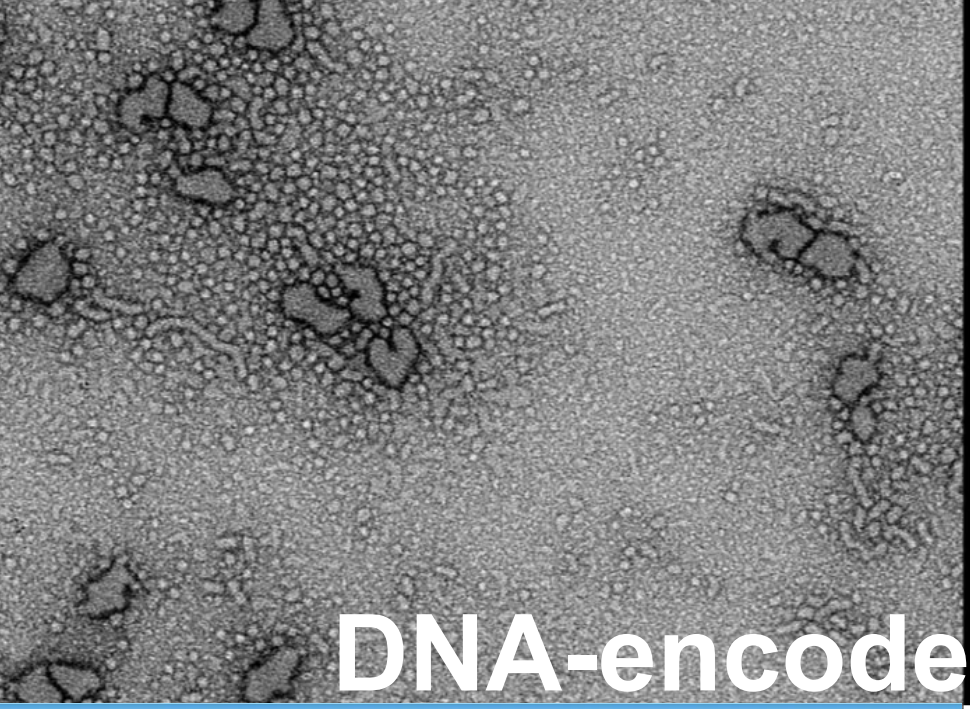
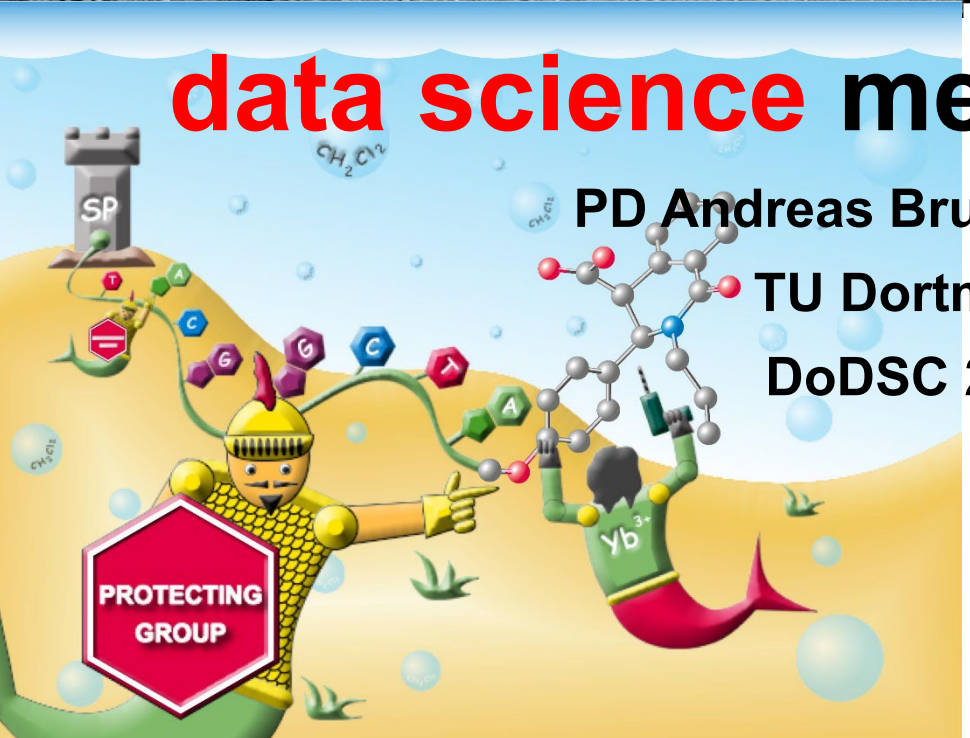


DNA-encoded libraries:

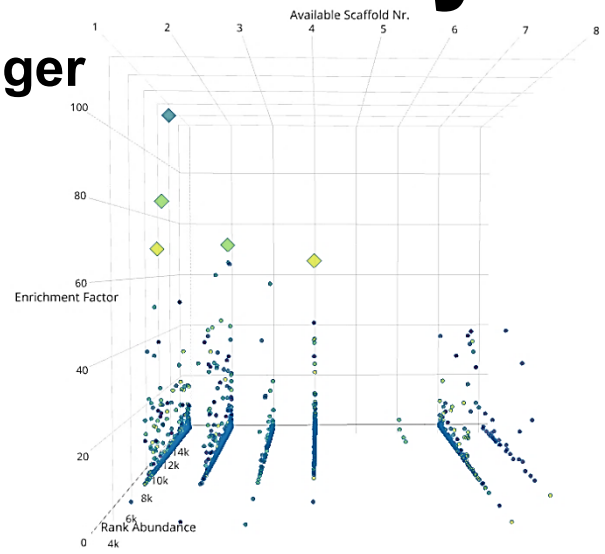
data science meets chemistry



PD Andreas Brunschweiger

TU Dortmund

DoDSC 2022



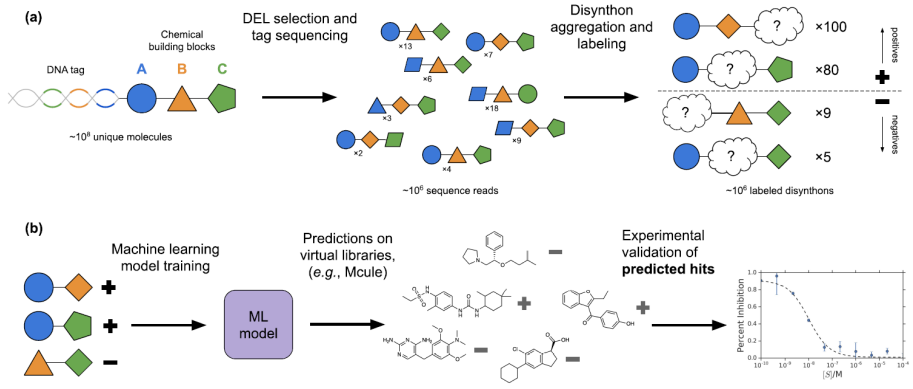
technische universität dortmund

Journal of Medicinal Chemistry

pubs.acs.org/jmc Article

Machine Learning on DNA-Encoded Libraries: A New Paradigm for Hit Finding

Kevin McCloskey,‡ Eric A. Sigel,‡ Steven Kearnes, Ling Xue, Xia Tian, Dennis Moccia, Diana Gikunju, Sana Bazzaz, Betty Chan, Matthew A. Clark, John W. Cuozzo, Marie-Aude Guié, John P. Guilinger, Christelle Huguet, Christopher D. Hupp, Anthony D. Keefe, Christopher J. Mulhern, Ying Zhang, and Patrick Riley*



