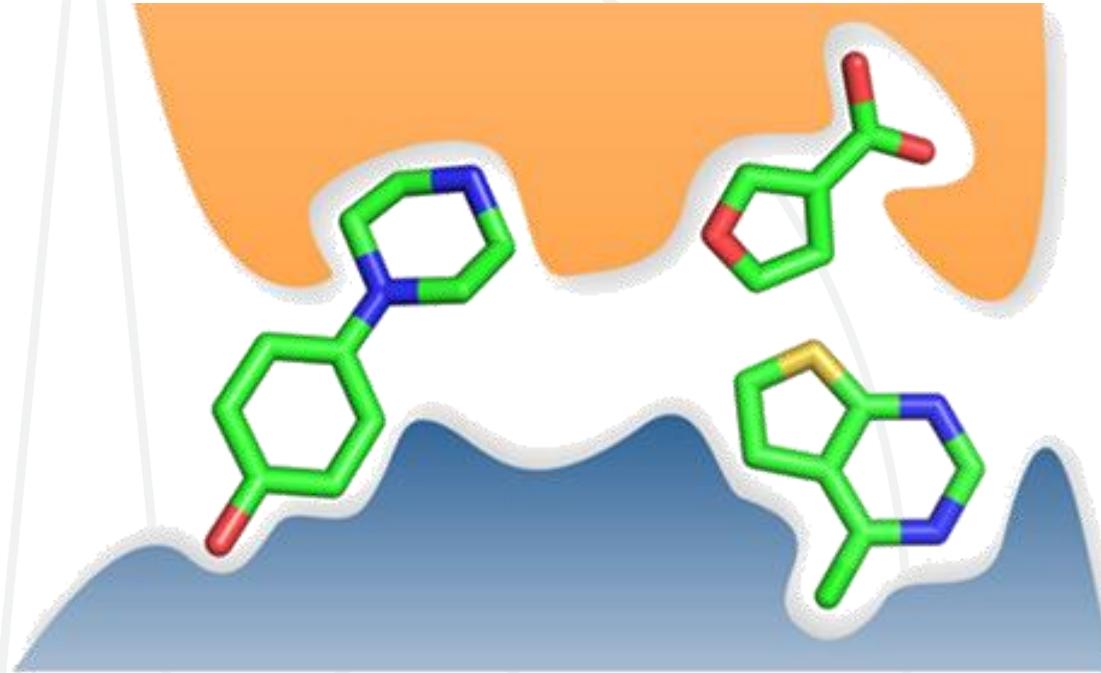




Accelerating Drug Discovery With High-Throughput Crystallographic Fragment Screening and Structural Enablement

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Fragment-Based Lead Discovery (FBLD)



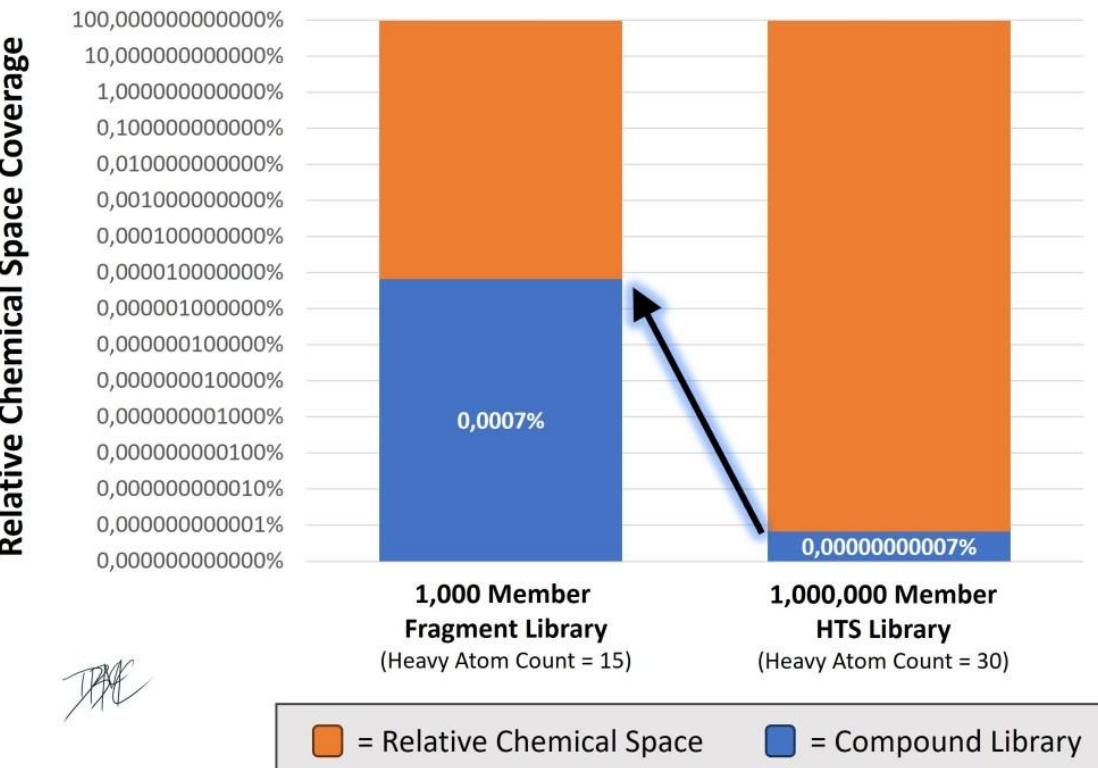
- Molecular weight < 300 Da
- mM - μM affinities **BUT** highly efficient
- Often identified by biophysical methods
- Libraries typically 500-1000 compounds

