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A blurred background image shows two scientists in a laboratory setting. On the left, a man wearing glasses looks through a microscope. On the right, a woman with dark hair tied back is focused on her work. The background is a soft blue.

Integrated Structural Cheminformatics Analysis Tools for Customisable Chemogenomics Driven Kinase and GPCR Drug Design

Dominique Sydow

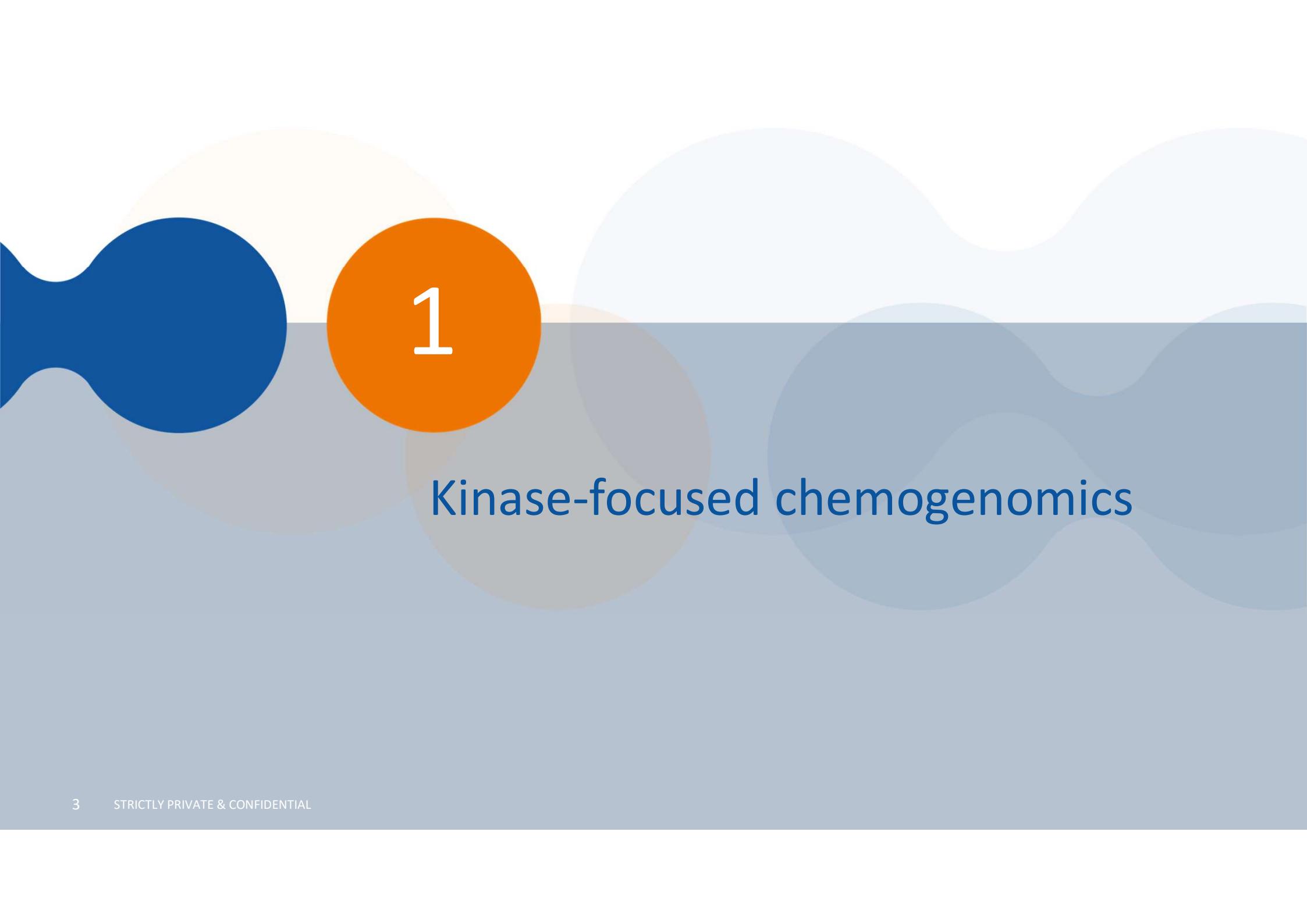
Agenda

1

Kinase-focused chemogenomics
Volkamer Lab, Charité

2

GPCR-focused chemogenomics
Sosei Heptares

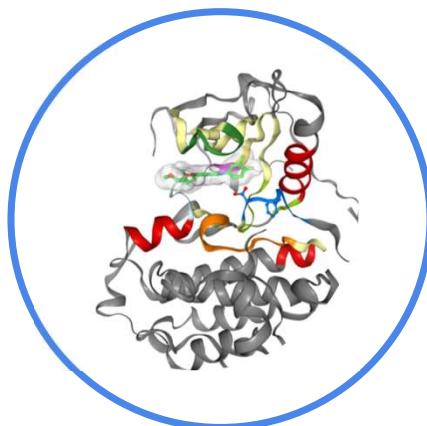


1

Kinase-focused chemogenomics

Challenges in kinase and GPCR research

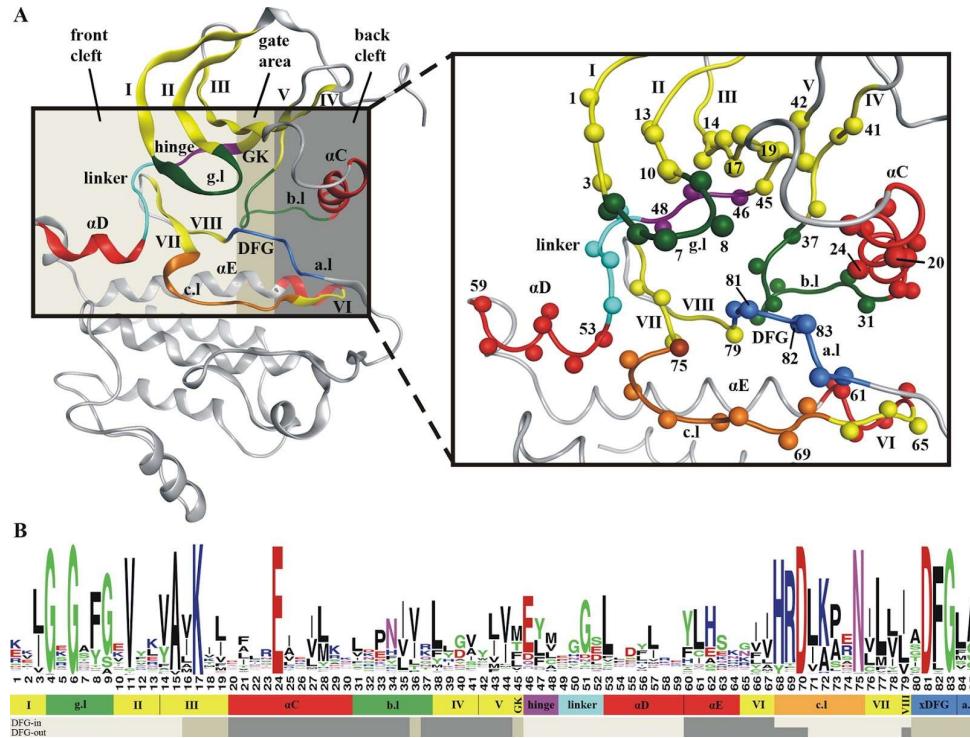
- Kinases as drug targets
 - Kinase-mediated phosphorylation is critical for signal transduction
 - Dysregulation is linked to cancer, inflammation, metabolic, autoimmune, and neurological conditions
- Advantages
 - Well-studied
 - High structural coverage
- Challenges
 - Competition with ATP
 - Selectivity
 - Physicochemical properties
 - Intellectual property



Computational tools

- Kinase data acquisition
- Virtual screening
- Kinome-wide off-target prediction
- Fragment-based drug design

Data: KLIFS binding site annotation!



KiSSim

Kinome-Wide Off-Target Prediction

KiSSim: Kinase Structure Similarity

Pharmacological goal

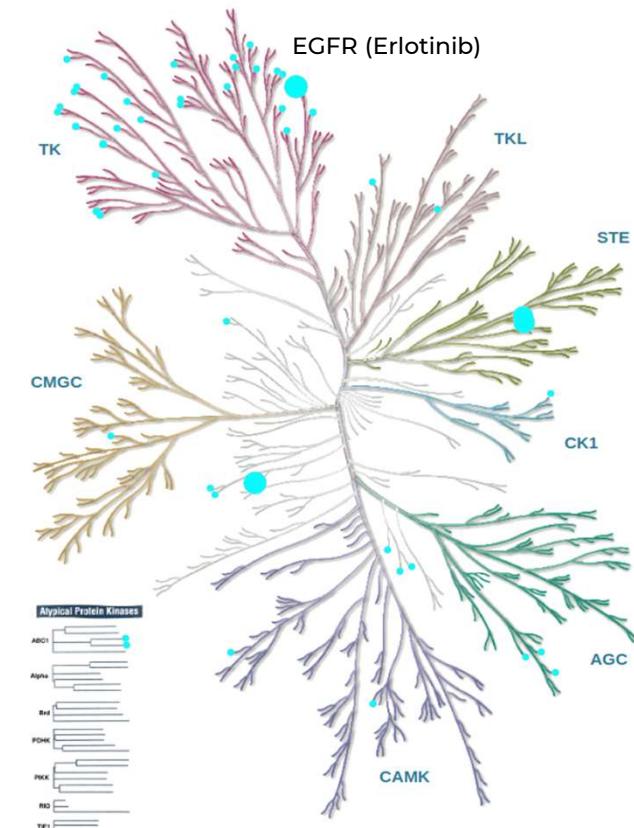
Explain and predict polypharmacology and side effects for kinases.

Technical goal

Explain and predict (dis)similarities in kinase pockets.

Approach

KiSSim: Structure-based kinase (sub)pocket fingerprint

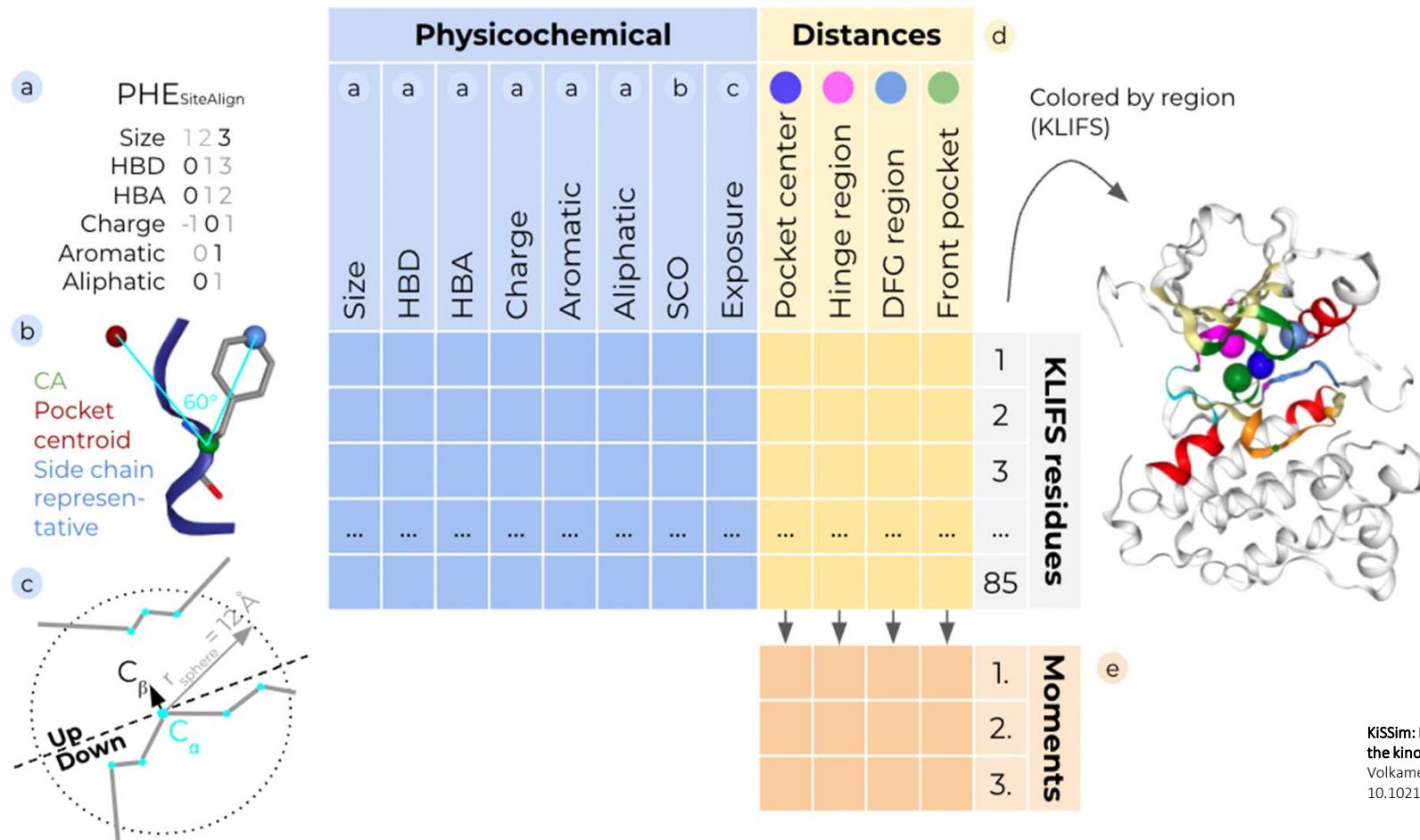


"Illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com)"