VIP Peptidomimetics Very Important Paper

How to cite:
International Edition: doi.org/10.1002/anie.202006280
German Edition: doi.org/10.1002/ange.202006280

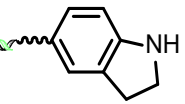
TEAD–YAP Interaction Inhibitors and MDM2 Binders from DNA-Encoded Indole-Focused Ugi Peptidomimetics

*Verena B. K. Kunig, Marco Potowski, Mohammad Akbarzadeh, Mateja Klika Škopić, Denise dos Santos Smith, Lukas Arendt, Ina Dormuth, Hélène Adihou, Blaž Andlovic, Hacer Karatas, Shabnam Shaabani, Tryfon Zarganes-Tzitzikas, Constantinos G. Neochoritis, Ran Zhang, Matthew Groves, Stéphanie M. Guéret, Christian Ottmann, Jörg Rahnenführer, Roland Fried, Alexander Dömling, and Andreas Brunschweiger**

Navigating Chemical Reaction Space – Application to DNA-encoded Chemistry

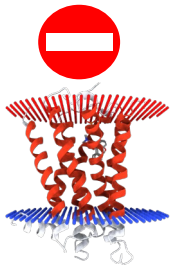
Silvia Chines,[a] Christiane Ehrt,[b] Marco Potowski,[a,c] Felix Biesenkamp,[a] Lars Grützbach,[a] Susanne Brunner,[d] Frederik van den Broek,[e] Shilpa Bali,[e] Katja Ickstadt,[d] and Andreas Brunschweiger.[a]*

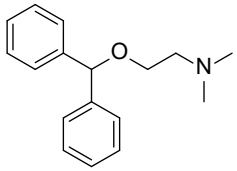
Chemical Science, in revision



The background

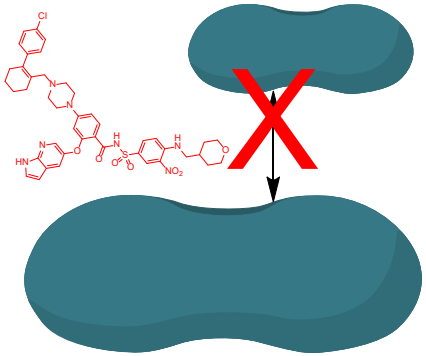
receptor block

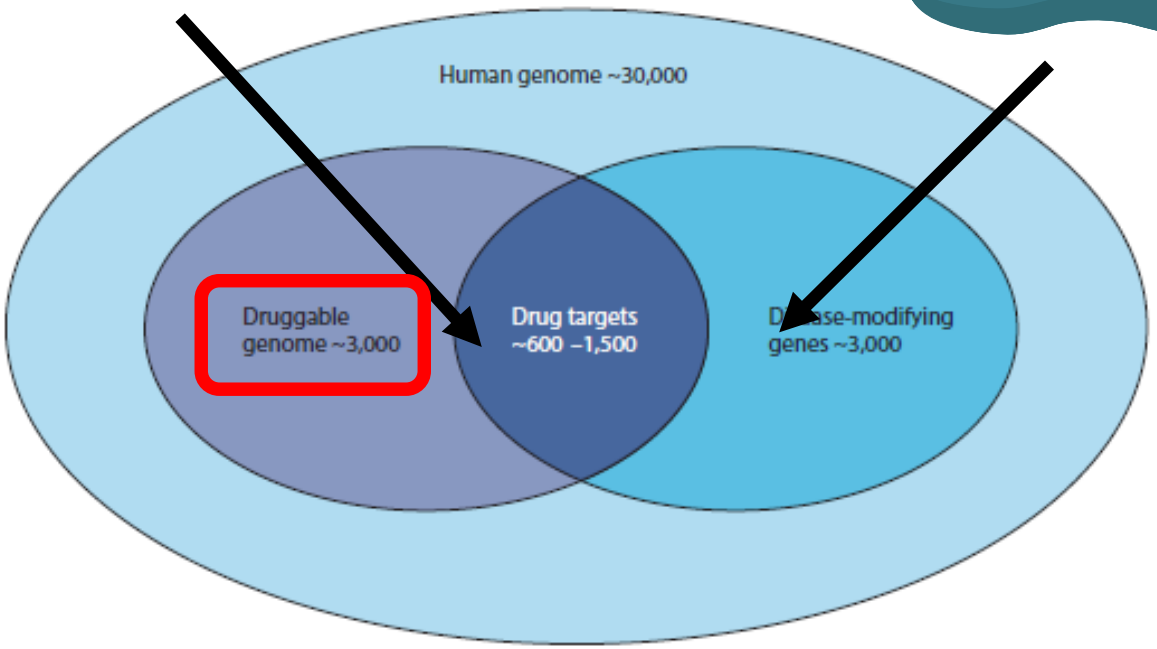




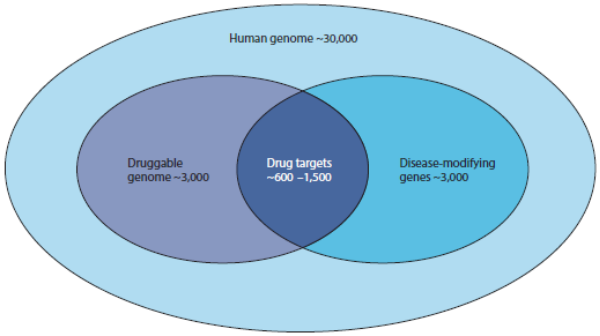
Diphenhydramine

protein-protein interaction

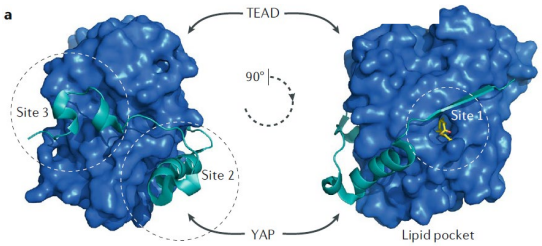




druggable versus undruggable



druggable versus undruggable

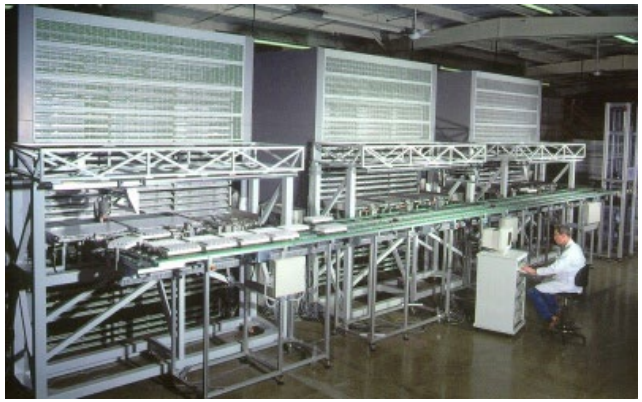


Journal of Medicinal Chemistry
Article
Cite This: J. Med. Chem. 2019, 62, 9732−9742
pubs.acs.org/jmc

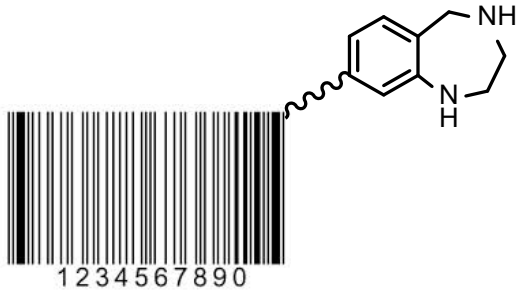
Exhaustive Repertoire of Druggable Cavities at Protein−Protein Interfaces of Known Three-Dimensional Structure