doi.org/10.1021/bi3005126

doi.org/10.3389/fchem.2020.00093

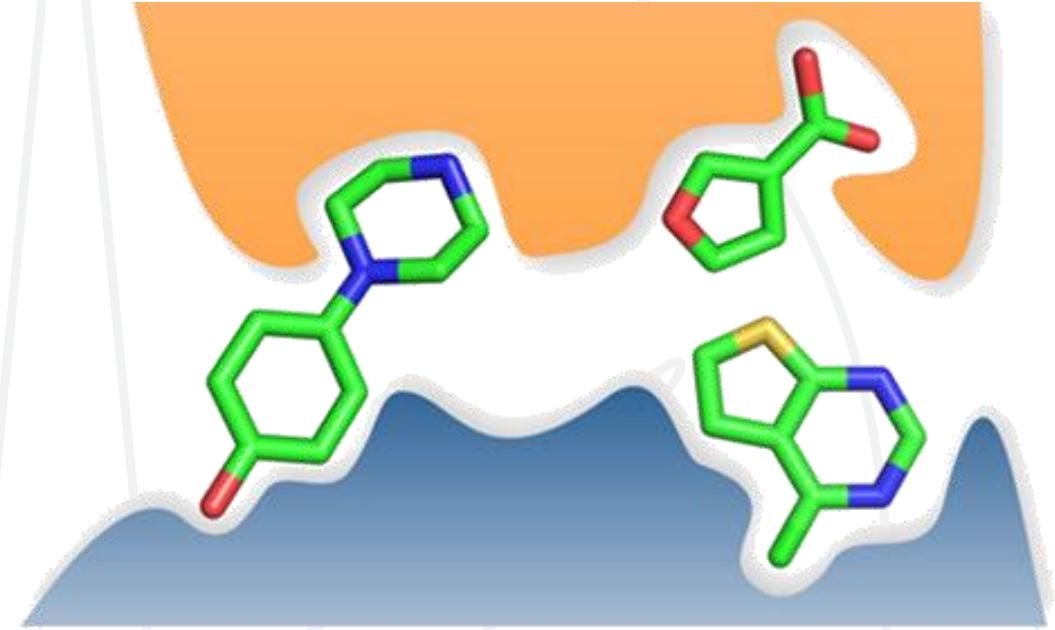
mcconnellsmedchem.com/2024/01/09/chemical-space-is-big/

Fragment Library covers relative chemical space 10 million times more with a thousand times less compounds



Crystallographic Fragment Screening (CFS)

