Philochem DEL Technology Platform

Innovative Solutions for Drug Discovery

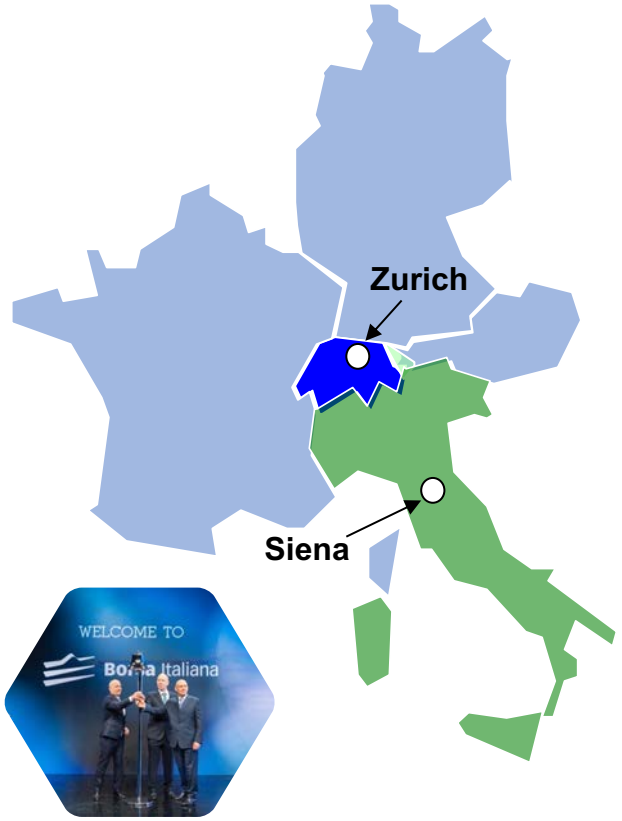
October 2023

Philochem
innovating chemistry

Philochem: a member of the Philogen Group

Philogen
innovating targeting

Headquarters
Antibody Therapeutics



Listed on the Italian Stock Exchange

Philochem
innovating chemistry

Discovery Center
Small Molecule Therapeutics

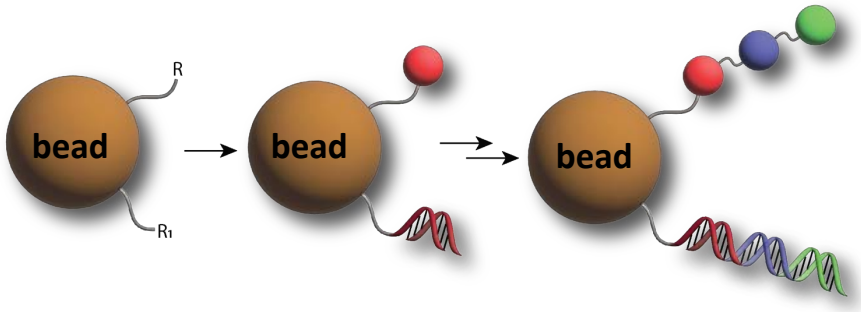
Collaborations with large pharmaceutical companies over the years

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

1992

White Paper

DNA-Encoded Chemical Libraries

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

Encoded combinatorial chemistry

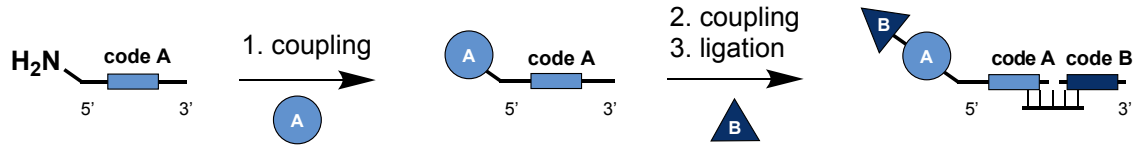
(chemical repertoire/encoded libraries/commaless code)

SYDNEY BRENNER AND RICHARD A. LERNER

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

DNA-Recorded Synthesis

Dario Neri's lab



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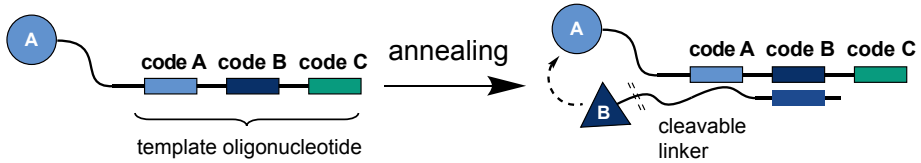
ETH zürich

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

2004

HARVARD UNIVERSITY



David Liu's lab

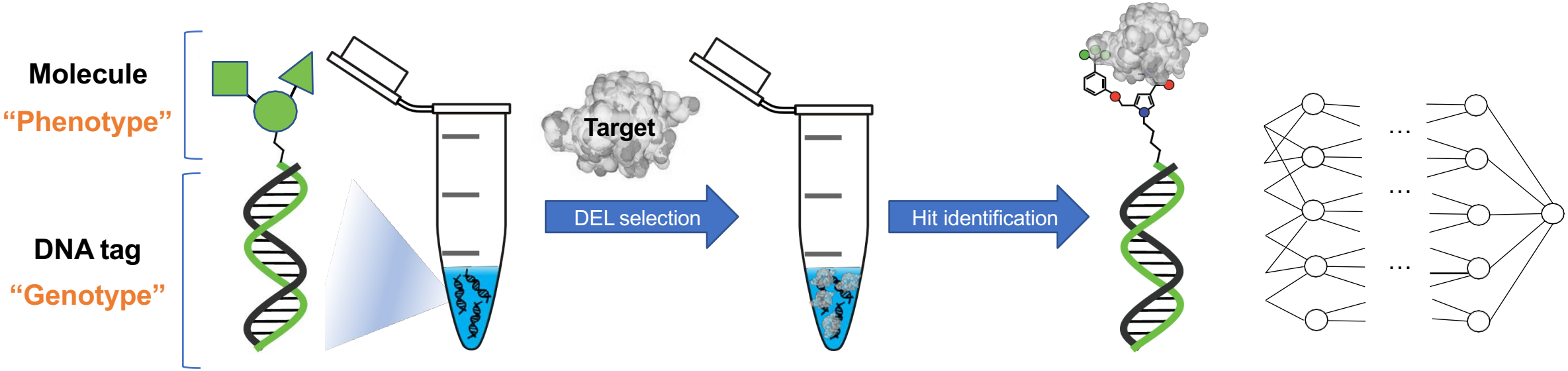
Gartner et al., *Science*, **2004**; 305(5690):1601-5