Franck Da Silva,† Guillaume Bret,† Leandro Teixeira,‡ Claudio F. Gonzalez,‡ and Didier Rognan*,†

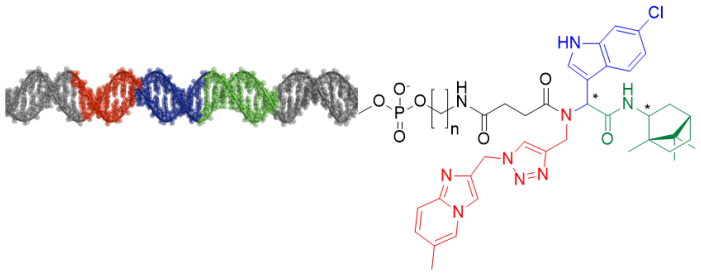
"almost no overlap in property space between PPI and „druggable" pockets"



discrete, static

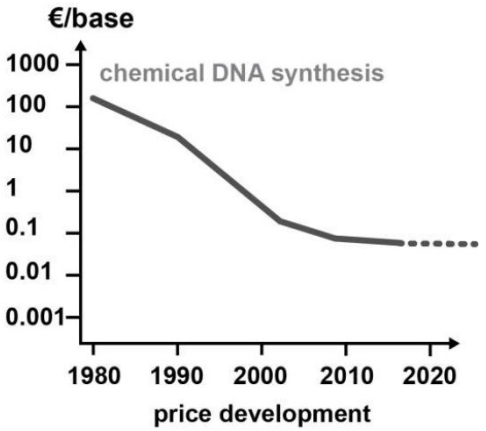


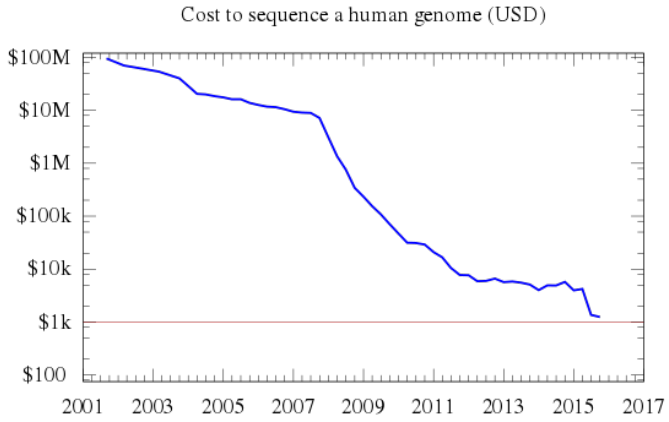
genotype - phenotype

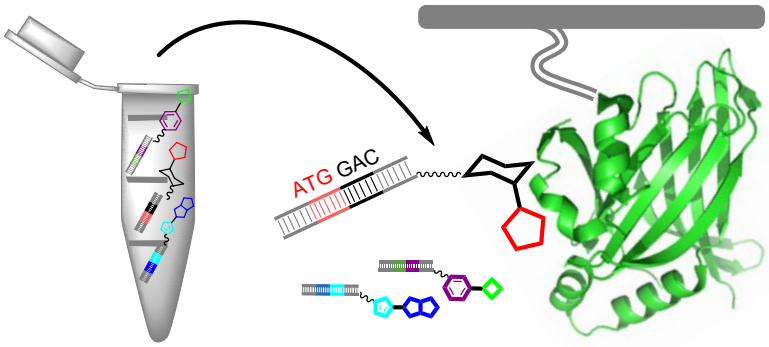


pooled, dynamic

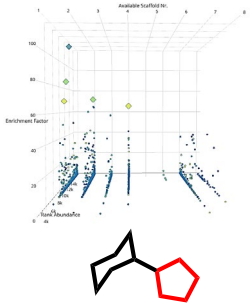
DNA as a compound barcode







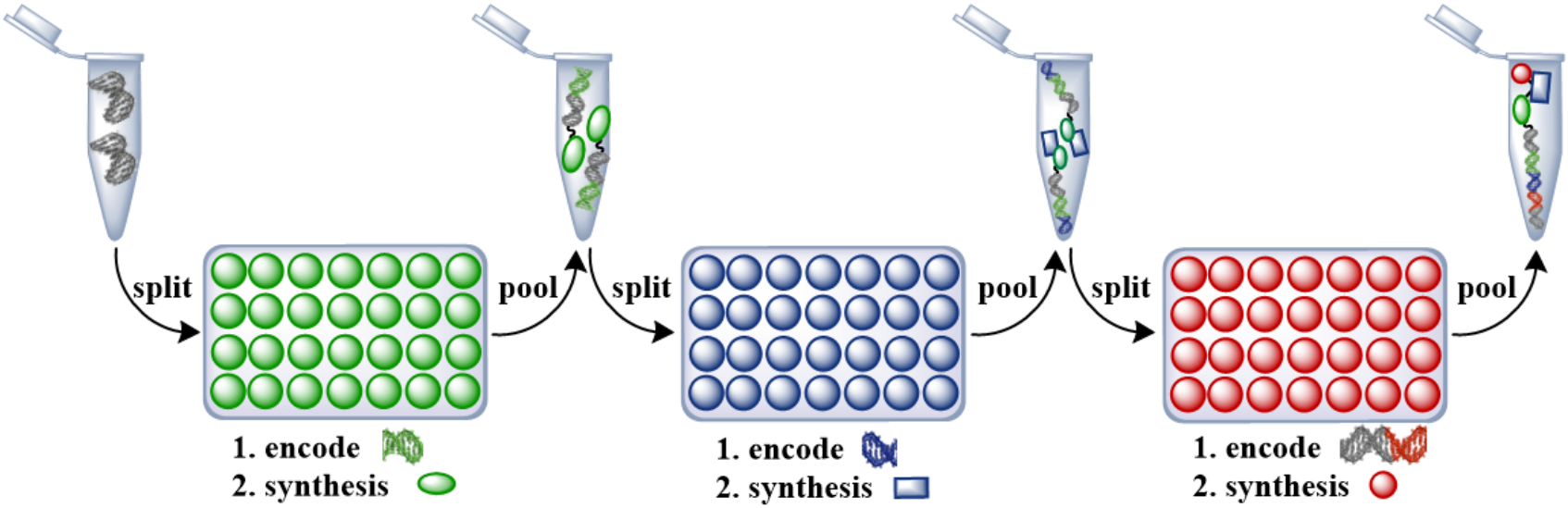
DNA sequencing



Molecular evolution, „***survival of the fittest***“

- Generic, disease- and target-agnostic assay design
- Purified recombinant tagged proteins
- Efficient: microgramm amounts

Encoded combinatorial chemistry



100 x 100 x 100 = 1.000.0000 compounds

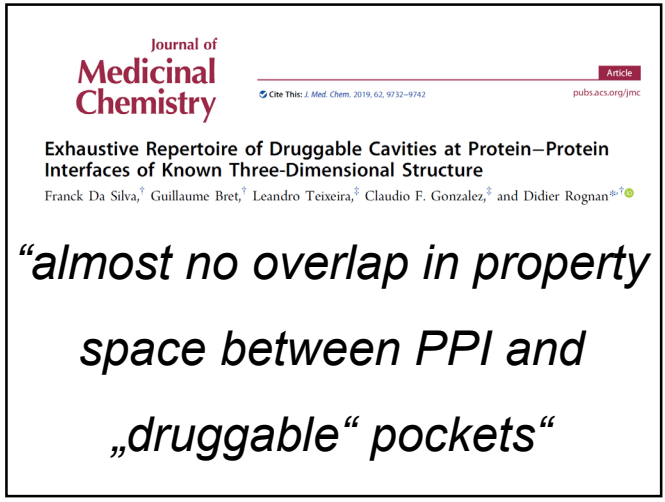
Scalable, efficient

Expanding chemical space, de novo library design

Chemical reaction space?