KiSSim: Predicting off-targets from structural similarities in the kinaseome. Sydow D, Aßmann E, Kooistra A, Rippmann F, Volkamer A. *J Chem Inf Model* 2022
10.1021/acs.jcim.2c00050

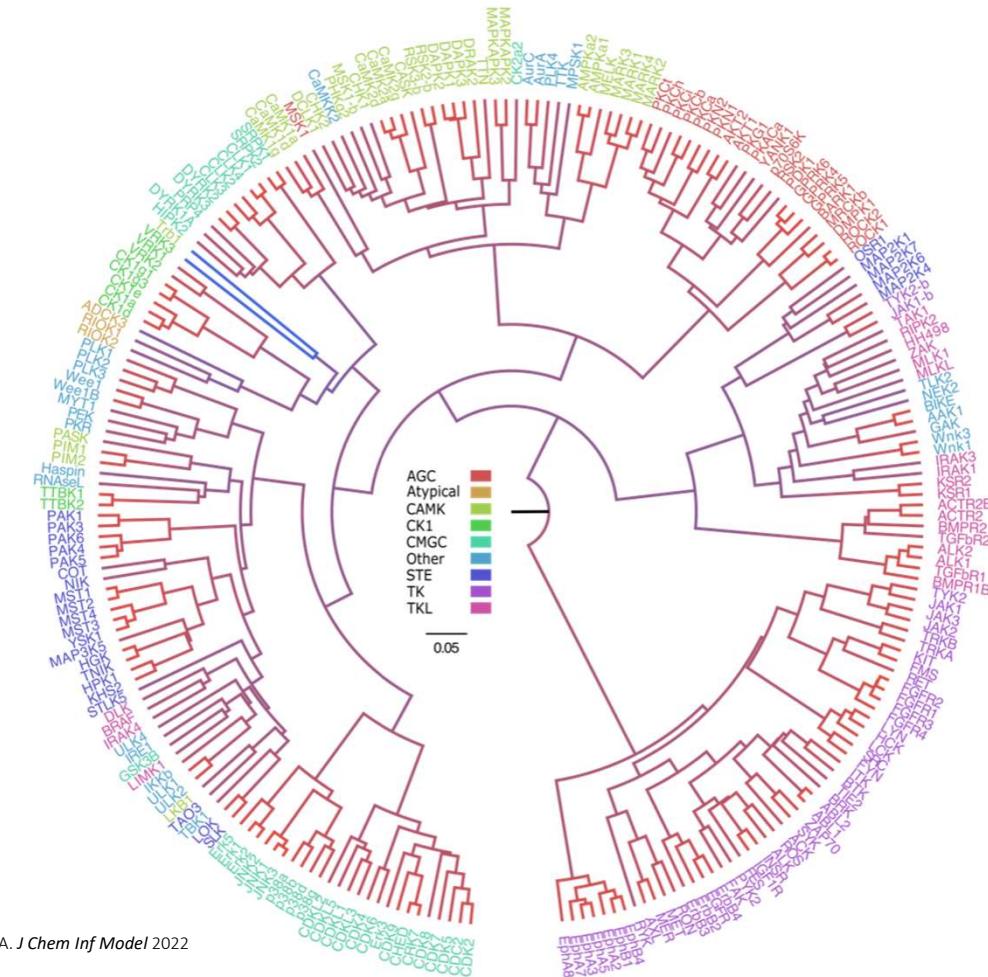
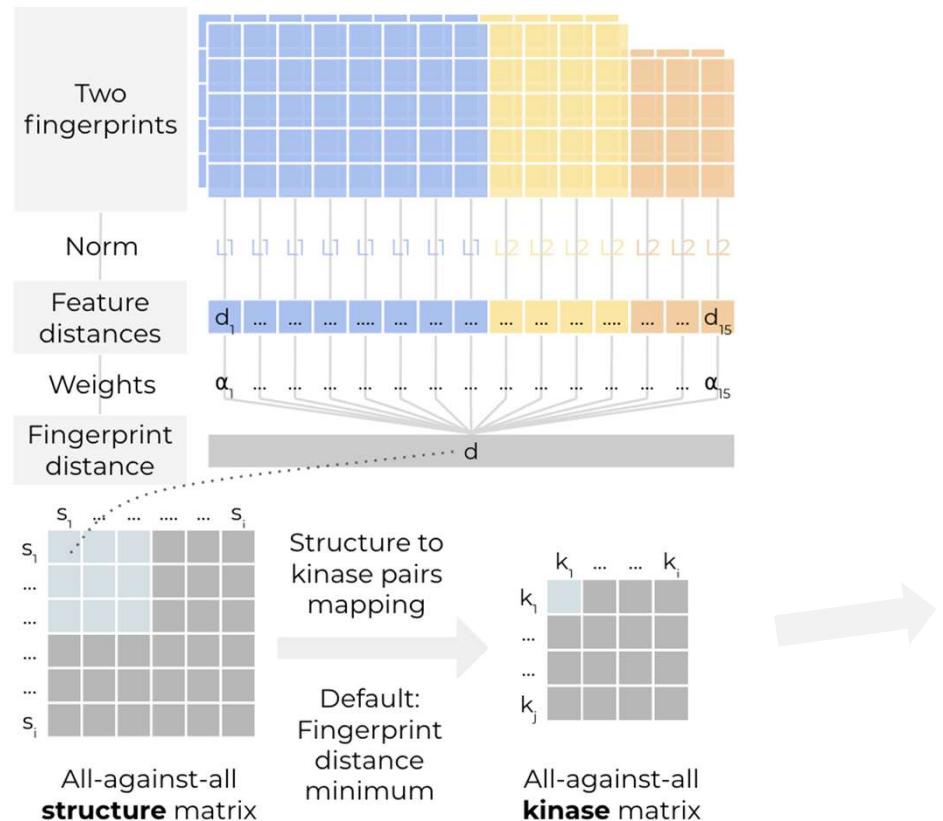
ref

KiSSim: Kinase-focused pocket fingerprint



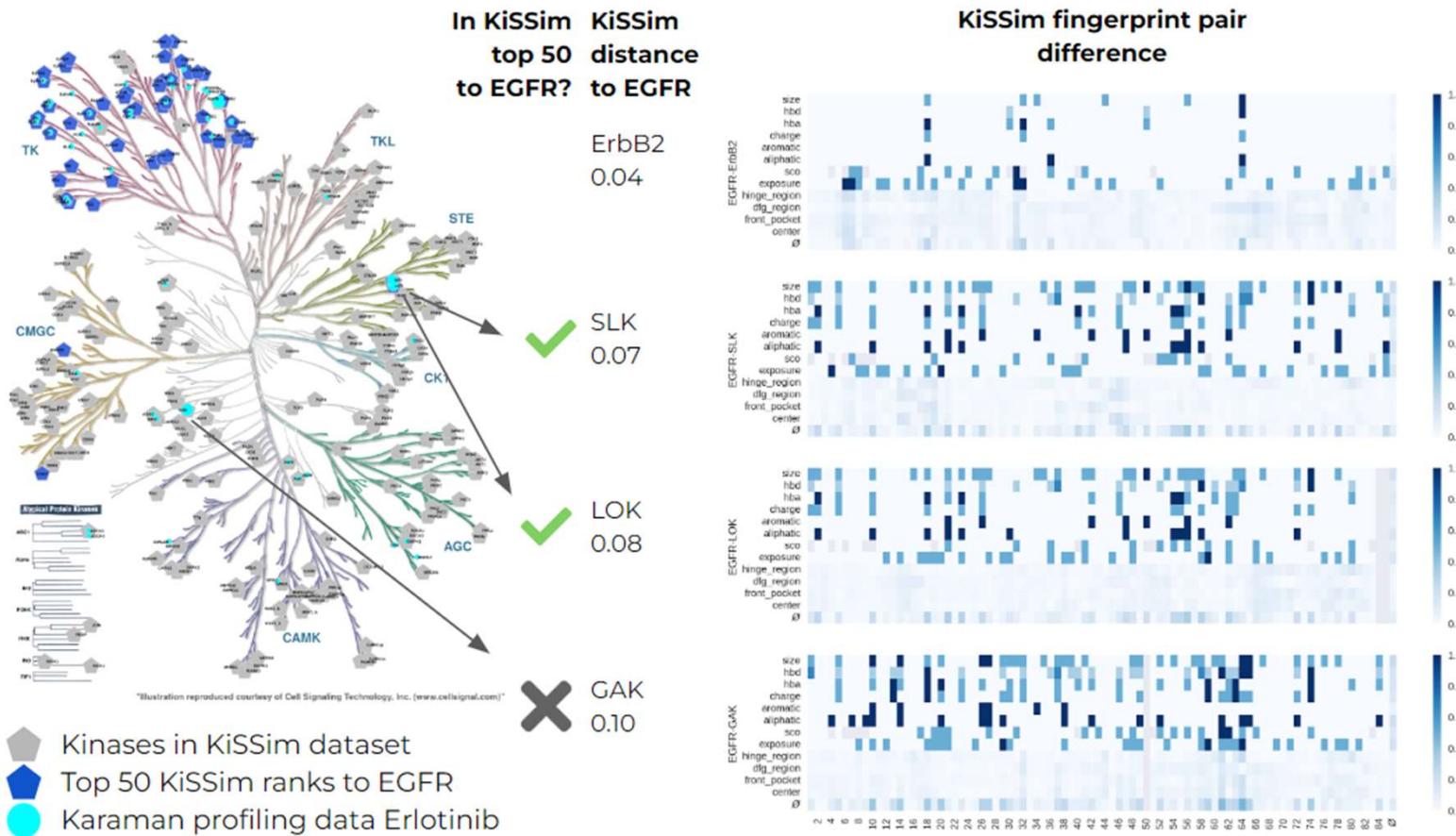
KiSSim: Predicting off-targets from structural similarities in the kinase. Sydow D, Aßmann E, Kooistra A, Rippmann F, Volkamer A. *J Chem Inf Model* 2022
10.1021/acs.jcim.2c00050

KiSSim: All-against-all comparison



KiSSim: Predicting off-targets from structural similarities in the kinome. Sydow D, Aßmann E, Kooistra A, Rippmann F, Volkamer A. *J Chem Inf Model* 2022
10.1021/acs.jcim.2c00050