DNA-Templated Synthesis

2023

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**

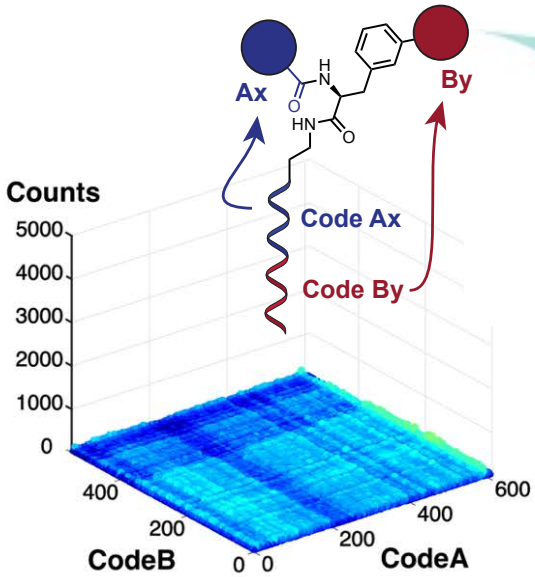
Machine Learning enables identification of **highly potent ligands**

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

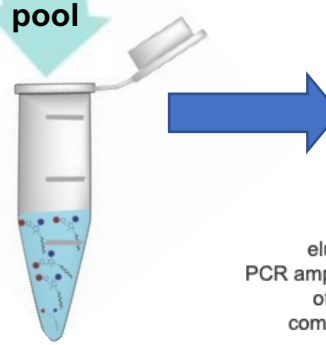
McCloskey et al., *J Med Chem*, **2020**; 63, 16, 8857–8866
Torng et al., *ACS Omega*, **2023**;8(28):25090-25100