Building block selection?

Reactivity of chemicals?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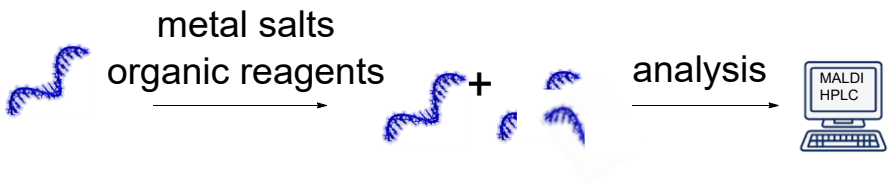
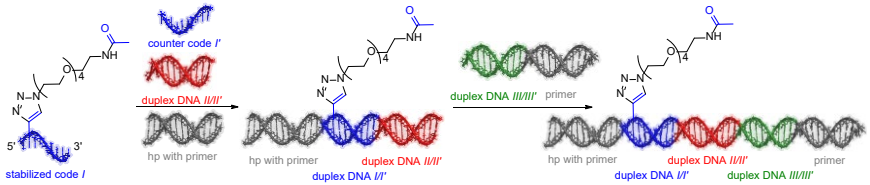
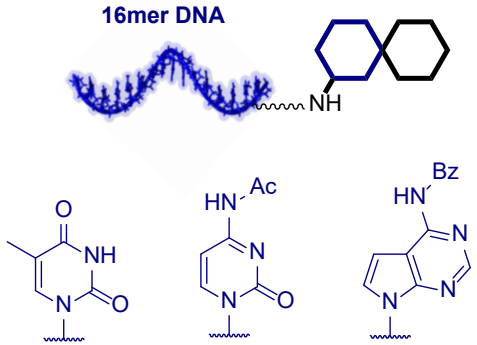
"almost no overlap in property space between PPI and „druggable" pockets"

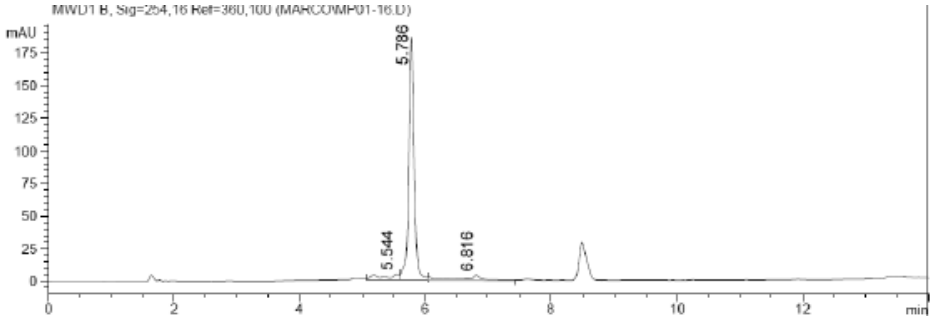
1. Machine-learning approaches for screening library design?

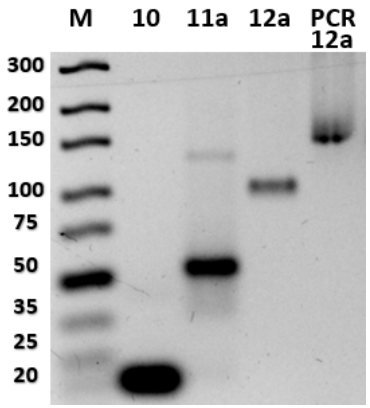
Chemically stabilized DNA











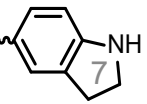
after treatment with 10 % TFA

7-deazaA-DNA

chemically stable to protic acids and to many Lewis acids

ligatable, amplifiable, readable code for DEL

→ *expanding chemical reaction space for DEL*



Potowski and Kunig, Angew. Chem. Int. Ed. 2021; EP 20 166 145.1

Navigate chemical reaction space

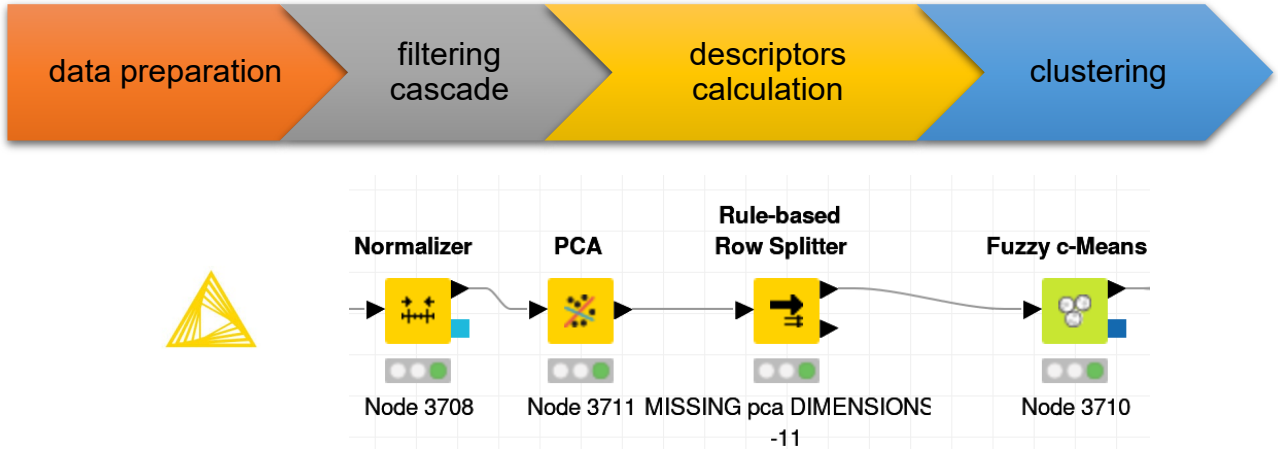
A barcode with enhanced chemical stability