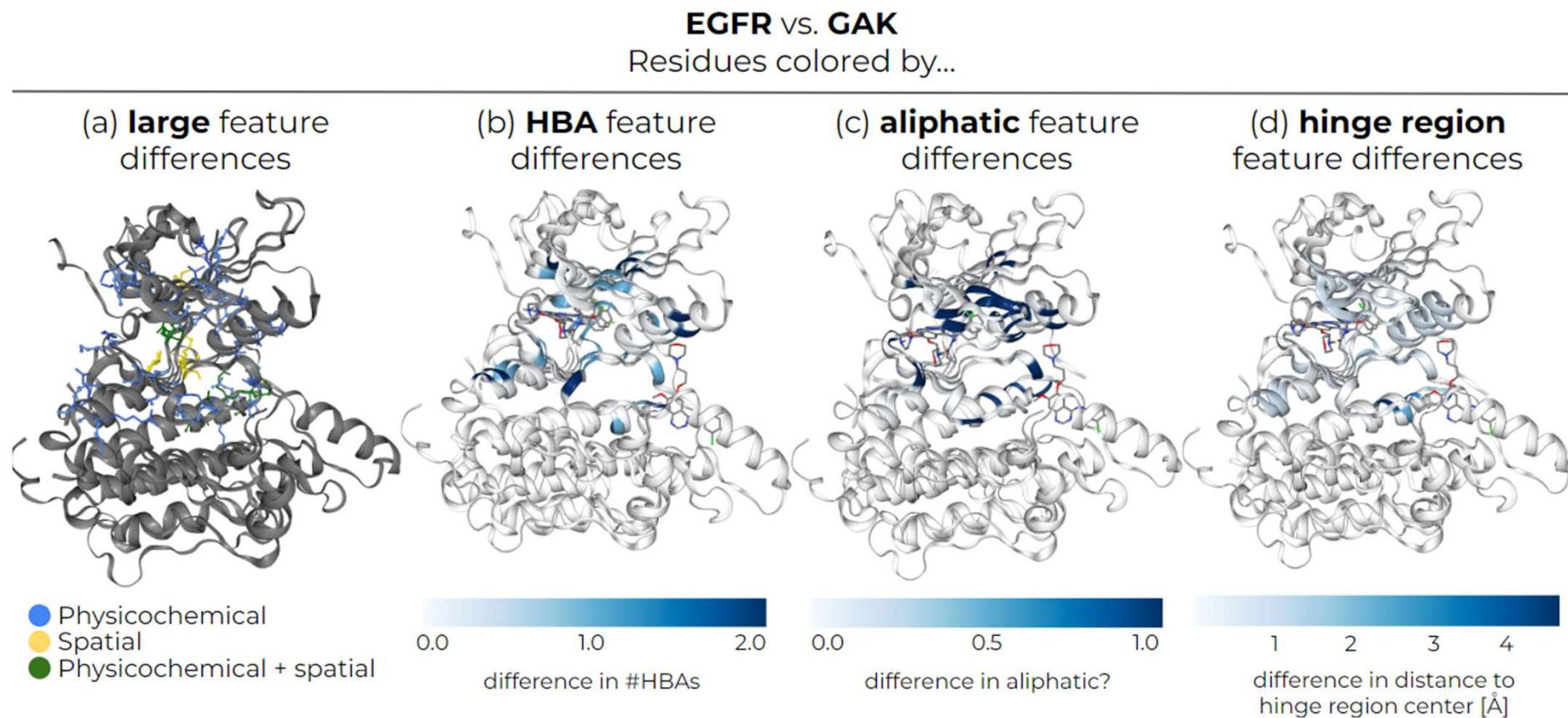
KiSSim: Kinome-wide pocket comparison



KiSSim: Predicting off-targets from structural similarities in the kinase. Sydow D, Aßmann E, Kooistra A, Rippmann F, Volkamer A. *J Chem Inf Model* 2022
10.1021/acs.jcim.2c00050

Eid et al., *BMC Bioinf*
(2017)
Karaman et al
Davis et al.

Visualize fingerprint distances for lead optimization



KISSim: Predicting off-targets from structural similarities in the kinome. Sydow D, Aßmann E, Kooistra A, Rippmann F, Volkamer A. *J Chem Inf Model* 2022
10.1021/acs.jcim.2c00050

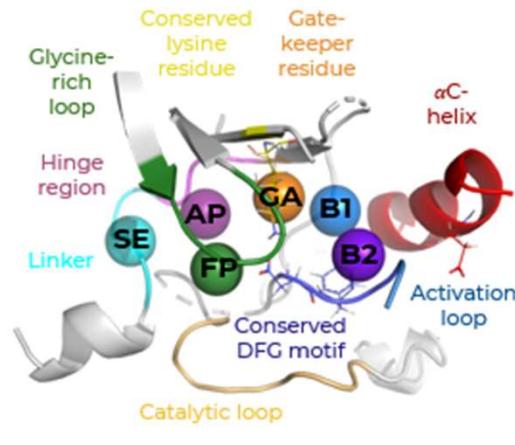
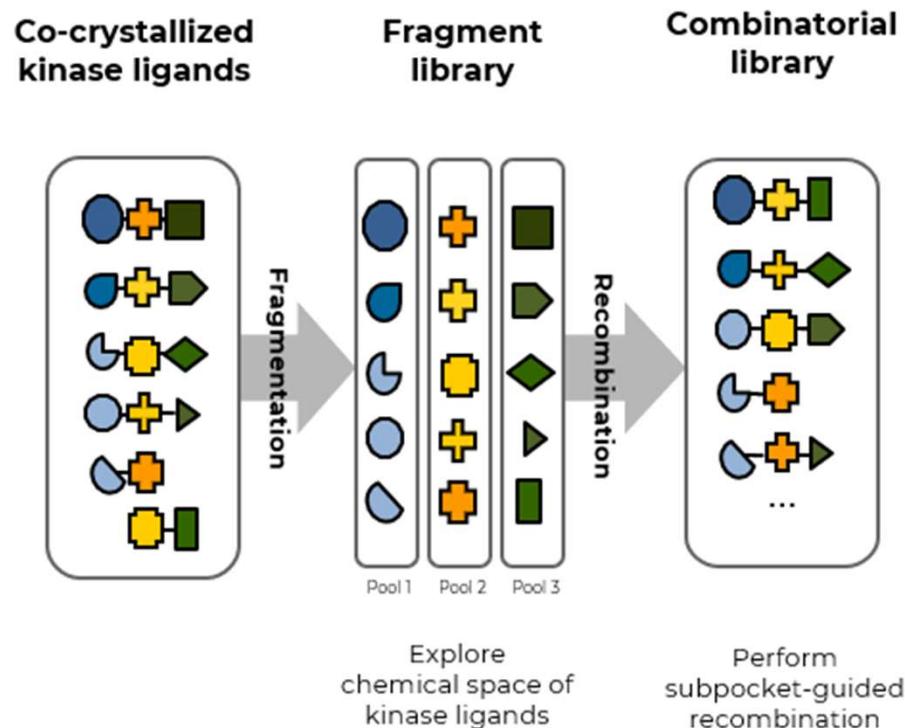
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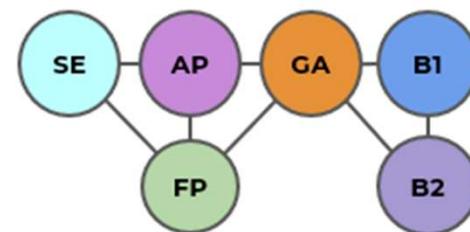
KinFragLib