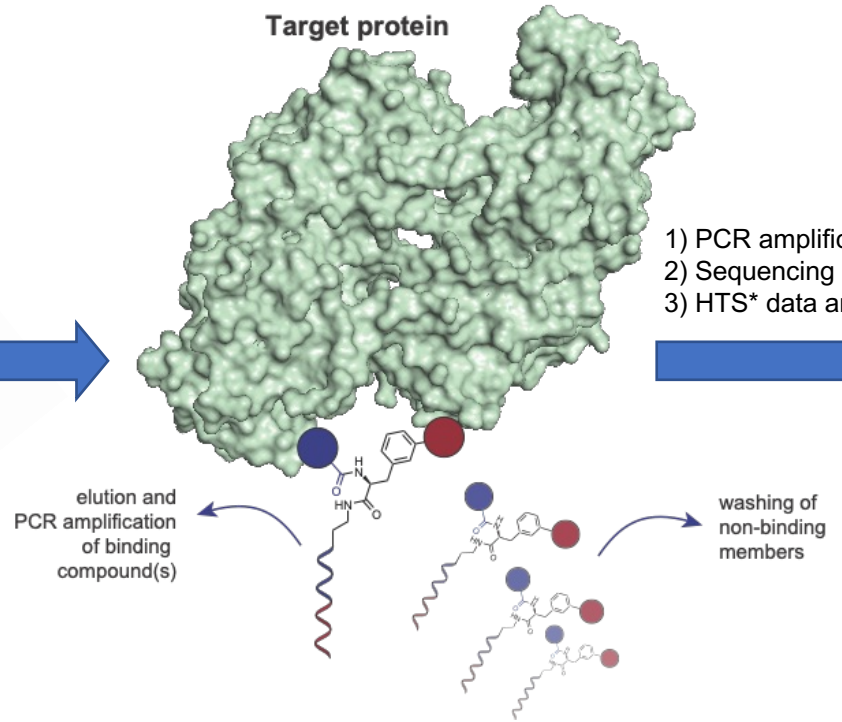
Overview of DEL Selections

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



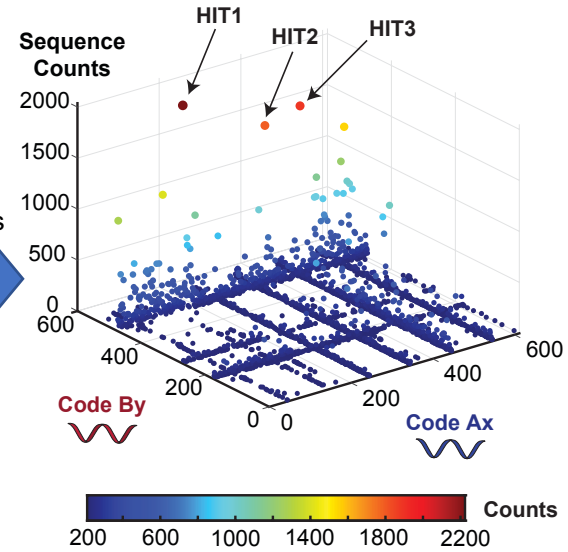
DEL before selections





Affinity selections

1) PCR amplification
2) Sequencing
3) HTS* data analysis



DEL after selections

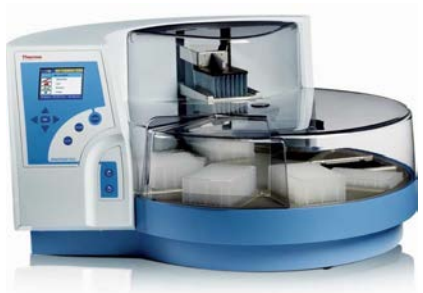
Data analysis and HIT re-synthesis

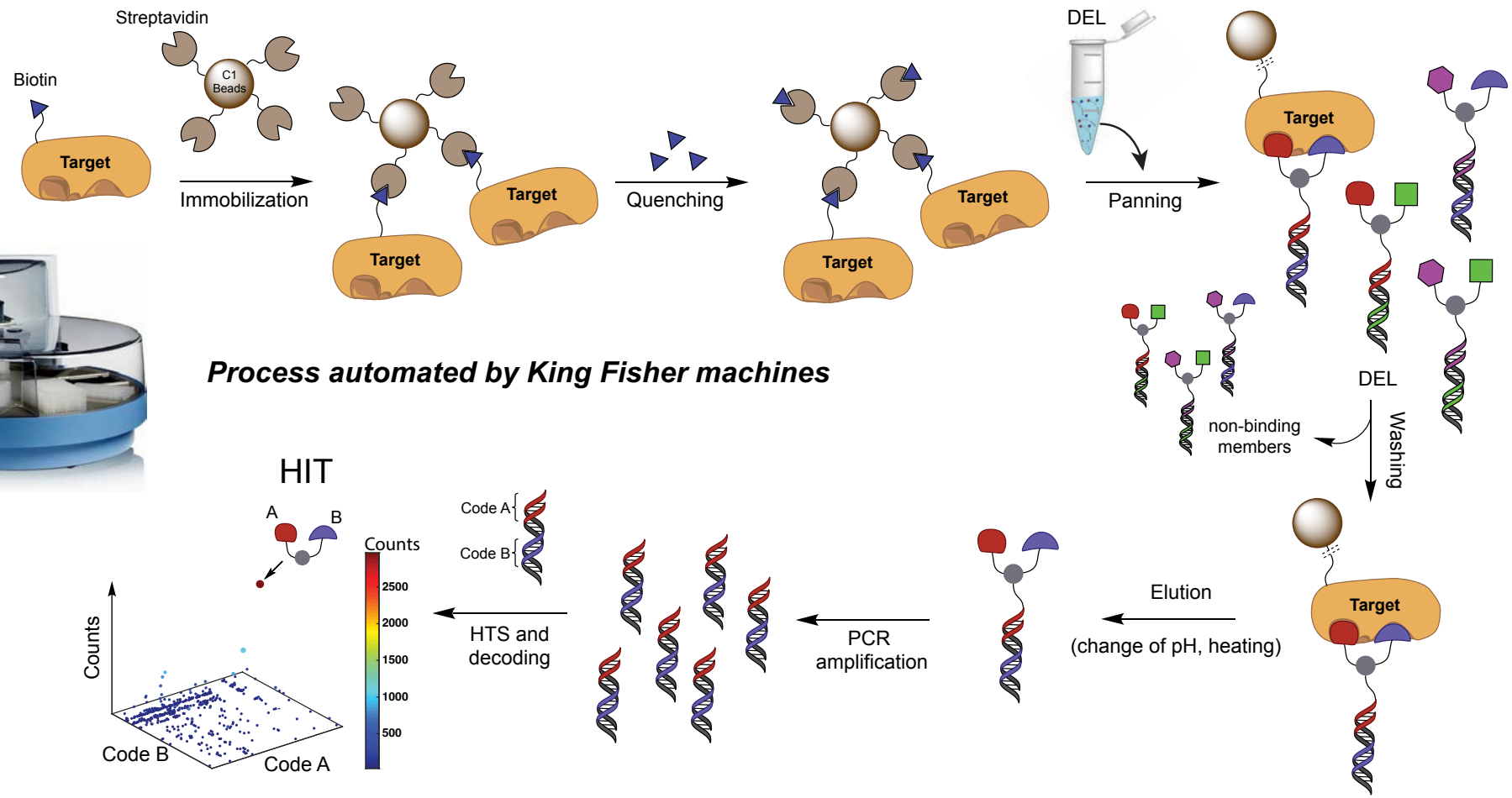
Neri D., Lerner R.A., *Annu Rev Biochem.*, **2018**; 87:479-502
Favalli et al., *FEBS Lett.*, **2018**; 592(12):2168-2180
Decurtins et al., *Nat. Prot.*, **2016**; 11(4):764-80

*HTS = high throughput sequencing

Automated DEL Affinity Selections

We have automated DEL affinity selections using King Fisher machines





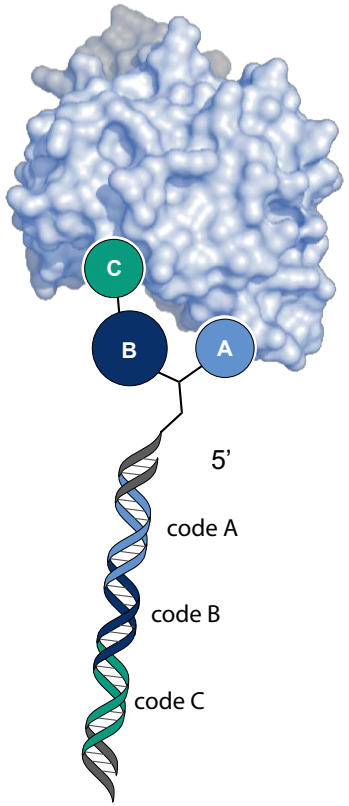
Process automated by King Fisher machines

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

Single and Dual Pharmacophore DELs

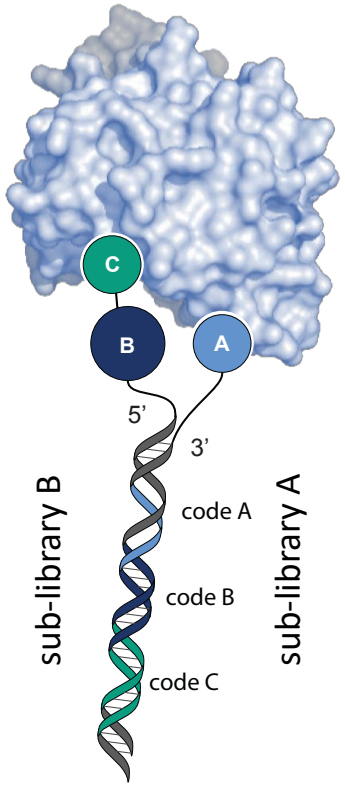
We have constructed innovative DELs in both single- and dual-pharmacophore format