→ ***2. Selection of reactions from vast chemistry databases?***

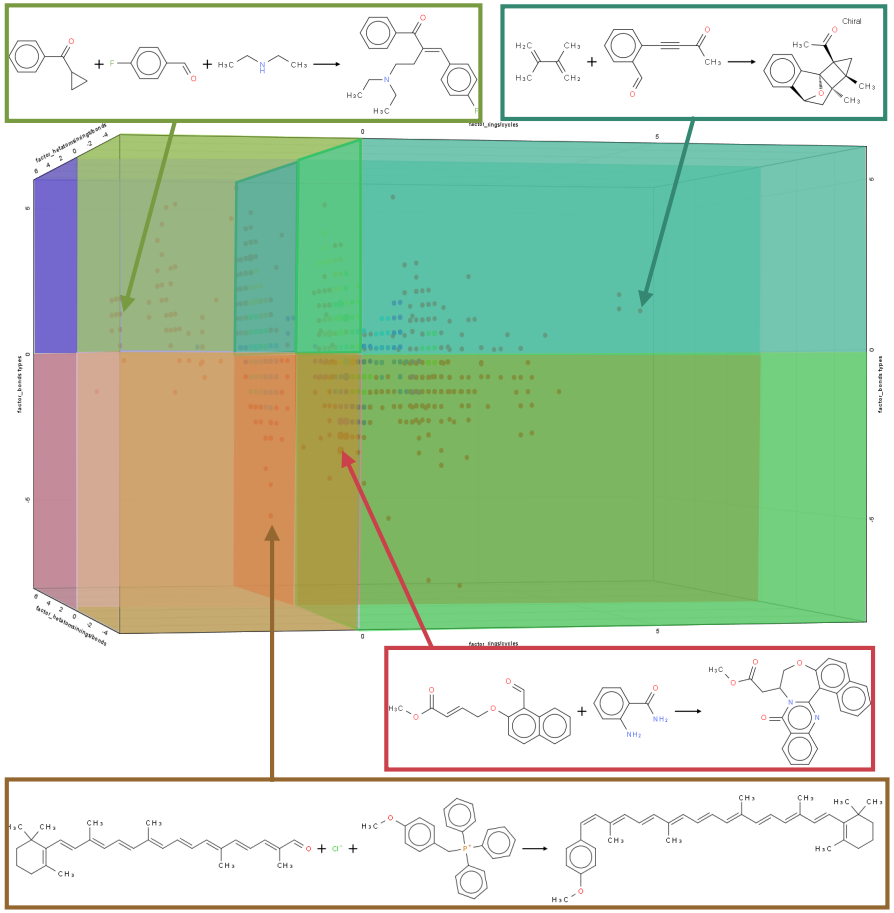
→ Application of data science tools

→ Navigate chemical reaction space

100k reactions



Navigate chemical reaction space

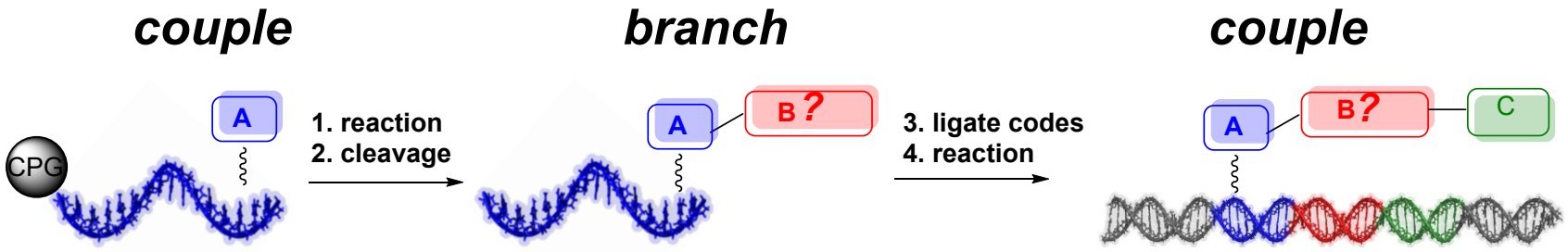


Comprehensive chemistry databases are commercial.

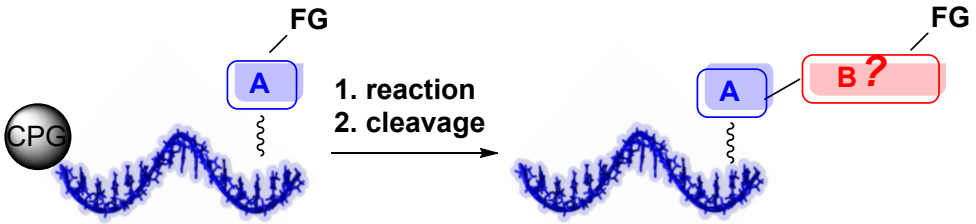
3. Access to chemistry data, e.g. from patents?

Chines… Ickstadt, Chemical Science, in revision

DEL design



branch: key step - structural diversity from reactions



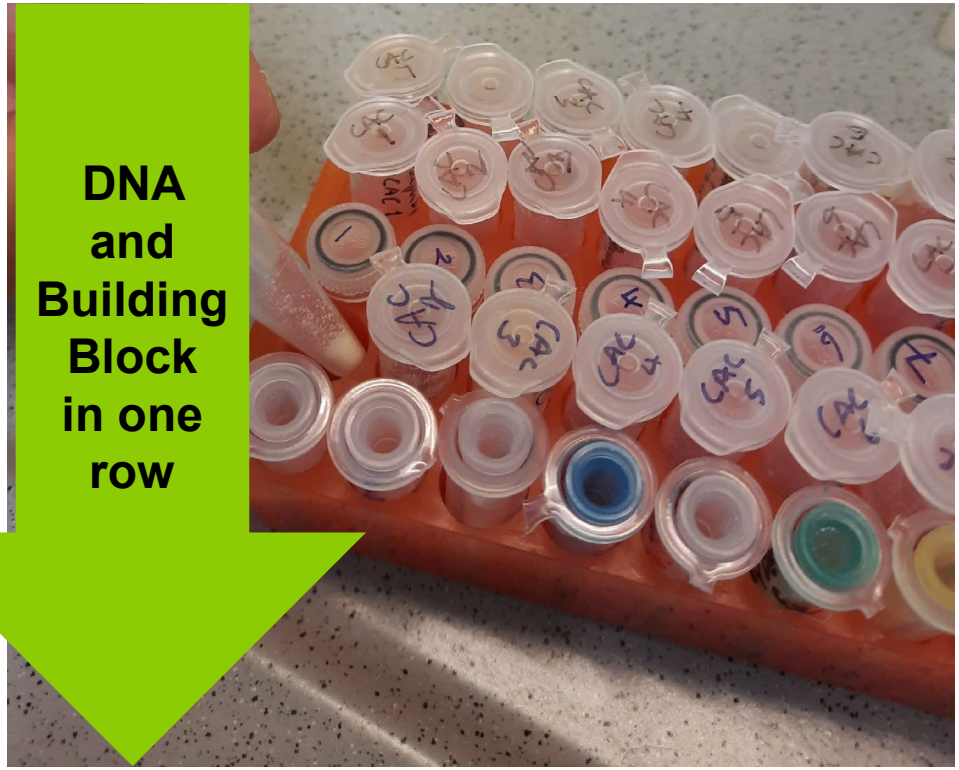
- aim: DELs w. 1 mio compounds
- bifunctional starting materials
- diverse chemistries

on-DNA reactions:

Klika Škopić	Chem. Sci. 2017
Klika Škopić	Org. Biomol. Chem. 2017
Potowski	Chem. Sci. 2019
Kunig	Org. Lett. 2019
Potowski	Bioorg. Med. Chem. Lett. 2020
Klika Škopić	J. Am. Chem. Soc. 2019
Kunig	Angew. Chem. Int. Ed. 2020
Potowski	Org. Lett. 2021
Potowski	Angew. Chem. Int. Ed. 2021
Klika Škopić	Org. Lett. 2022