Fragment-Based Drug Design for Kinases

KinFragLib



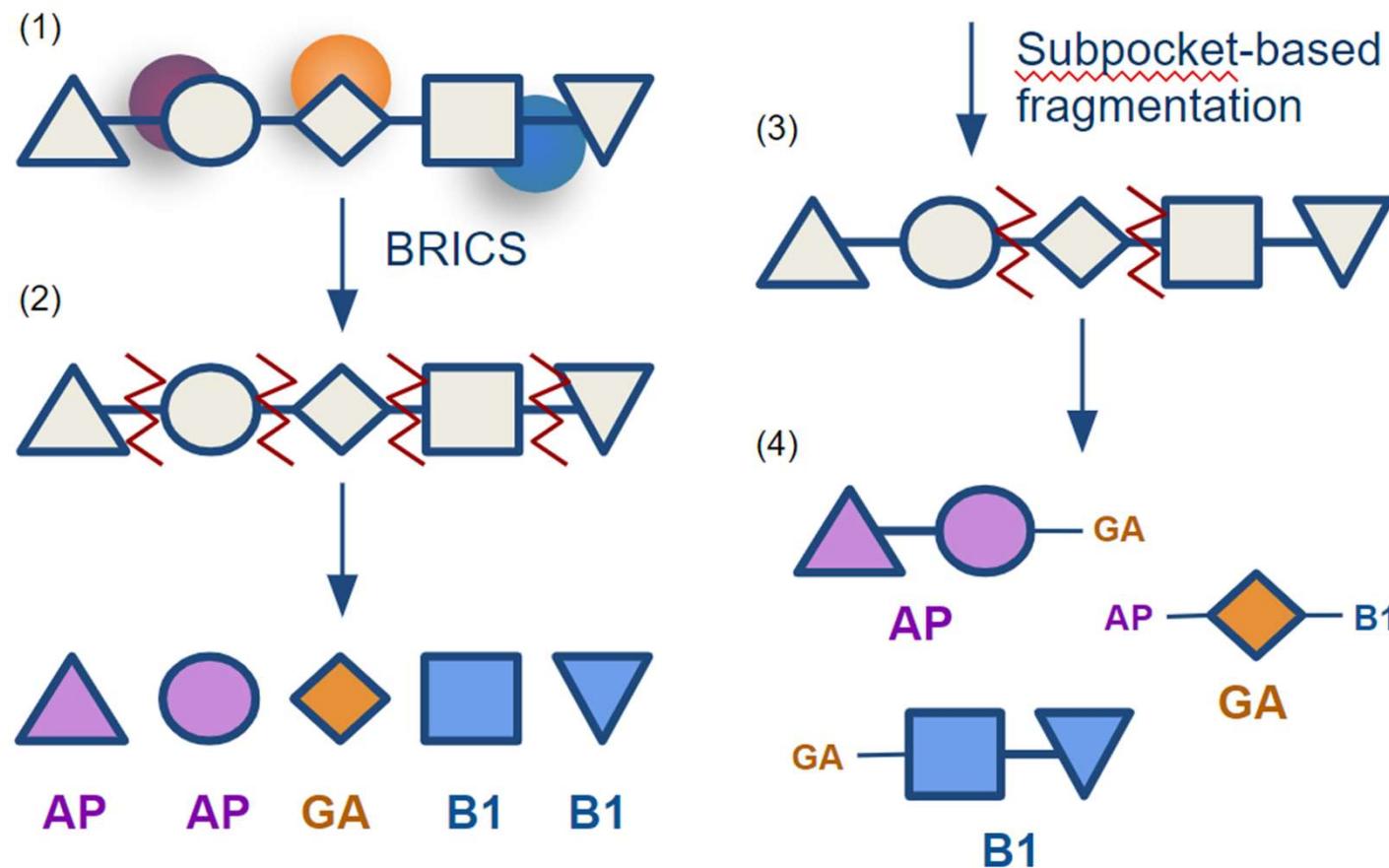
Subpockets and allowed connections



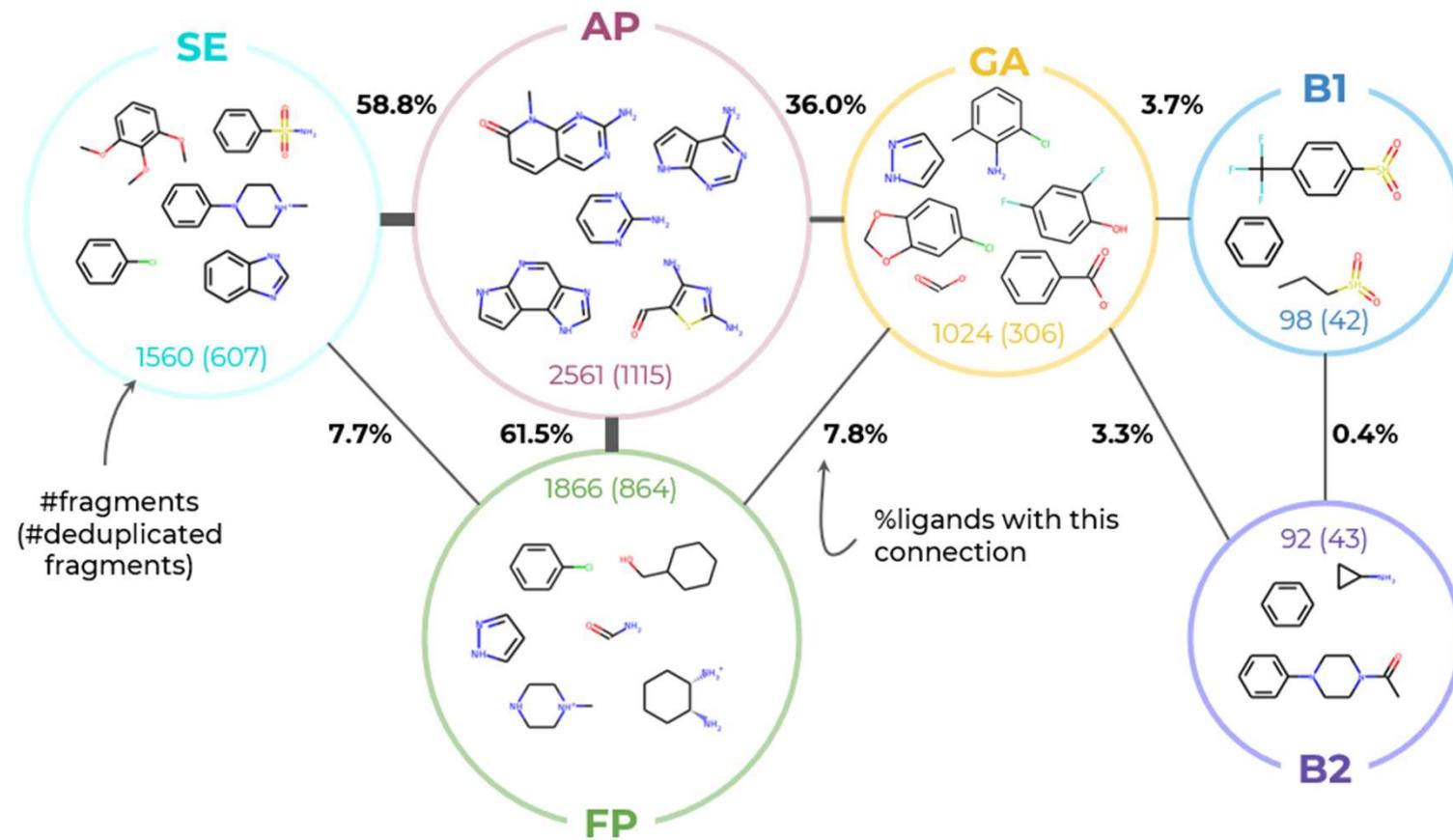
- AP - Adenine pocket
- SE - Solvent exposed pocket
- FP - Front pocket
- GA - Gate area
- B1 - Back pocket 1
- B2 - Back pocket 2

KinFragLib: Exploring the Kinase Inhibitor Space Using Subpocket-Focused Fragmentation and Recombination. Sydow D and Schmiel P, Mortier J, Volkamer A. *J Chem Inf Model* (2020) 10.1021/acs.jcim.0c00839

Subpocket-guided fragmentation of kinase inhibitors



KinFragLib: Zooming into the subpocket pools



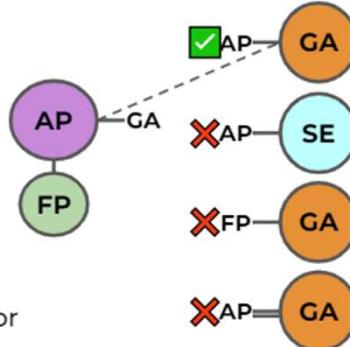
AP - Adenine pocket
 SE - Solvent exposed pocket
 FP - Front pocket
 GA - Gate area
 B1 - Back pocket 1
 B2 - Back pocket 2

KinFragLib: Combinatorial library properties

Enumeration

Enumerate all matching fragment combinations

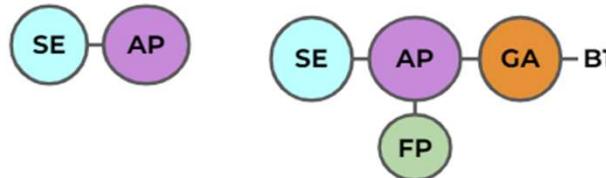
- Always start from AP
- Recombine according to BRICS rules (accounting for synthetically accessibility)



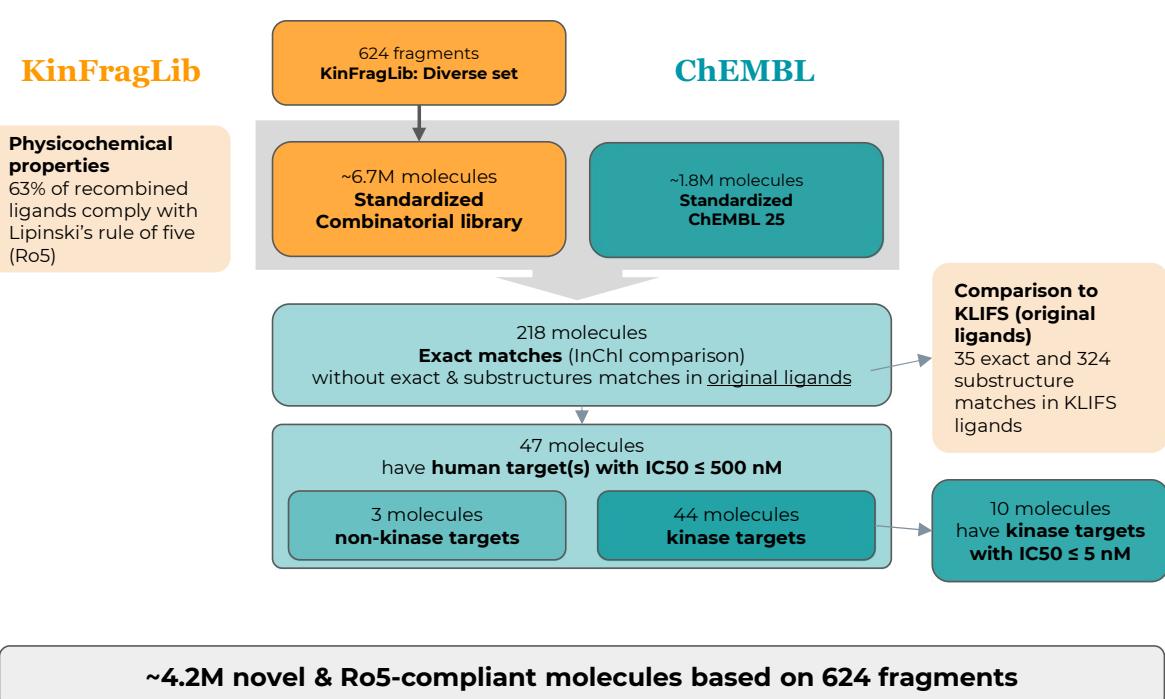
Termination conditions

No open bonds left

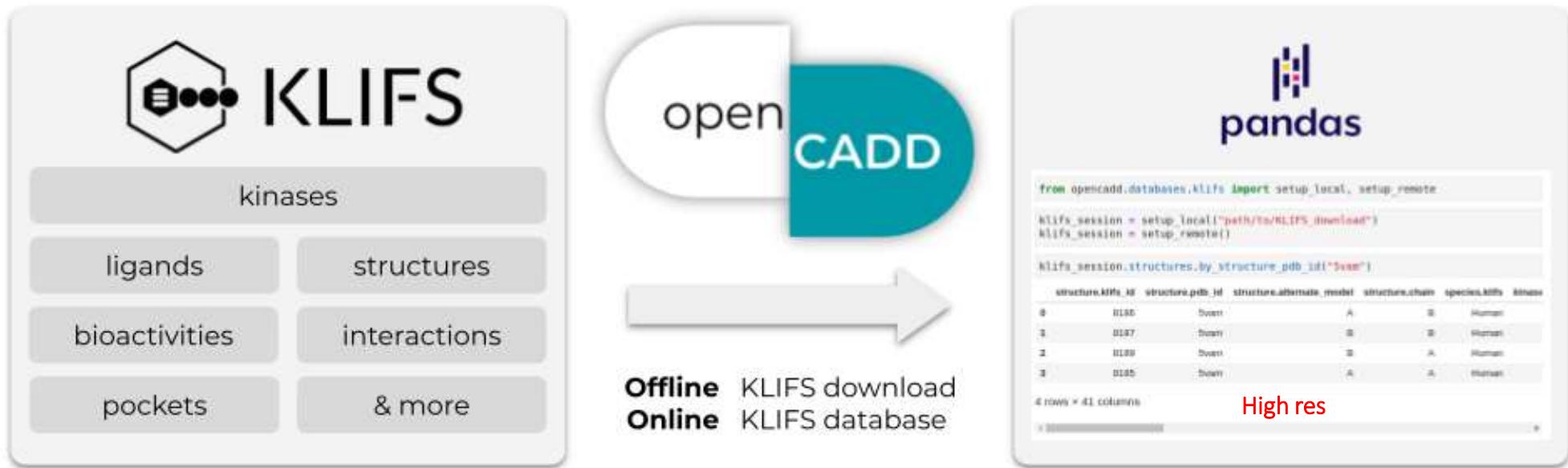
4 fragments combined



KinFragLib: Exploring the Kinase Inhibitor Space Using Subpocket-Focused Fragmentation and Recombination. Sydow D and Schmiel P, Mortier J, Volkamer A. *J Chem Inf Model* (2020)
10.1021/acs.jcim.0c00839



OpenCADD-KLIFS



	kinases	ligands	structures	bioactivities	interactions	pockets
by_kinase_klifs_id	x	x	x	x	x	
by_kinase_name	x	x	x			
by_ligand_klifs_id		x	x	x	x	
by_ligand_expo_id	x	x	x			
by_structure_klifs_id		x		x	x	
by_structure_pdb_id		x				

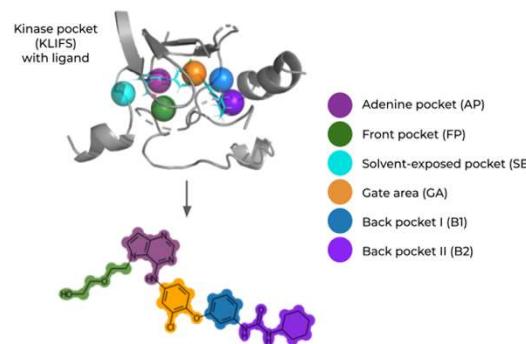
<https://github.com/volkamerlab/opencadd>

OpenCADD-KLIFS: A Python package to fetch kinase data from the KLIFS database. Sydow D, Rodríguez-Guerra J, Volkamer A. *J Open Source Softw* (2022) <https://doi.org/10.21105/joss.03951>

Open-source analysis tools for the kinome

KinFragLib

Kinase-focused inhibitor fragmentation and recombination

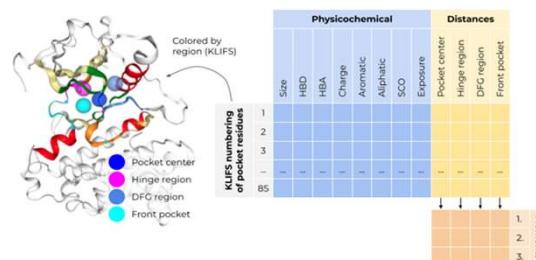


🔗 <https://github.com/volkamerlab/kinfraglib>

KinFragLib: Exploring the Kinase Inhibitor Space Using Subpocket-Focused Fragmentation and Recombination. Sydow D and Schmiel P, Mortier J, Volkamer A. *J Chem Inf Model* (2020) 10.1021/acs.jcim.0c00839

KiSSim

Kinome-wide pocket comparison

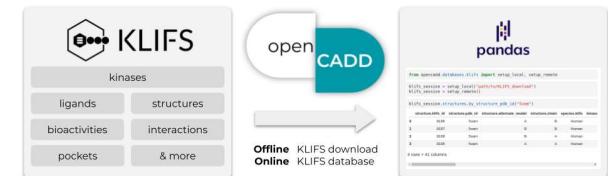


🔗 <https://github.com/volkamerlab/kissim>

KiSSim: Predicting off-targets from structural similarities in the kinome. Sydow D, Alßmann E, Kooistra A, Rippmann F, Volkamer A. *J Chem Inf Model* 2022 10.1021/acs.jcim.2c00050

OpenCADD-KLIFS

KLIFS Python client



🔗 <https://github.com/volkamerlab/opencadd>

OpenCADD-KLIFS: A Python package to fetch kinase data from the KLIFS database. Sydow D, Rodríguez-Guerra J, Volkamer A. *J Open Source Softw* (2022) 10.21105/joss.03951

TeachOpenCADD

Workflows for Structural Cheminformatics Using Open Source Packages
and Data

TeachOpenCADD

Workflows for Structural Cheminformatics Using Open Source Packages and Data

- Stack of 28 introductory lessons for central cheminformatics and structural bioinformatics topics
 - Database queries
 - Chemical properties, compound similarity, virtual screening
 - Docking, molecular dynamics simulations, ...
- Conceived as “from students for students”
- Starting material to solve diverse research questions
- Each lesson is comprised of a Jupyter Notebook
 - Theory + code in a single executable document
- Availability
 - GitHub: <https://github.com/volkamerlab/TeachOpenCADD>
 - Website: <https://projects.volkamerlab.org/teachopencadd>

T002 - Molecular filtering: ADME and lead-likeness criteria

1

Aim of this talktorial

In the context of drug design, it is important to filter candidate molecules by e.g. their physicochemical properties. In this talktorial, the compounds acquired from ChEMBL (Talktorial 001) will be filtered by Lipinski's rule of five to keep only orally bioavailable compounds.