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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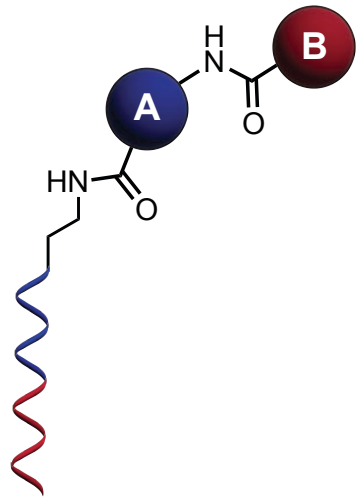
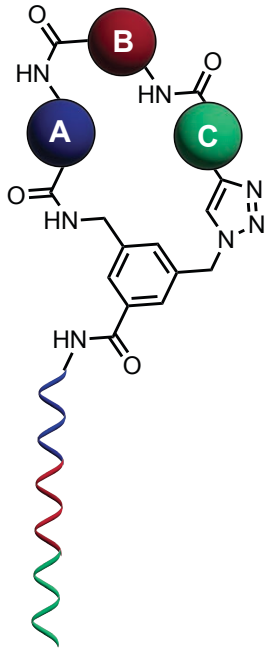
Examples of Philochem DELs in the Literature

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

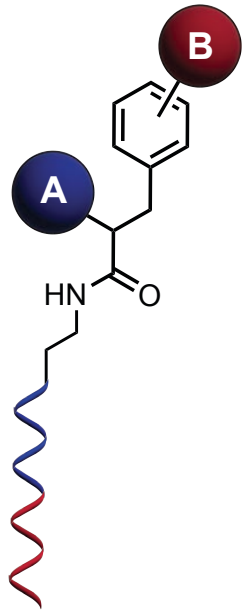


Leimbacher et al., Chemistry **2012**; 18(25):7729-37

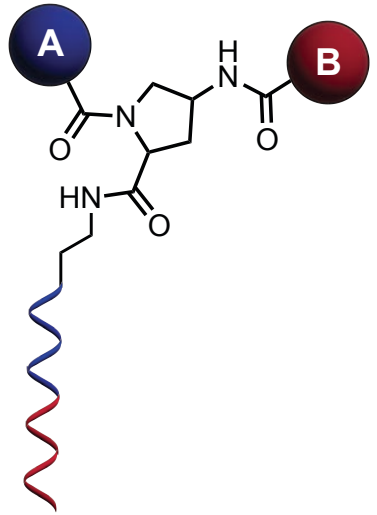
Gironda et al., *J. Med. Chem.* **2021**; 64(23):17496-17510



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



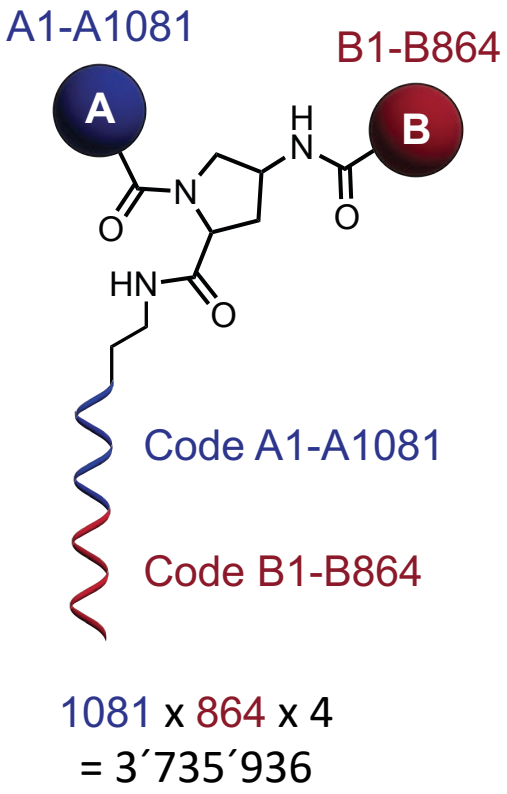
Favalli et. al., Nat. Chem. **2021**; 13(6):540-548



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

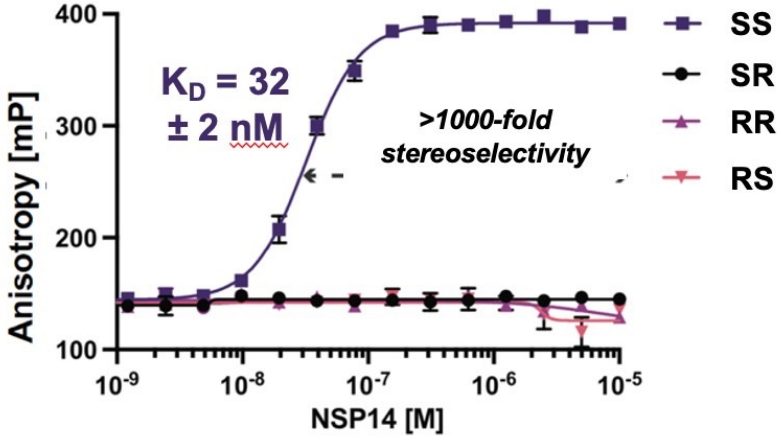
Stereoselectivity of Philochem DELs

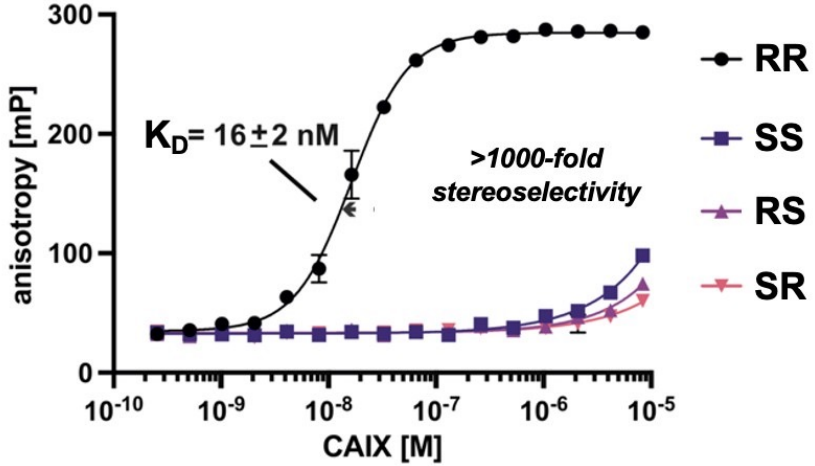
Ligands isolated from our stereo-defined DELs show huge differences in binding affinity between stereoisomers