A glimpse into the lab

DNA and Building Block in one row



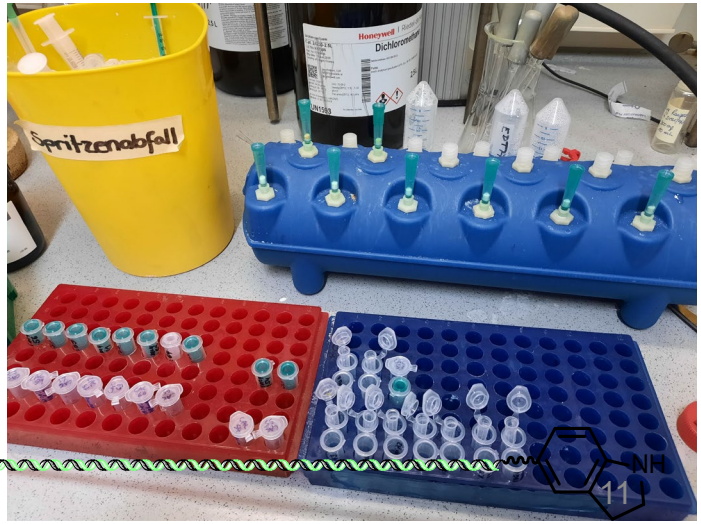
Reaction solution

DNA

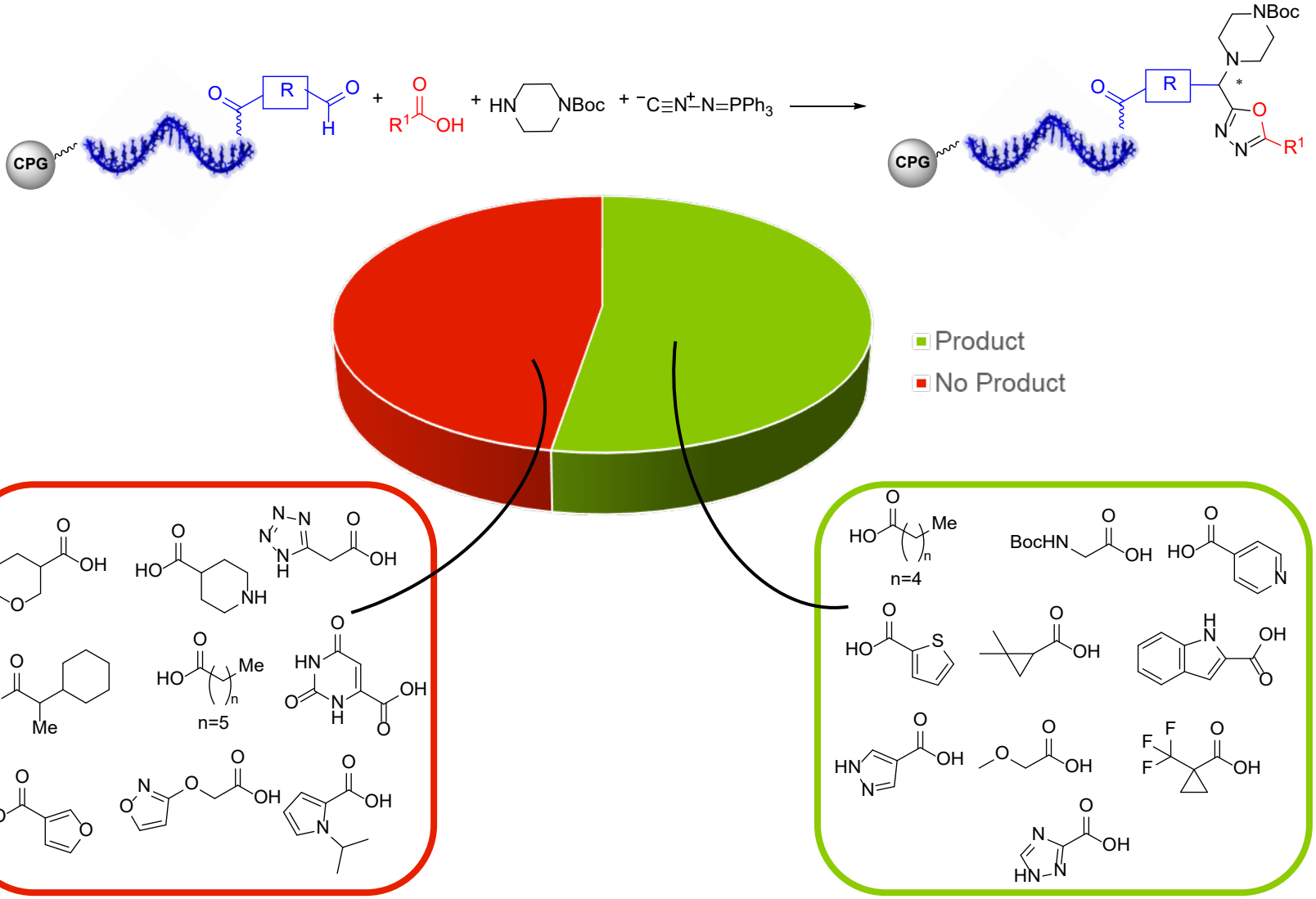
Carboxylic Acid

DNA-wash-column

Wash colums and rack:
Same positioning of samples!

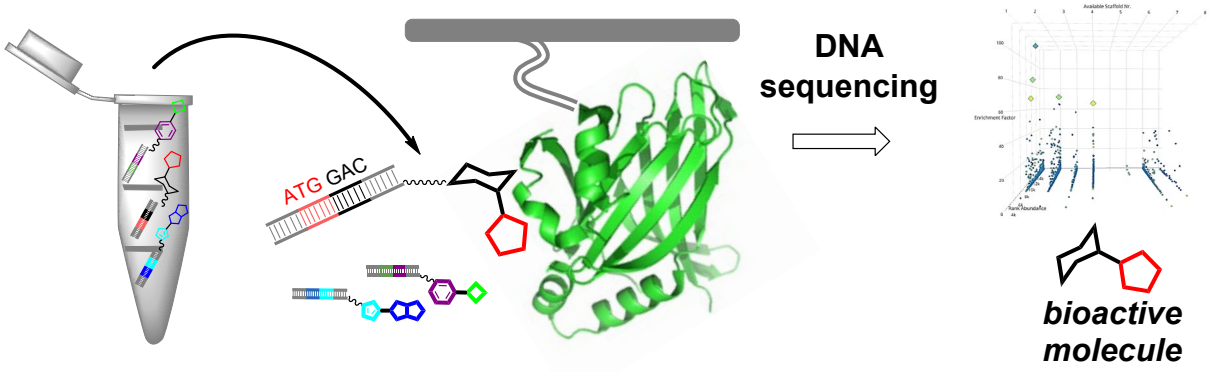


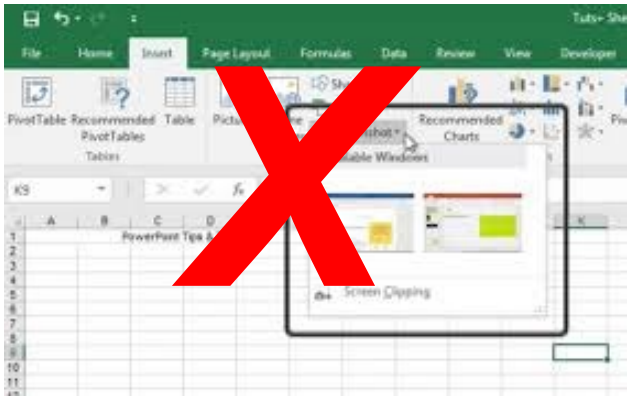
Building block reactivity



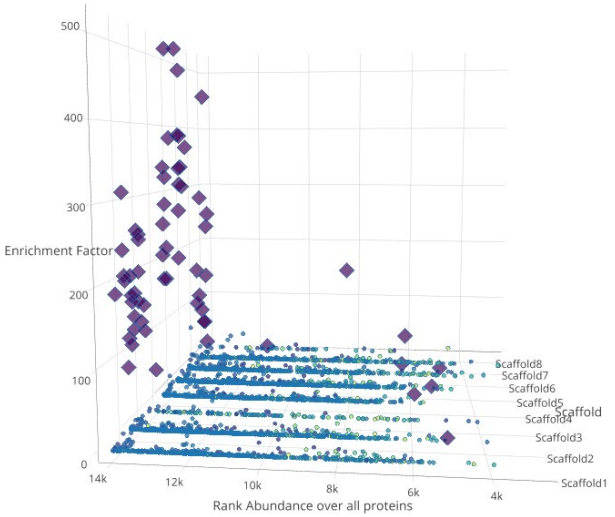
4. Every BB to be profiled: Machine-learning for reactivity prediction?