2

Content in Theory

- ADME - absorption, distribution, metabolism, and excretion
- Lead-likeness and Lipinski's rule of five (Rule)
- Radar charts in the context of lead-likeness

Content in Practical

- Define and visualize example molecules
- Calculate and plot molecular properties for Rule
- Investigate compliance with Rule
- Visualize Rule properties radar plots

References

- ADME criteria ([ChEMBL and JChemPhe](#), [PubChem](#), [RDF](#), [SDF](#), [JSON](#))
- What is a Rule? ([lipinski](#))
- What is the LogP value? ([lipinski](#))
- Lead-likeness ([leadlikeness](#))
- Lead-likeness and computational approaches to estimate solubility and permeability in drug discovery and development settings. ([Drug Dev. Res.](#), [1997, 33, 3-20](#))
- Peltier et al., "Computational representations of ADME-related molecule properties for medicinal chemists" ([Drug Discov. Today](#), [2021, 16, 55-72](#))

3

Talktorial sections

1. Aim, content & references
2. Theory
3. Practical
4. Discussion
5. Quiz

In [16]:

```
molecules["molecular_weight"] = molecules["ROMol"].apply(Descriptors.ExactMolWt)
molecules["n_hba"] = molecules["ROMol"].apply(Descriptors.NumHAcceptors)
molecules["n_hbd"] = molecules["ROMol"].apply(Descriptors.NumHDonors)
molecules["logP"] = molecules["ROMol"].apply(Descriptors.MolLogP)

# Colors are used for plotting the molecules later
# Rule.CHECK_OUTPUT
# Rule.CHECK_OUTPUT(["red", "green", "blue", "cyan"])

molecules[["molecular_weight", "n_hba", "n_hbd", "logP"]]
```

Out[16]:

	molecular_weight	n_hba	n_hbd	logP
0	1201.841368	12	5	3.26900
1	306.184447	4	1	1.68462
2	536.438202	0	0	12.05050
3	314.224580	2	2	5.84650

In [8]:

```
# full preview
molecules
```

Out[8]:

name	smiles	ROMol	molecular_weight	n_hba	n_hbd	logP
0	cyclosporine	<chem>CC1(C(=O)N(CC(=O)N(C(C(=O)N(C=C)C(=O)N2C=C(C=C2)C=C3C=C(C=C3)C=C4C=C(C=C4)C=C5C=C(C=C5)C=C6C=C(C=C6)C=C7C=C(C=C7)C=C8C=C(C=C8)C=C9C=C(C=C9)C=C1)O)C=C1)C=C1</chem>	1201.841368	12	5	3.26900
1	diazepam	<chem>CN1CCON(C1)C2=C3C=C2C=C3N=NC4=CC=C(C=C4)C=C5C=C(C=C5)C=C6C=C(C=C6)C=C7C=C(C=C7)C=C8C=C(C=C8)C=C9C=C(C=C9)C=C1</chem>	306.184447	4	1	1.68462
2	beta-carotene	<chem>CC1=C(C(CCC1)(C)C)C=C2C=C(C=C2)C=C3C=C(C=C3)C=C4C=C(C=C4)C=C5C=C(C=C5)C=C6C=C(C=C6)C=C7C=C(C=C7)C=C8C=C(C=C8)C=C9C=C(C=C9)C=C1</chem>	536.438202	0	0	12.05050
3	cannabinol	<chem>C1CCCC1C=C2C=C(C=C2)C=C3C=C(C=C3)C=C4C=C(C=C4)C=C5C=C(C=C5)C=C6C=C(C=C6)C=C7C=C(C=C7)C=C8C=C(C=C8)C=C9C=C(C=C9)C=C1</chem>	314.224580	2	2	5.84650

4

Discussion

In this talktorial, we have learned about Lipinski's Rule as a measure to estimate a compound's oral availability and we have applied the rule on a dataset using rdkit. Note that drugs can also be administered via alternative routes, i.e. inhalation, skin penetration and injection.

In this talktorial, we have looked at only one of many more ADME properties. Web servers such as [Salts3D](#) give a more comprehensive view on compound properties.

5

Quiz

- In what way can the chemical properties described by the Rule affect ADME?
- Find or design a molecule which violates three or four rules.
- How can you plot information for an additional molecule in the radar charts that we have created in this talktorial?

Explanatory text
Executable code
Code output

All-in-one Jupyter Notebook

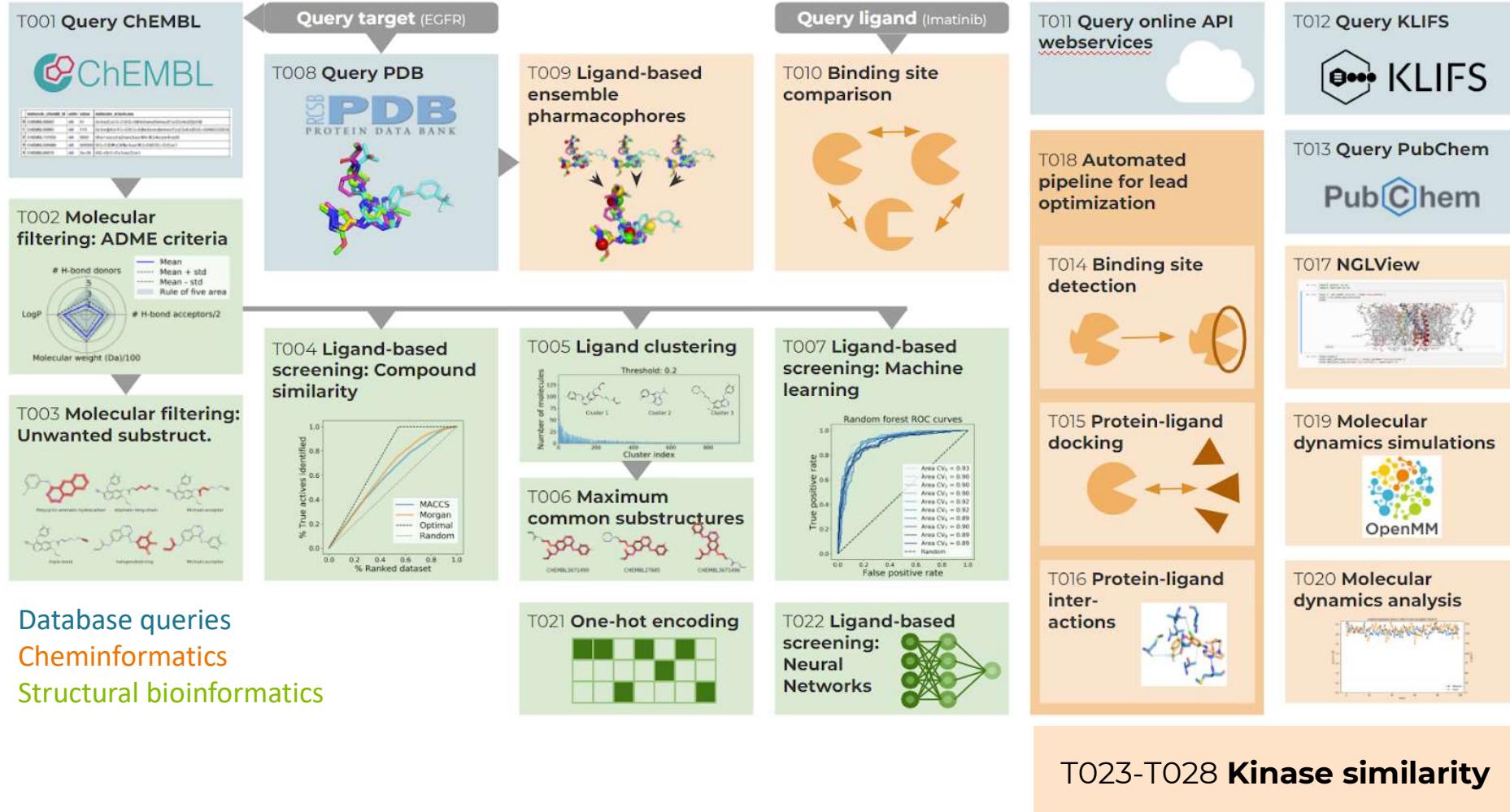
TeachOpenCADD: a teaching platform for computer-aided drug design using open source packages and data. Sydow D, Morger AL, Driller M, Volkamer A. *J Cheminf* (2019) 10:1186/s13321-019-0351-x

TeachOpenCADD-KNIME: A Teaching Platform for Computer-Aided Drug Design Using KNIME Workflows. Sydow D and Wichmann M, Rodríguez-Guerra J, Goldmann D, Landrum G, Volkamer A. *J Chem Inf Model* (2019) 10:1021/acs.jcim.9b00662

Teaching Computer-Aided Drug Design Using TeachOpenCADD. Sydow D, Rodríguez-Guerra J, Volkamer A. *Teaching Programming Across the Chemistry Curriculum ACS* (2021) 10:1021/bk-2021-1387.ch010

TeachOpenCADD 2021: Open Source and FAIR Python Pipelines to Assist in Structural Bioinformatics and Cheminformatics Research. Sydow D and Rodríguez-Guerra J, Kimber T, Schaller D, Taylor C, Chen Y, Leja M, Misra S, Wichmann M, Ariamajd A, Volkamer A. *NAR* (2022) 10:1093/nar/gkac267