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

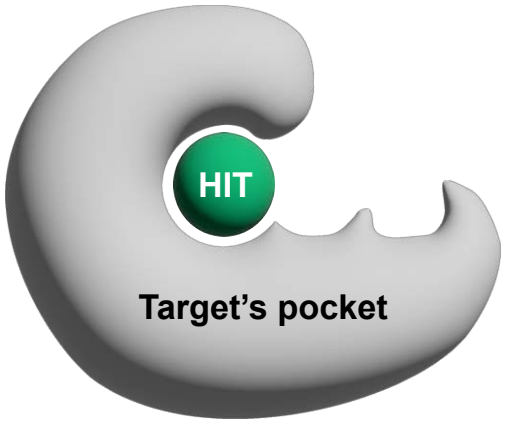




Oehler et al., *Nat. Chem.*, **2023**; 15(10):1431-1443

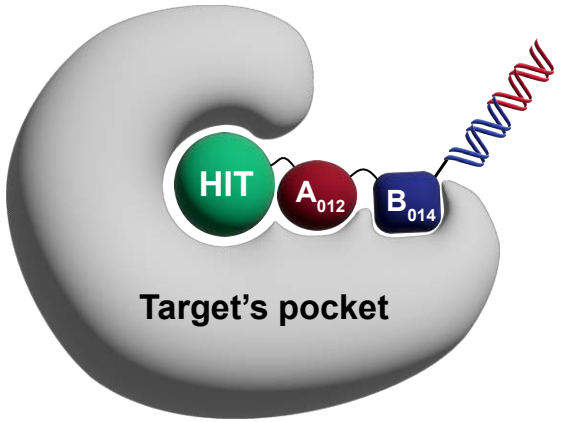
Strategies for Lead Expansion: Affinity Maturation DELs

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

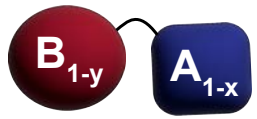


A: Affinity Maturation

Customized DEL Libraries

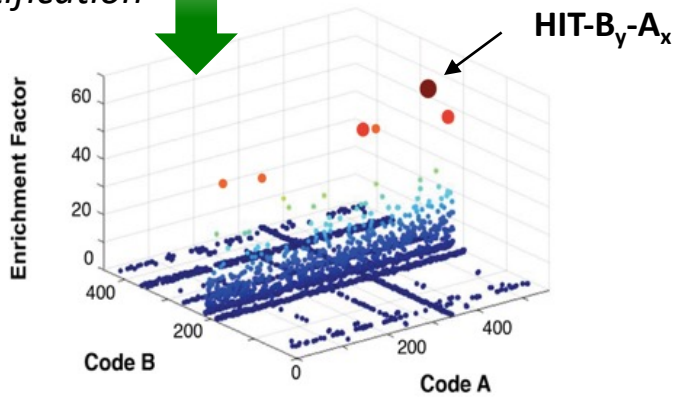


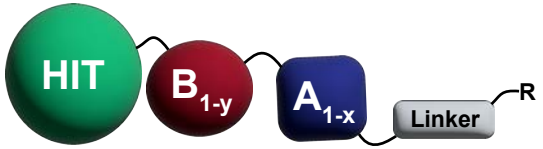
HIT potency in the high nM to low µM range



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

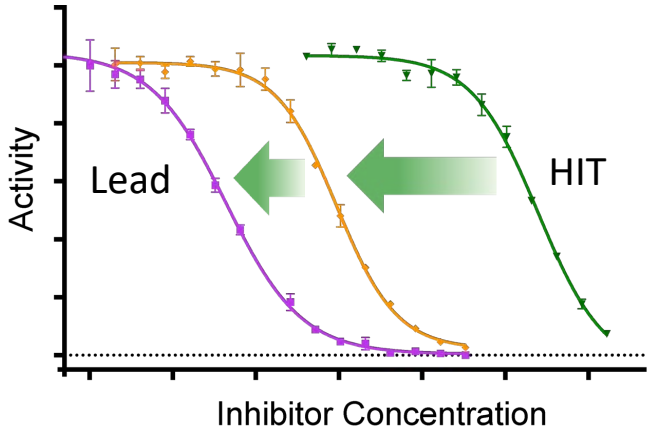
DEL selection
A-B fragment identification





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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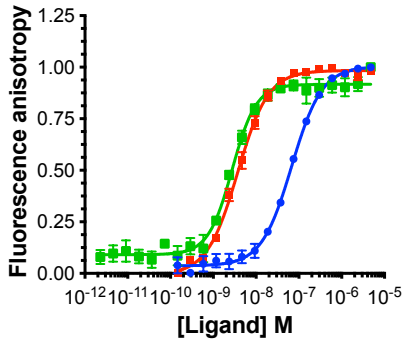
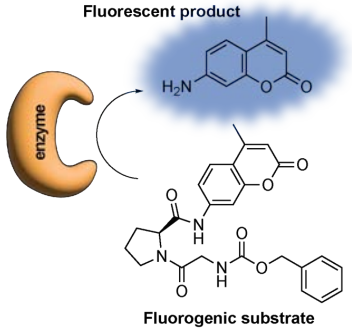
Hit Validation