From DEL synthesis to compound identification



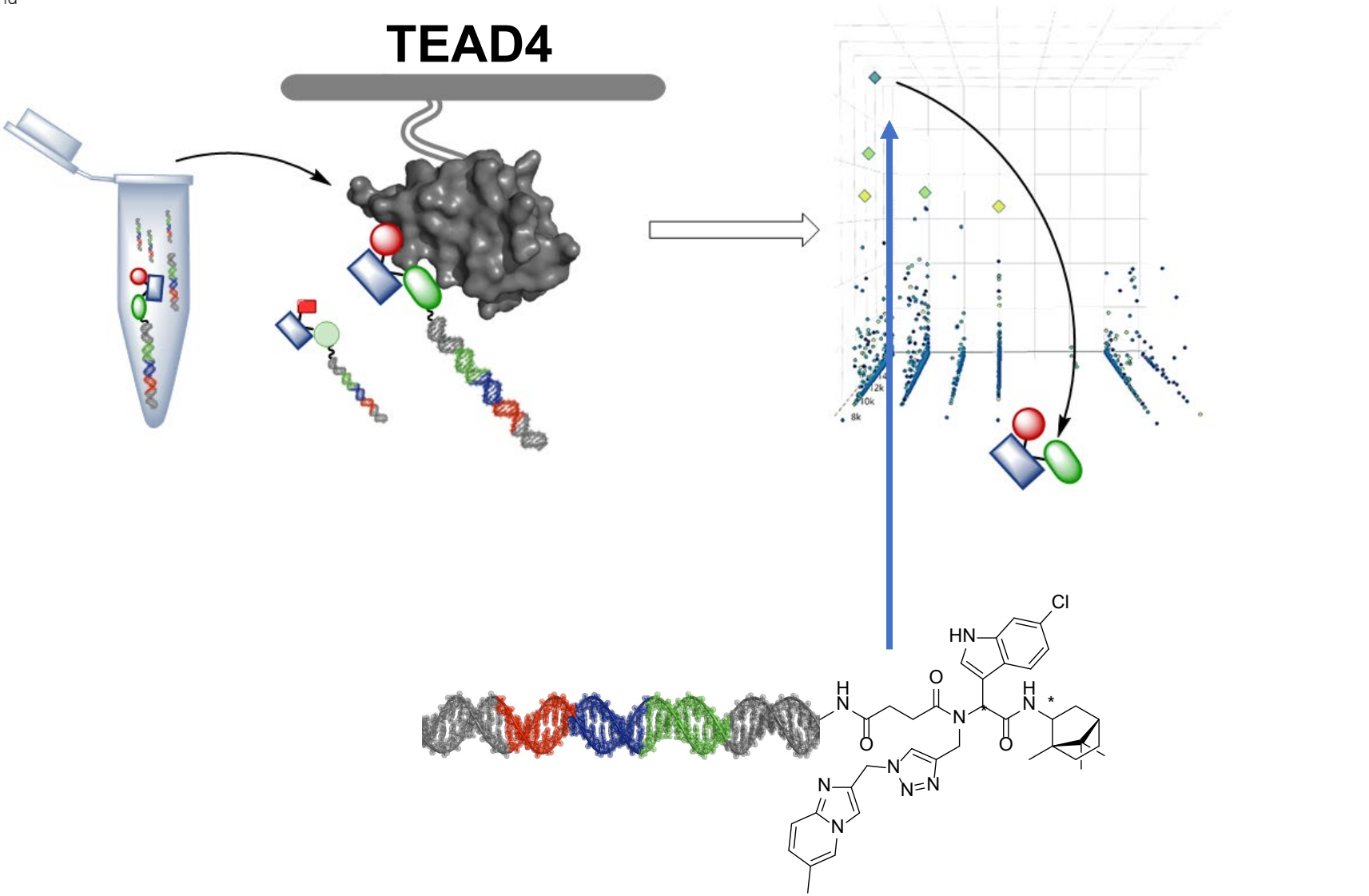


~~manual analysis~~



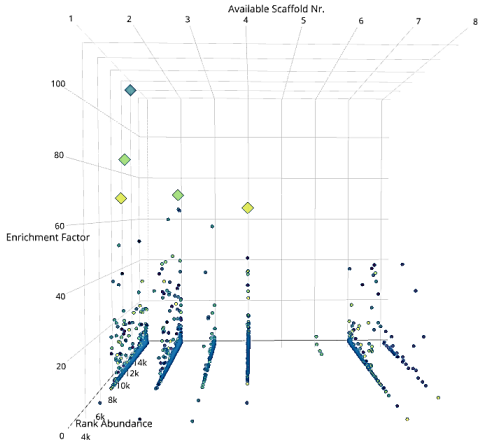
enrichment factor analysis

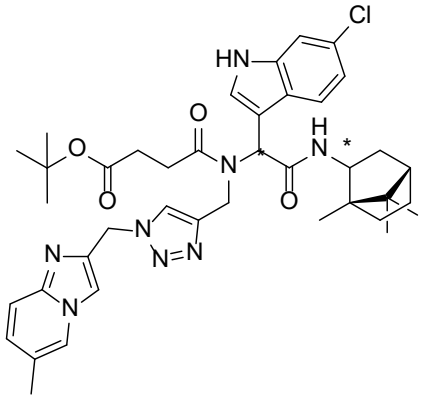
- barcode PCR encodes selection experiments
- algorithm calculates enrichment factors
- accounts for differences in individual DNA amplification efficency



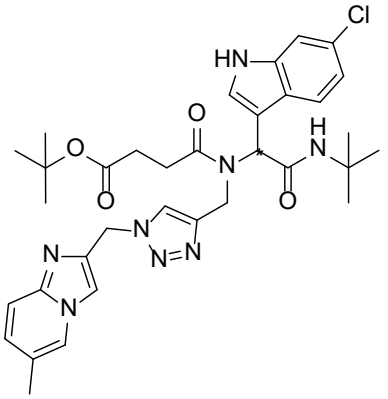
5. Machine learning for compound identification?

