1852
Puglioli et al., Chem, **2023**; 9(2):411-429



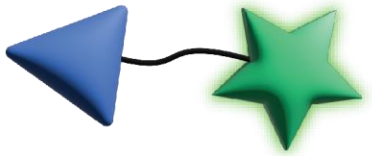
Drug Conjugates

Cazzamalli et al., *J Am Chem Soc*, **2018**, 140, 1617
Cazzamalli *et al., Clin Cancer Res.* **2018**, 24, 3656
Millul *et al*., *Mol Cancer Ther*, **2021**, 20, 512
Zana *et al*., *Clin Cancer Res*., **2022**, 28(24), 5440



Bispecific Immuno-Modulators

Dakhel et al., *Chem.Med.Chem.*, **2022**; 17(21):e202200350



Adaptor for Universal CAR-Ts

Pellegrino *et al., Bioconj Chem* **2020**, 31, 1775

= radiometal chelator (DOTA or DOTAGA)

= linker-drug

= small molecule immunomodulator

= fluorescein

Philochem
innovating chemistry

Standard Collaborative Structure

Our standard collaborative structure offers **clear Stop/Go provisions**, the option for **target exclusivity**, and **no milestones and no royalties**

Stage 1		*Stage 2*		*Stage 3*
Screening of DELs		**Hit validation**		**Option exercise and unblinding**
Time: 2-3 months		Time: 2-3 months		
Cost: 10% of total amount	Stop/Go	Cost: 40% of total amount	Stop/Go	Cost: 50% of total amount
Deliverables:		Deliverables:		Deliverables:
Library Screening Report (blinded)		Hit Validation Report (blinded)		Structural information Exclusive license

Why partner with Philochem?

Advantages of the Philochem Technology Platform

- We **pioneered DEL technology** (more than 20 years of track-record)
- We are the only company with proprietary **single and dual-pharmacophore (ESAC)** libraries
- **DEL derived ligands** have been moved **“from the bench to the clinic”**
- We provide **customized solutions** according to the needs of our partners
- We offer a flexible business structure with **no milestones and no royalties**
- We offer the **internalization** of our **proprietary DEL technology**
- We have **successful collaborations** with leading pharmaceutical companies & academia

BRACCO · NOVARTIS · Boehringer Ingelheim · SERVIER · AstraZeneca · BAYER · janssen PHARMACEUTICAL COMPANIES OF Johnson&Johnson · Google · Scripps Research · ETH zürich