We use multiple orthogonal methodologies to validate our Hits

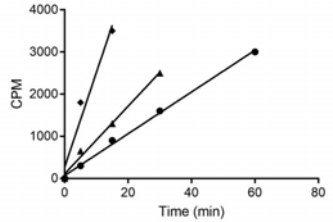
Fluorescence Polarization



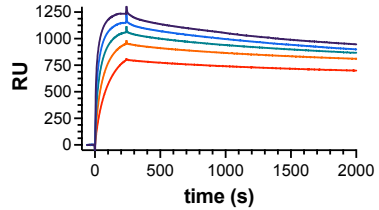
Enzymatic assay



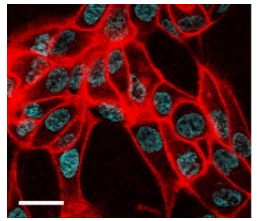
Radiometric assays



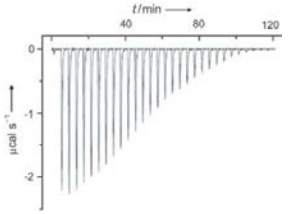
Surface Plasmon Resonance



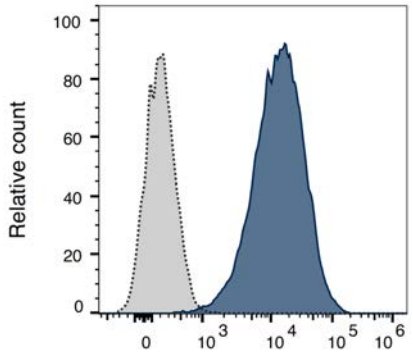
Confocal Microscopy



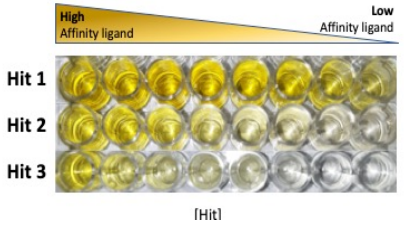
Isothermal Titration Calorimetry



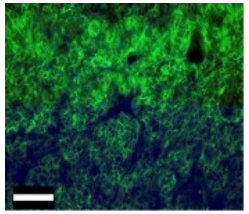
Flow Cytometry



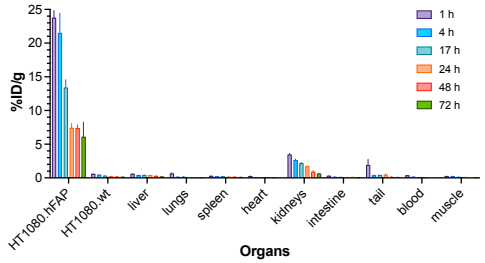
ELISA



Ex vivo BD in mice



Biodistribution (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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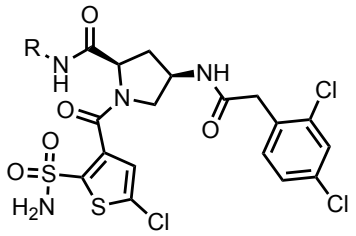
Success Stories of the Philochem DEL Platform

Tumor Associated Antigens (TAAs)

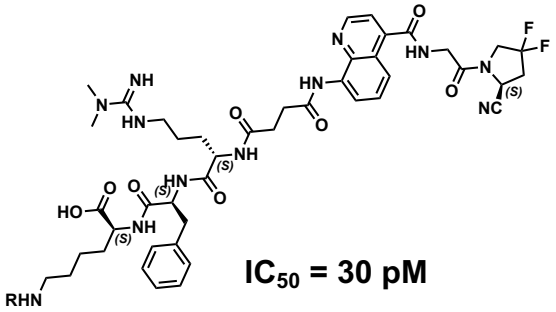
CAIX



K_D = 16 nM (isoform-specific)

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

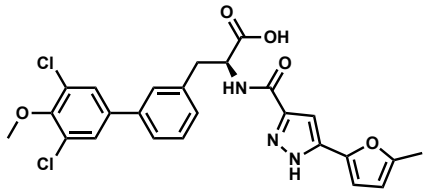
FAP



IC_{50} = 30 pM

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

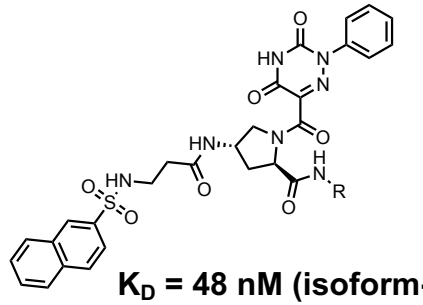
PLAP



IC_{50} = 32 nM

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

PSMA

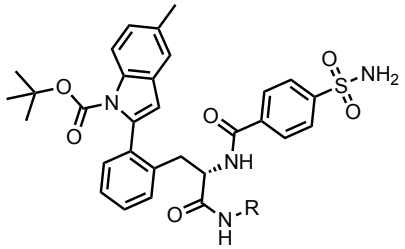


K_D = 48 nM (isoform-specific)

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

Immunological targets

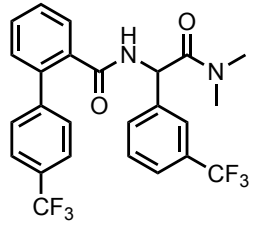
NKG2D



K_D = 410 nM

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

Collaboration with Janssen



IC_{50} = 1 µM

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

Phosphatases

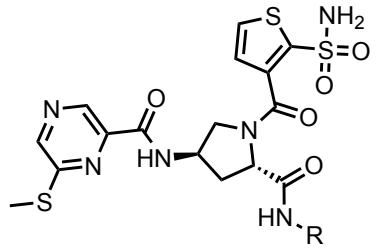
TC-PTP

- Undisclosed Structure -

K_D = 65 nM

Partnered Project

TNAP



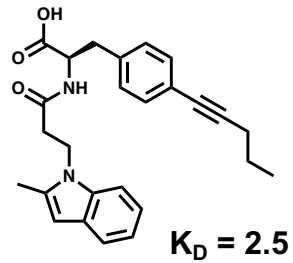
IC_{50} = 39 nM (isoform-specific)