TeachOpenCADD - Version 2021.12.1

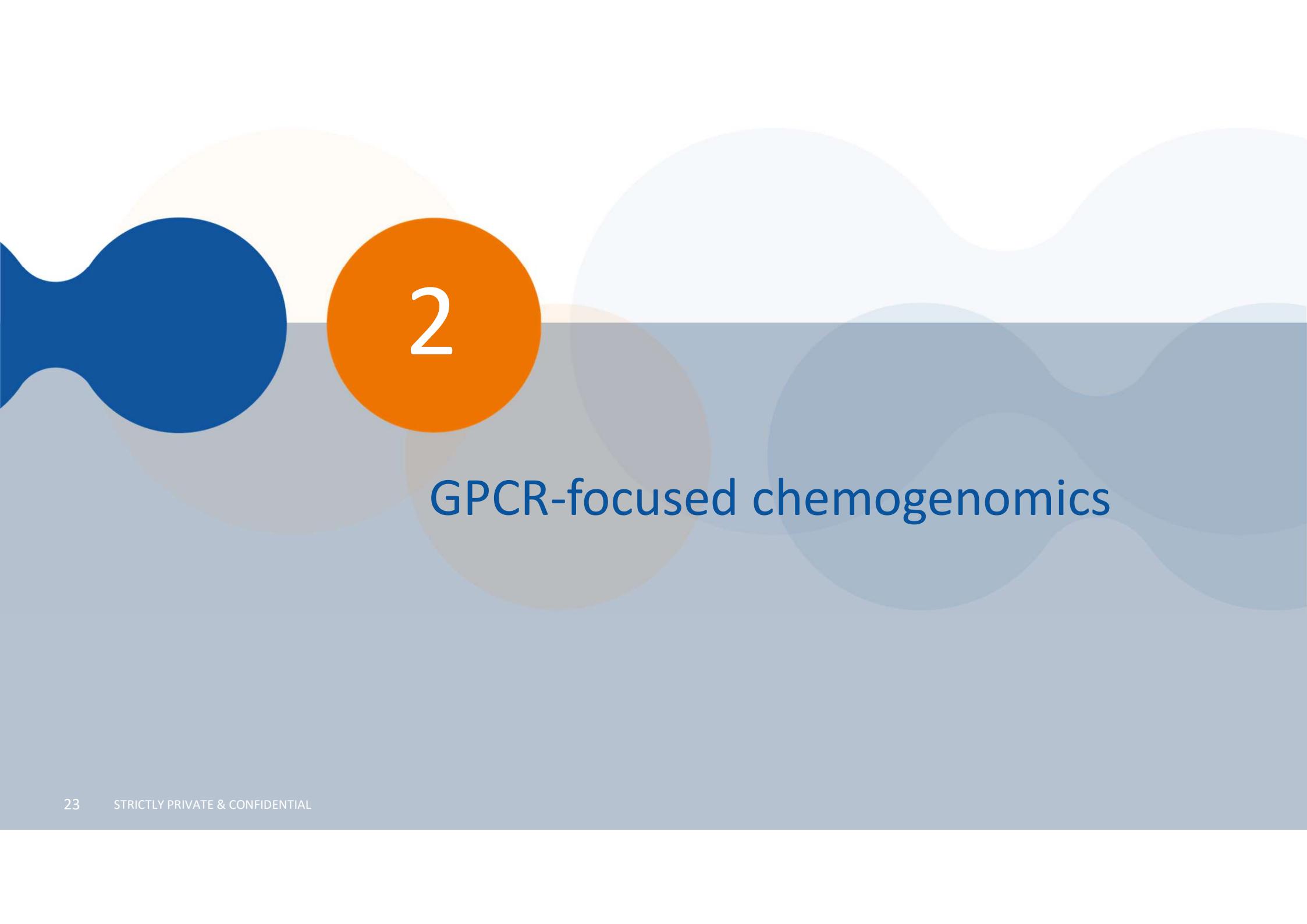


TeachOpenCADD for KNIME



TeachOpenCADD-KNIME: A Teaching Platform for Computer-Aided Drug Design Using KNIME Workflows. Sydow D and Wichmann M, Rodríguez-Guerra J, Goldmann D, Landrum G, Volkamer A. *J Chem Inf Model* (2019) 10.1021/acs.jcim.9b00662

- Subset of TeachOpenCADD topics is available as KNIME workflows
 - Cheminformatics topics T001 – T009 → W1-9
 - Available on the KNIME Hub
 - <https://hub.knime.com/volkamerlab/spaces/Public/latest/TeachOpenCADD/TeachOpenCADD>
 - Last update May 2022
 - Workflow fragments can be used as templates for your own applications
 - E.g. use our Brenk/PAINS workflow (W3) as a template to filter your dataset based on user-defined SMARTS patterns



2

GPCR-focused chemogenomics

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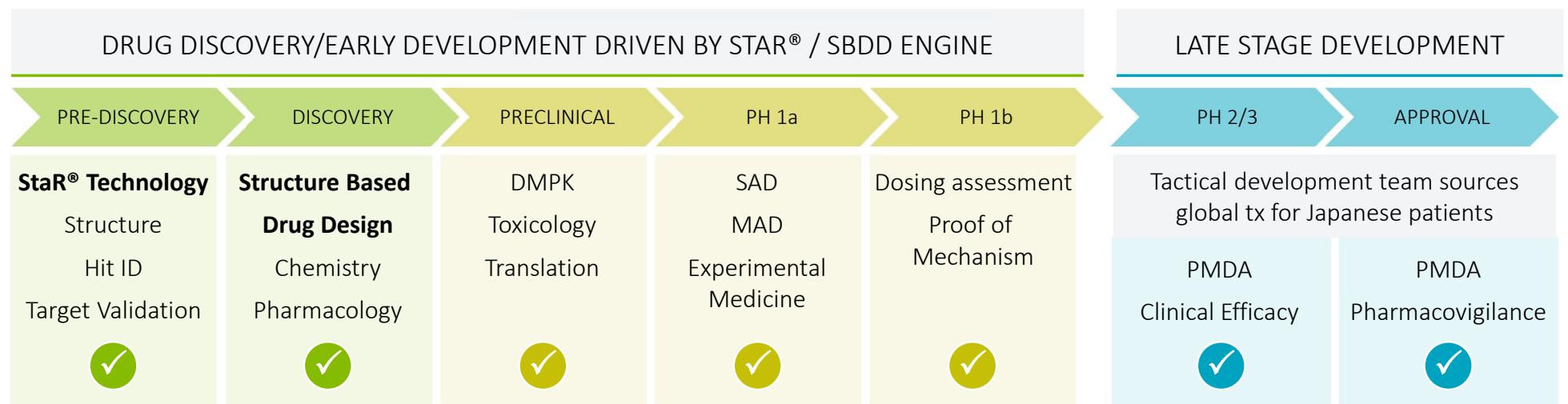
Sosei Heptares GPCR Structure-Based Drug Discovery Company

R&D CENTRE OF EXCELLENCE
CAMBRIDGE, UK (Heptares)

~170 EMPLOYEES

HEADQUARTERS
TOKYO, JAPAN (Sosei K.K.)

~25 EMPLOYEES

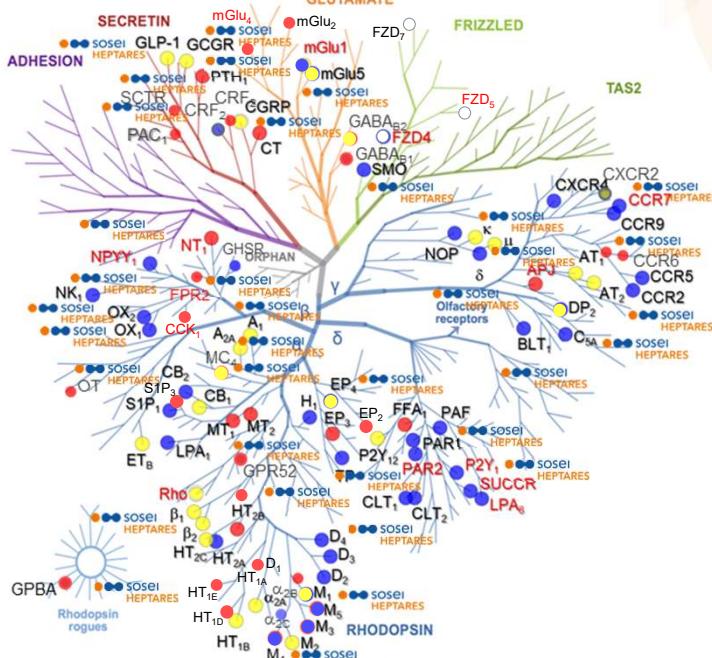


<https://soseiheptares.com>

Exciting Era of GPCR Structure-Based Drug Design

GPCR structures

- PDB: 374 unique GPCR-ligand complexes, 119 GPCRs
 - Sosei Heptares: 354 GPCR structures, 42 GPCRs, 70+ StaRs



- agonist
- antagonist
- agonist and antagonist without approved drug/ligand in clinical development

Congreve, de Graaf, Swain, Tate (2020) *Cell* 181: 81

GPCR Tree Mapper [AJ Kooistra, C de Graaf]

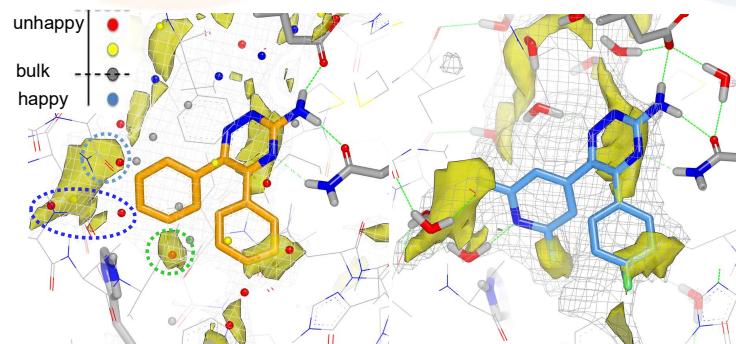
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© Sosei Heptares

SBDD to improve GPCR drug quality

- **Atom by atom optimisation** -Target **lipophilic hotspots** & displace energetically unfavorable water molecules
 - **Balance lipophilicity**– Design & stabilise polar (water-mediated) receptor-ligand interaction networks
 - **Optimise selectivity** - Address receptor flexibility & receptor selectivity using multiple structures

A_{2A} hit docked with predicted water energetics (apo)



- Unhappy waters displaced by methyl / Cl of HTL1071 in A_{2A}, but trapped in larger A₁ subpocket
 - Unhappy apo waters stabilised by pyridine N of HTL1071

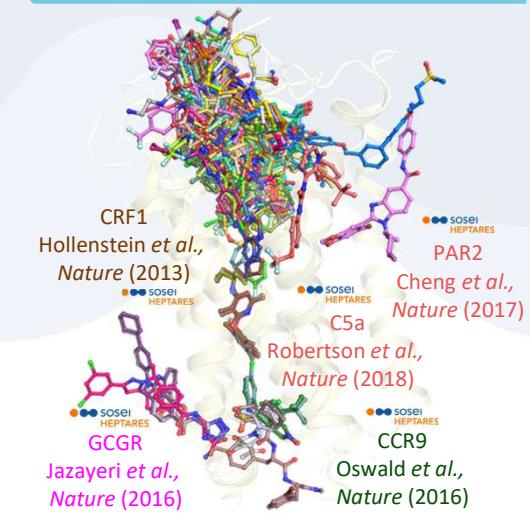
HTL1071/AZD4635: Phase 2 clinical trial for patients with metastatic castration resistant prostate cancer [NCT04089553]

Congreve et al. (2012) J Med Chem 55: 1898

Mason et al. (2012) *TiPS* 33: 249

Borodovsky et al. (2020) J Immunther Cancer 8: e000417

GPCR binding mode diversity



Combination of **public** &
Sosei Heptares **proprietary**
GPCR SBDD data

ML / AI augmented
GPCR SBDD

De Graaf et al. (2018) *Tr Pharmacol Sci* 39: 494
Congreve (2017) *Tr Pharmacol Sci* 38: 837



The Stabilised Receptor (StaR[®]) is at the core of our SBDD platform



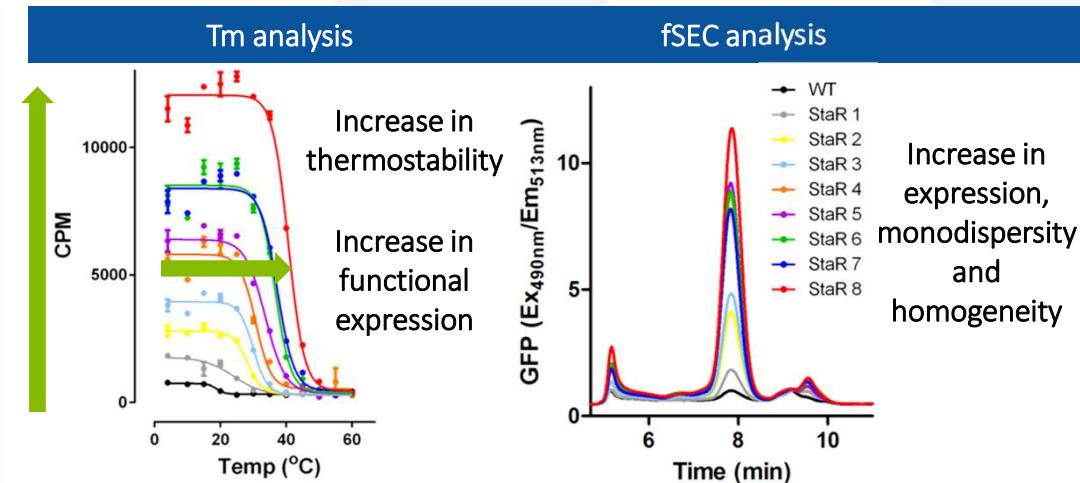
- **GPCR drug discovery remains challenging**

Low expression levels and difficult purification – Step-wise stabilisation by point mutations lead to increased thermostability thus maintaining structural integrity outside the membrane

Heterogeneity – receptor is trapped in a relevant conformation to match the drug product profile