Kunig, Angew Chem Int Ed.2020, with Prof. Dömling, U. Groningen

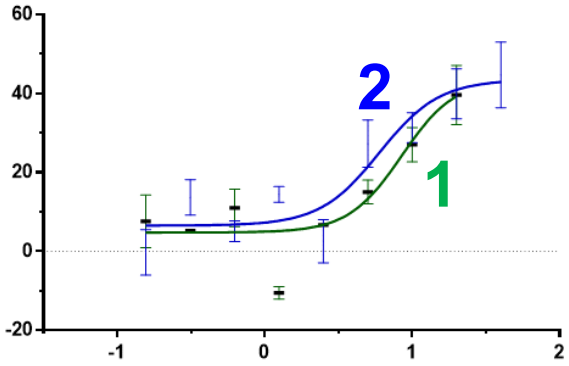


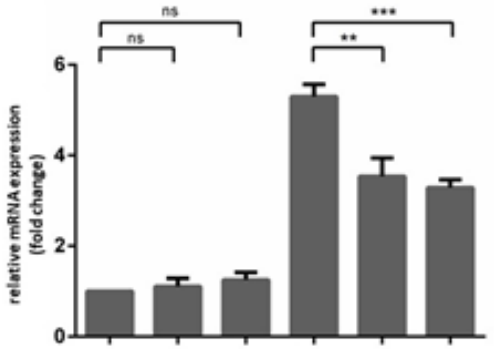


1 (VK57)



2 (VK67)



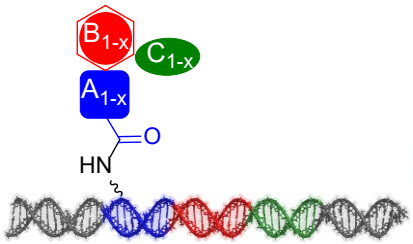


w/o Hippo-I w Hippo-I

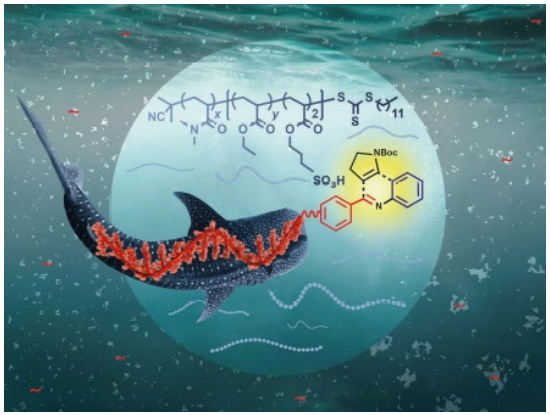
FP assay: H. Karatas; M. Akbarzadeh, MPI Do (Prof. Waldmann); qPCR: B. Andlovic, TU Einhoven

Data science impacts…

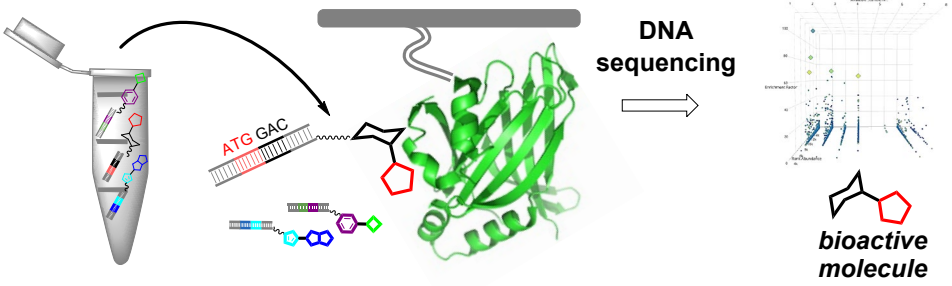
encoded library design



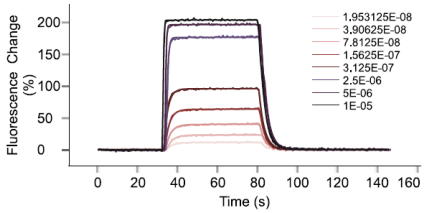
reactivity prediction of chemicals



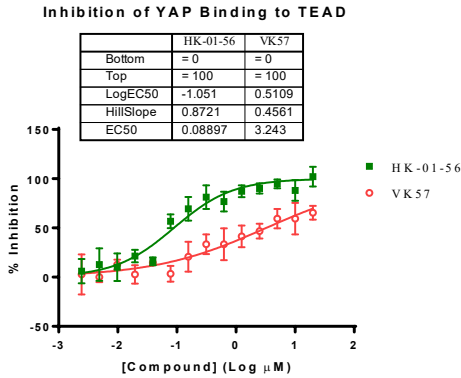
DEL screening data analysis



inhibitor validation and development



k_{ON} ($M^{-1}s^{-1}$)	k_{OFF} (s^{-1})	K_D (nM)
516 ± 21 E+3	349 ± 3 E-3	676 ± 28 E-9



	HK-01-56	VK57
Bottom	= 0	= 0
Top	= 100	= 100
LogEC50	-1.051	0.5109
HillSlope	0.8721	0.4561
EC50	0.08897	3.243

design – data analysis – prediction – design

technische universität dortmund

The DEL Team

Silvia Chines
Katharina Götte
Mateja Klika Škopić
Verena Kunig
Marco Potowski
Avinash Bhat
Suzanne Willems

Faculty

Prof. Rauh
Prof. Waldmann

Chemistry

Prof. Weberskirch, TU Do
Prof. Kockmann, TU Do
Prof. Dömling, U. Groningen
Prof. Bode, ETH Zürich
Prof. Waring, Newcastle
Dr. Vakalopoulos, Bayer
Prof. Fogg, U. Ottawa

Analysis of sequencing data

Ina Dormuth and Lukas Arendt
Prof. Rahnenführer, TUDo
Prof. Fried, TUDo

TEADI assays

Hélène Adhiou, MPI Do
Hacer Karatas, MPI Do
Mahyar Akbarzadeh, MPI Do
Blaz Andlovic, TU Eindhoven

DNA synthesis

Lukas Stratmann, TU Do
Prof. Clever, TU Do

DEL design, TEADI design

Dr. Christiane Ehrt, HHU
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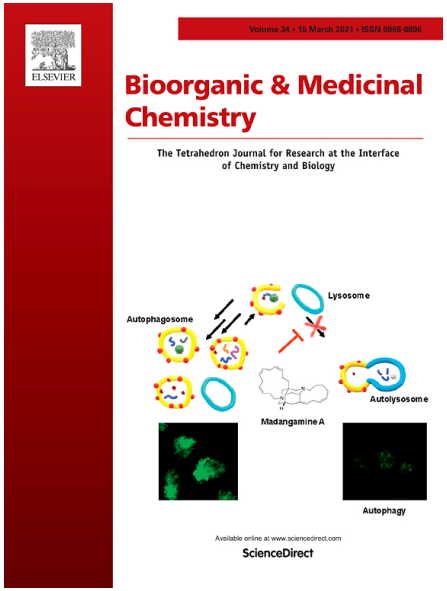

Special Issue on DELs

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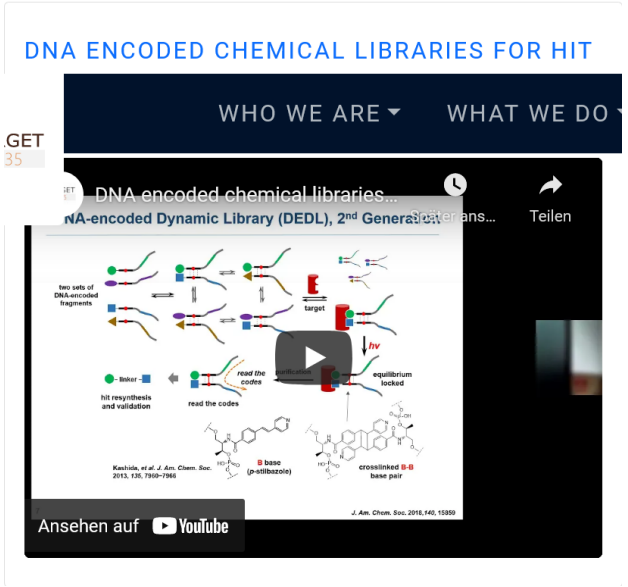

Thank you!