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

Success Stories of the Philochem DEL Platform

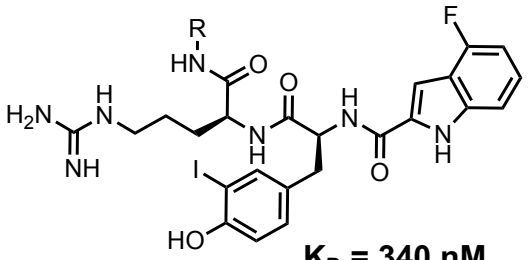
Cytokines

IL2



K_D = 2.5 µM

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

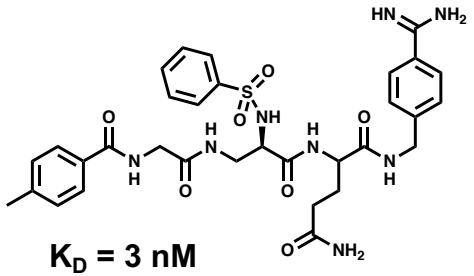


K_D = 340 nM

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

Proteases

Trypsin

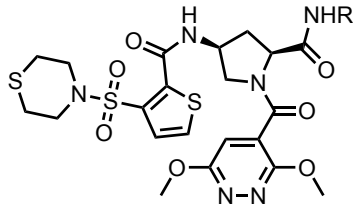


K_D = 3 nM

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

Viral methyltransferases

NSP-14

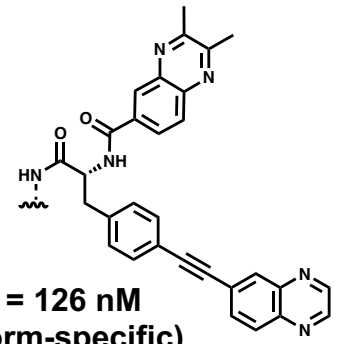


IC_{50} = 25 nM

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

Kinases

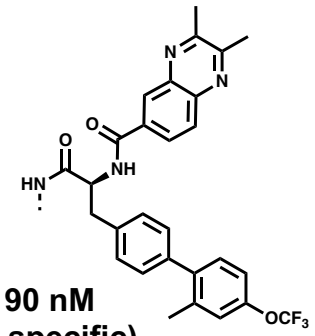
PI3K (WT)



K_D = 126 nM
(isoform-specific)

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

PI3K (H1047R)

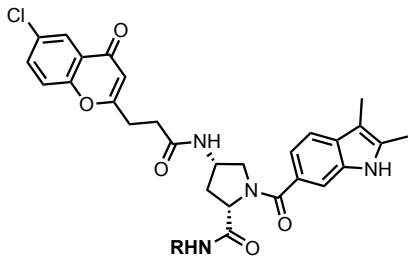


K_D = 190 nM
(isoform-specific)

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

Pro-X

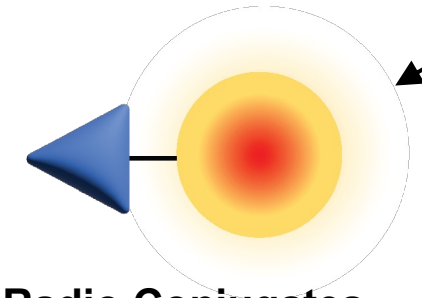
- Undisclosed Structure -

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

Unpublished

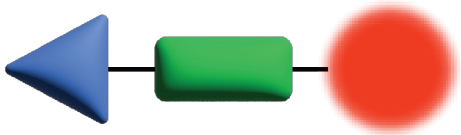
DEL inspired Product Development Activity at Philochem

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



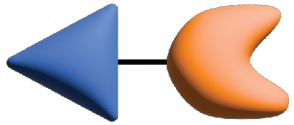
Radio Conjugates

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



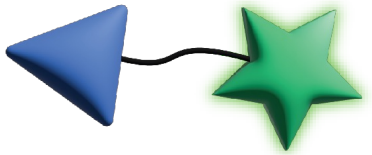
Drug Conjugates

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

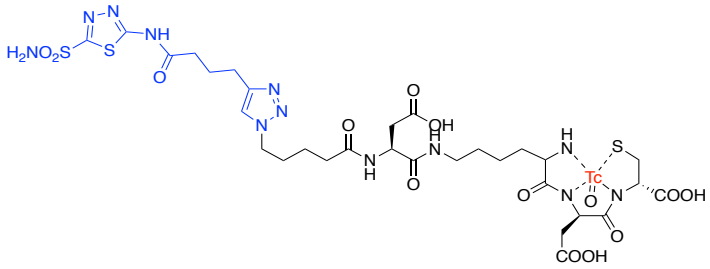
= fluorescein

Philochem
innovating chemistry

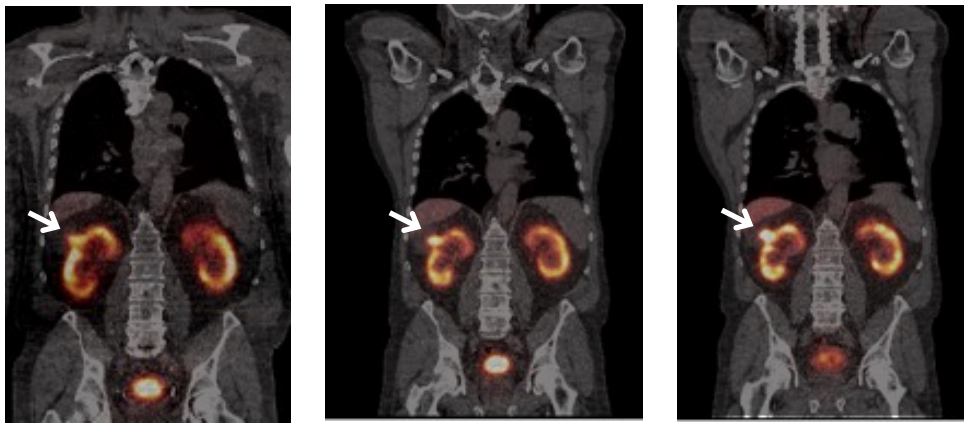
Onco IX: Ligands for Imaging and Therapy of Renal Cell Carcinoma