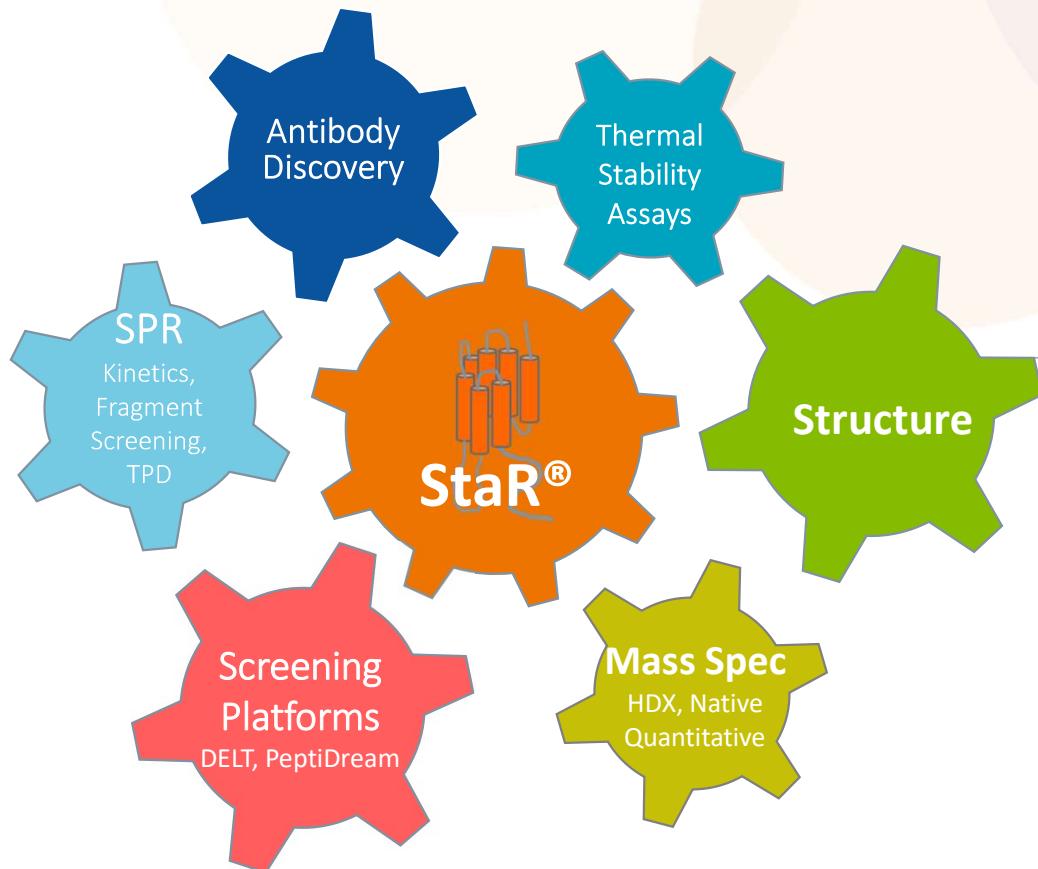
Stabilised receptor (StaR[®]) can be extracted from the membrane, purified and function retained

70+ Stabilised Receptors generated in agonist and/or antagonist conformations

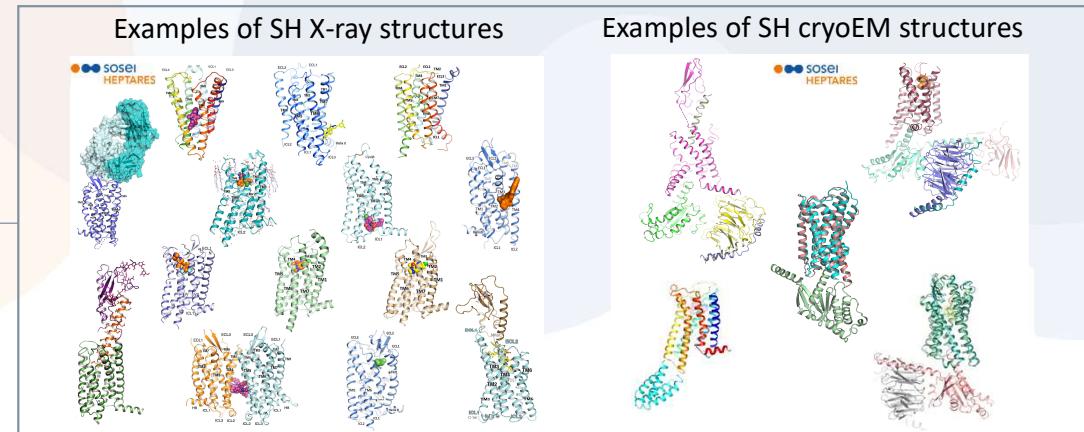


Flexibility to ‘harvest’ StaRs for downstream application e.g. HTS, SPR, antigen, cryo-EM, X-ray

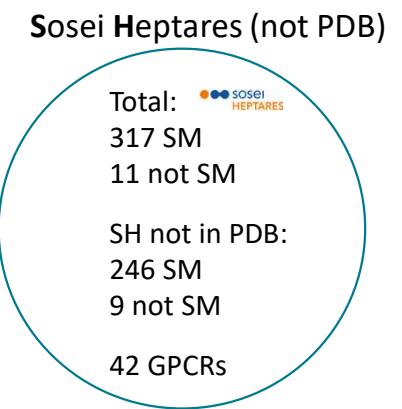
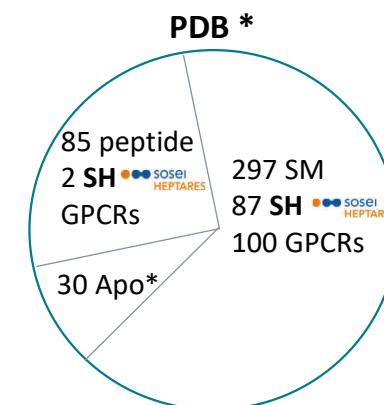
StaR® Technology driving GPCR Drug Discovery



Multiple methods to determine GPCR structures using StaRs

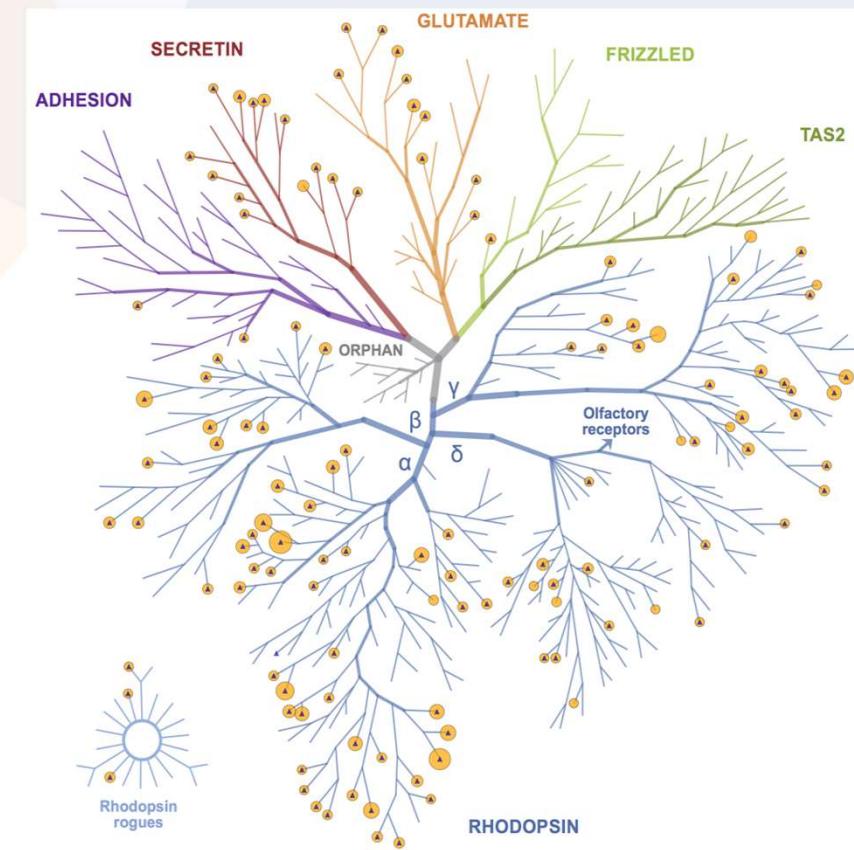


StaRs double the amount of GPCR structures for SBDD at SH



Chemical space of GPCR ligands

- Use chemical similarities between known ligands and experimentally resolved GPCR-bound ligands to...
 - Derive binding modes of known ligands from structure-bound ligands for a specific receptor
 - Derive interactions for a specific receptor from resolved GPCR structures
 - Transfer interactions of a specific receptor to other receptors
- Use chemical similarities between known ligands of different receptors to...
 - Predict cross-GPCR polypharmacology and cross-GPCR subfamily polypharmacology

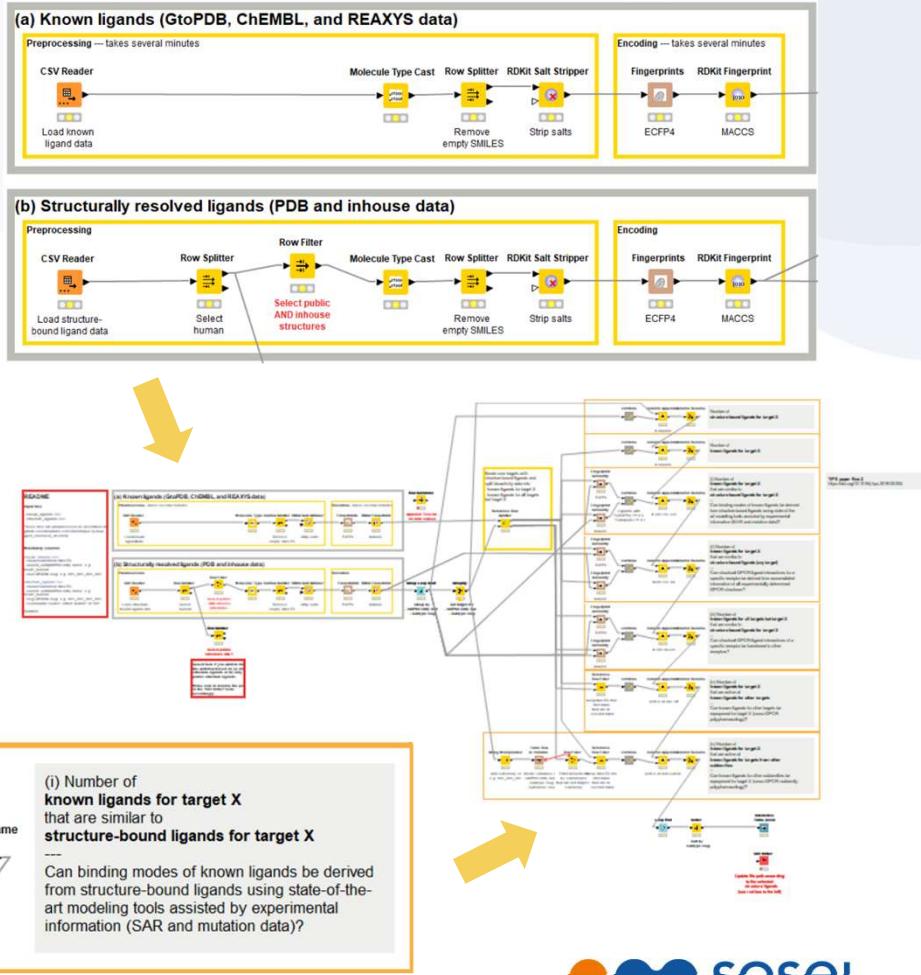


- Number of known ligands per receptor
- ▲ Structure-bound ligands available

Chemical Diversity in the G Protein-Coupled Receptor Superfamily, Vass et al., TiPS (2018)