We have validated our CAIX ligand (Onco IX) by nuclear medicine in patients with Renal Cell Carcinoma (RCC)

- CAIX is the most validated antigen for Renal Cell Carcinoma
- SPECT/CT imaging of patients with Renal Cell Carcinoma in a Phase I clinical trial
- Onco IX was able to detect metastatic lesions which were not known at diagnosis



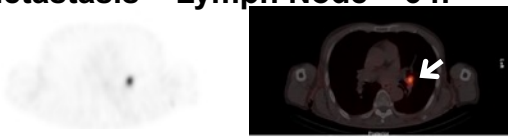
Primary Renal Cell Carcinoma (Patient A)



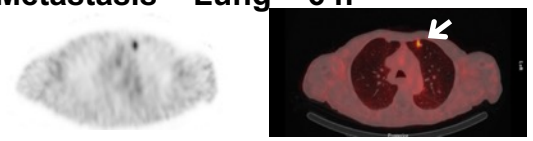
0.5 h | 2 h | 6 h

Metastatic Renal Cell Carcinoma (Patient B)

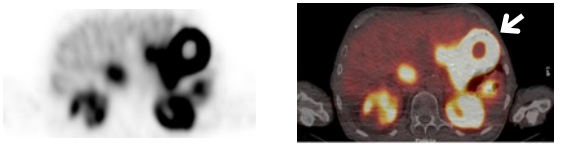
Metastasis – Lymph Node – 6 h



Metastasis – Lung – 6 h



Vena Cava Thrombus – 6 h

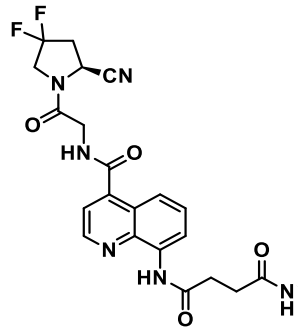


Kulterer et al., *J Nucl Med,* **2021,** 62, 360
RCC: Renal Cell Carcinoma

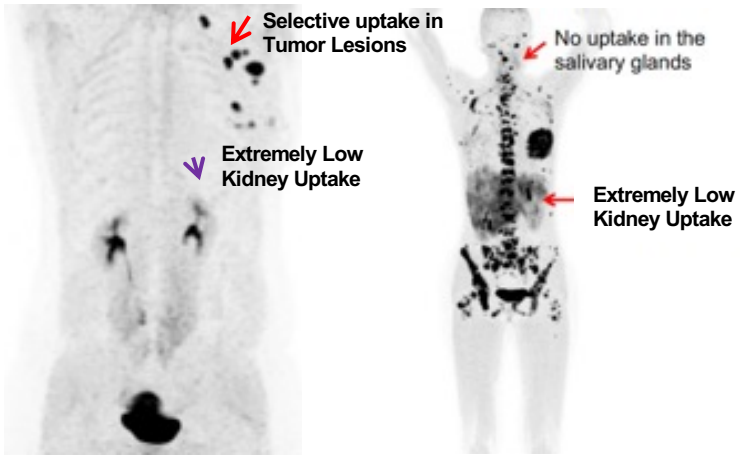
OncoFAP: Potential for Imaging and Therapy of a Variety of Tumors

We have validated our FAP ligand (OncoFAP) by nuclear medicine in more than 100 patients in a variety of tumors

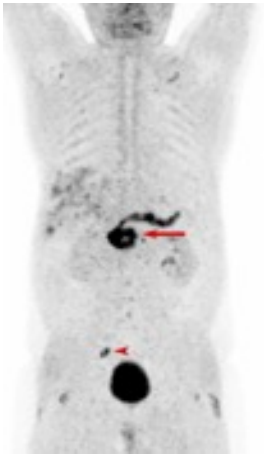
- Fibroblast Activation Protein (FAP) is a validated high-quality pan-tumoral target
- We have generated a proprietary FAP ligand (OncoFAP) which displays the highest affinity ever reported
- SPECT/CT imaging of more than 100 patients with various solid tumors



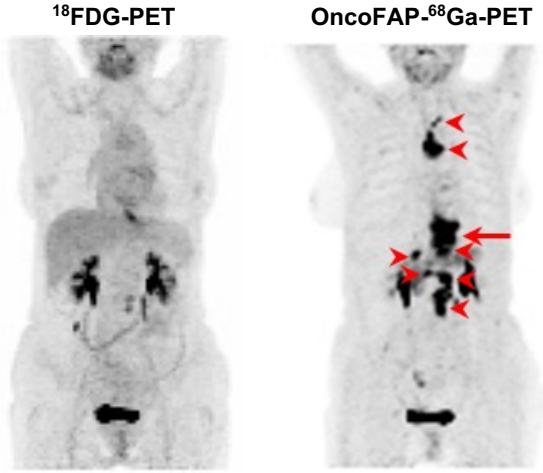
Breast Cancer



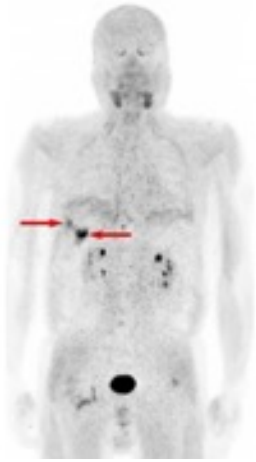
Pancreatic Cancer



Esophageal Cancer



HCC



Millul *et al., PNAS,* **2021**, 118, e2101852118
Backhaus et al., *Eur J Nucl Med Mol Imaging,* **2022,** 49, 1829

UKM Universitätsklinikum Münster

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 have **successful collaborations** with leading pharmaceutical companies & academia