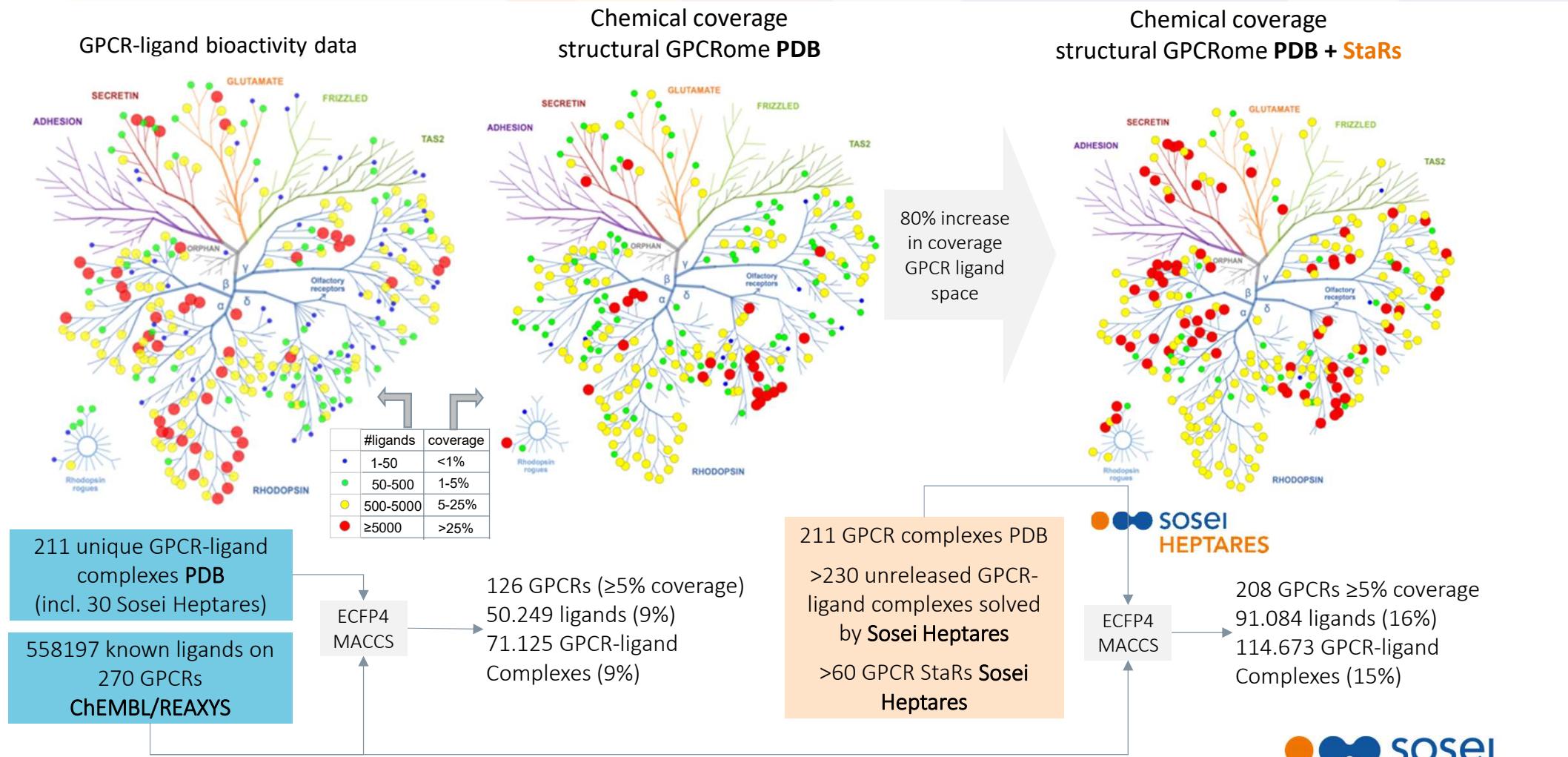
KNIME-based chemogenomics workflows

- Collect public and inhouse experimentally resolved GPCR-ligand structures (X-ray and cryo-EM)
 - Semi-automated process of fetching structural information from the GPCRdb and PDB + manual curation of ligand SMILES
 - Semi-automated binding site annotation of structure-bound ligands
 - Manual curation of structure-bound ligands
- Collect known ligands
 - Merge bioactivity data from different databases such as ChEMBL and REAXYS
 - Unique SMILES per receptor



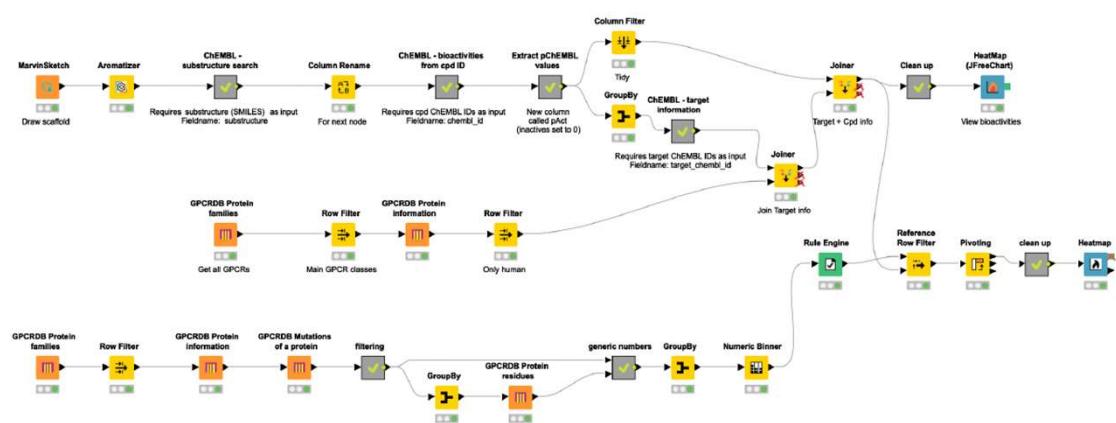
Chemical Diversity in the G Protein-Coupled Receptor Superfamily, Vass et al.,
TiPS (2018)

Bioactive Chemical Space of the Structural GPCRome with StaRs



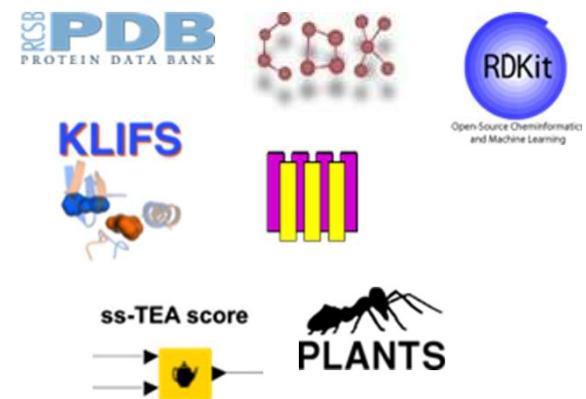
More Structural Cheminformatics KNIME workflows in the 3D-e-Chem Ecosystem

- Structural coverage of chemical GPCR ligand space
- Structure-based GPCR mutation data mapping
- Sequence-based GPCR binding site prediction ligand repurposing
- Structural interaction-based ligand scaffold hopping
- Structure-based kinase-GPCR ligand repurposing



Vass et al. *Tr Pharm Sci* 2018 – 10.1016/j.tips.2018.02.004
Kooistra et al. *ChemMedChem*, 2018 – 10.1002/cmdc.201700754
McGuire et al. *J Chem Info Model* 2017 - 10.1021/acs.jcim.6b00686
Kanev et al. *NAR*, 2021 – 10.1093/nar/gkaa895

<https://github.com/3D-e-Chem/workflows>



Join the Sosei Heptares GPCR SBDD Team

Current advertised positions across the company:

<https://www.soseiheptares.com/global-jobs-portal>

We are continuously looking for skilled researchers in: Protein Engineering, Biochemistry, Biophysics, Structure, Pharmacology, **Computational Chemistry**, Research Informatics, Medicinal Chemistry, Translational Sciences, Development.

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More Sosei Heptares presentations at the ICCS

Talk by **Morgan Thomas** (Thu)

Augmented Hill-Climb improves language-based de novo molecule generation as benchmarked via the open source MolScore platform

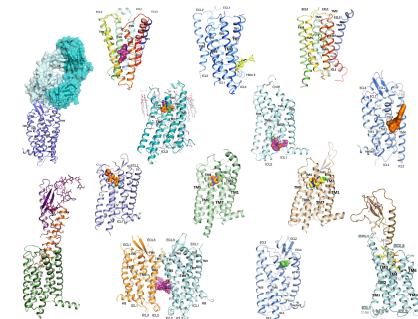
Poster by **Noel O'Boyle** (P10)

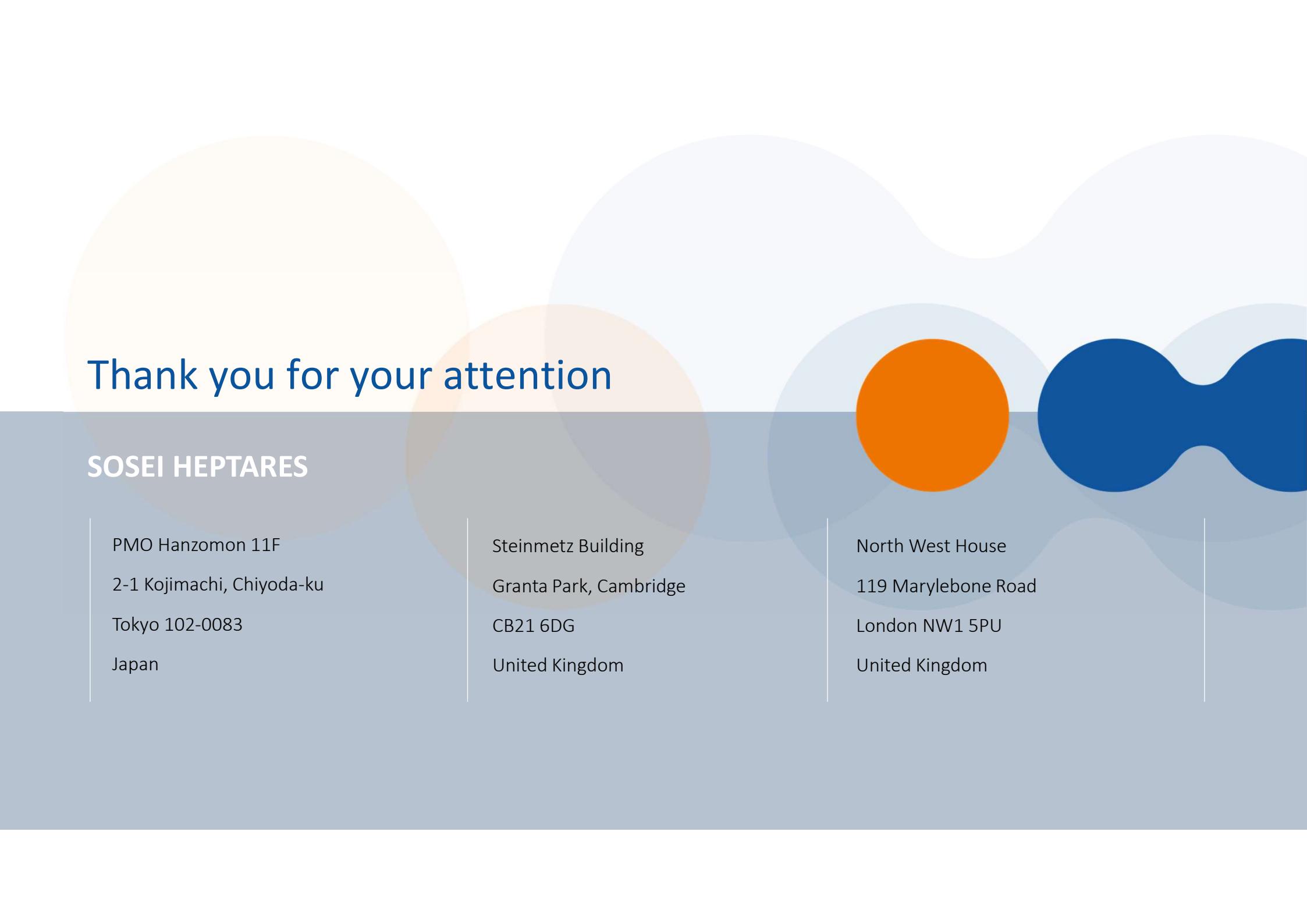
Application of DeepSMILES to machine-learning of chemical structures

Solved **350+** molecular structures
from **42+** different receptors / **70+** StaRs

500+ Global Patent / **66+** patent families
Incl. StaR®, mini-G, GPCR ligands

150+ Scientific publications
Incl. *Nature, Science, Cell*





Thank you for your attention

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