A state-of-the-art technique for hit identification

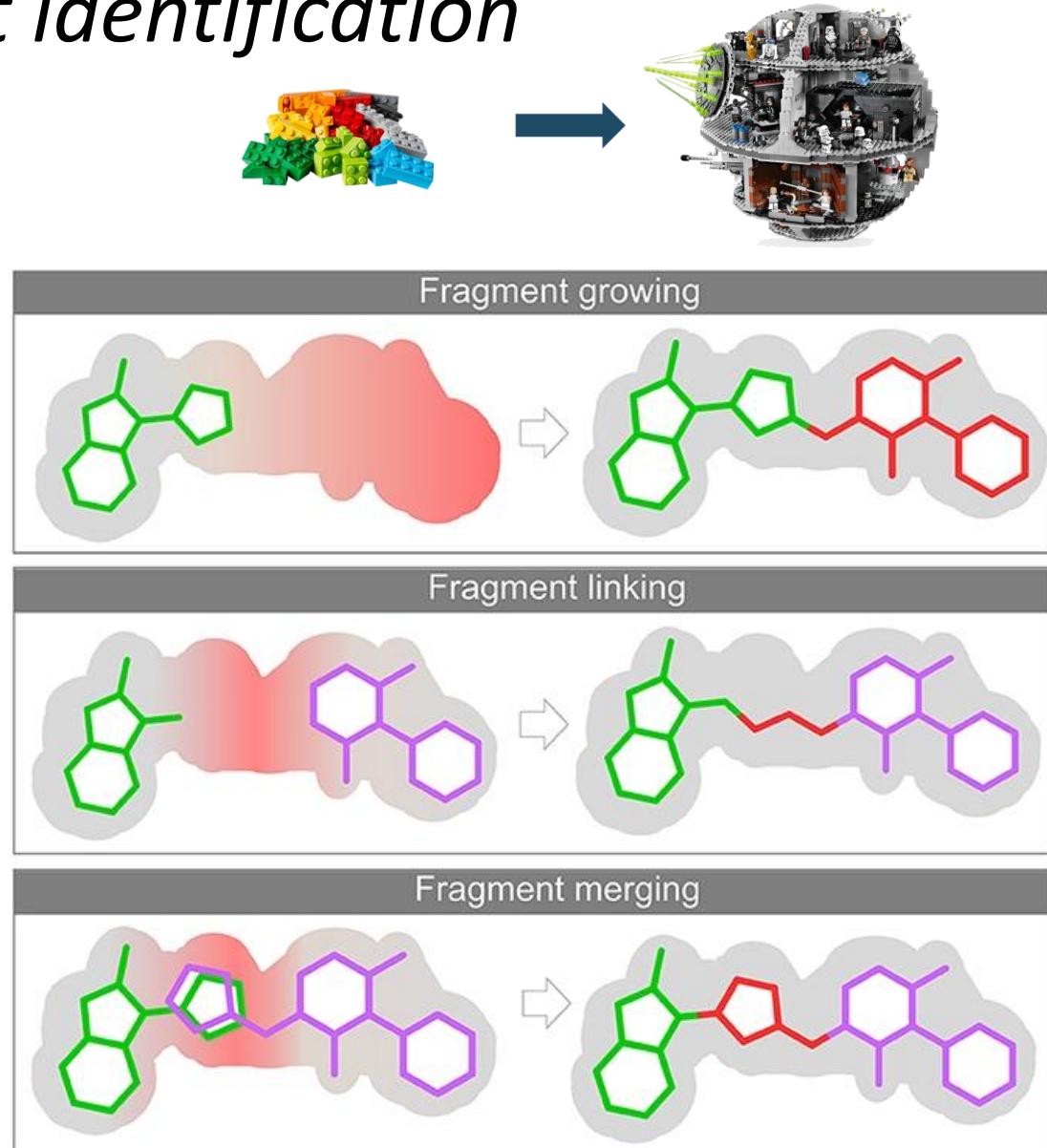


- Highly sensitive
- Target and binding site agnostic
- Directly yields structural information that can drive hit-to-lead and lead optimisation

doi.org/10.1021/bi3005126

doi.org/10.3389/fchem.2020.00093

mcconnellsmedchem.com/2024/01/09/chemical-space-is-big/



Structural Enablement Is Critical For Efficient Hit-To-Lead and Lead Optimisation



X-ray screening one of many techniques used for fragment hit identification

- **8% of examples in 2022**

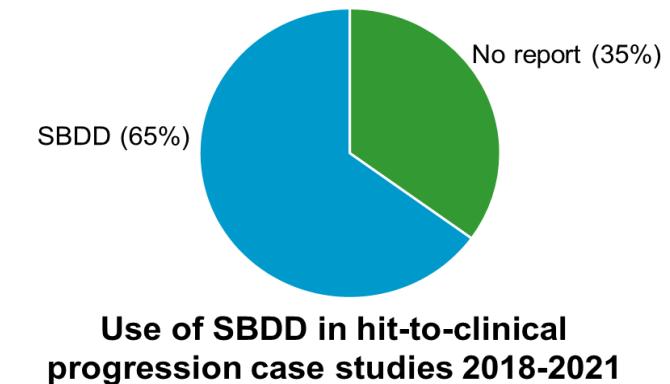
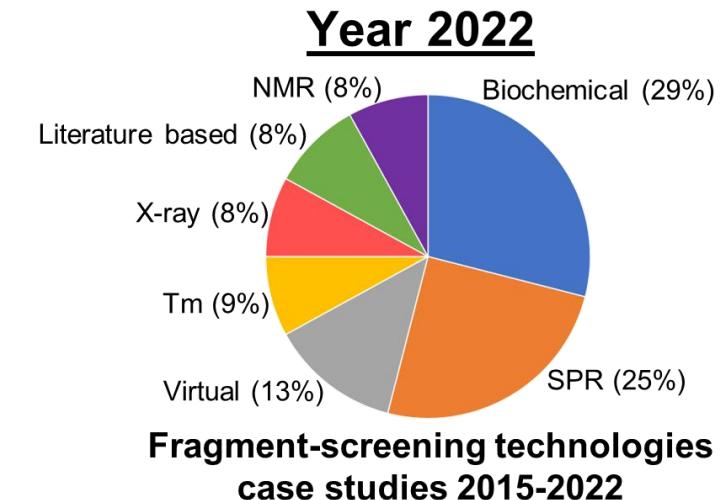
Successful fragment-to-lead case studies use structural data:

- 83% generated a structure for the fragment hit
- 78% generated a structure for the lead compound
- 100% entries used structural information during lead optimization

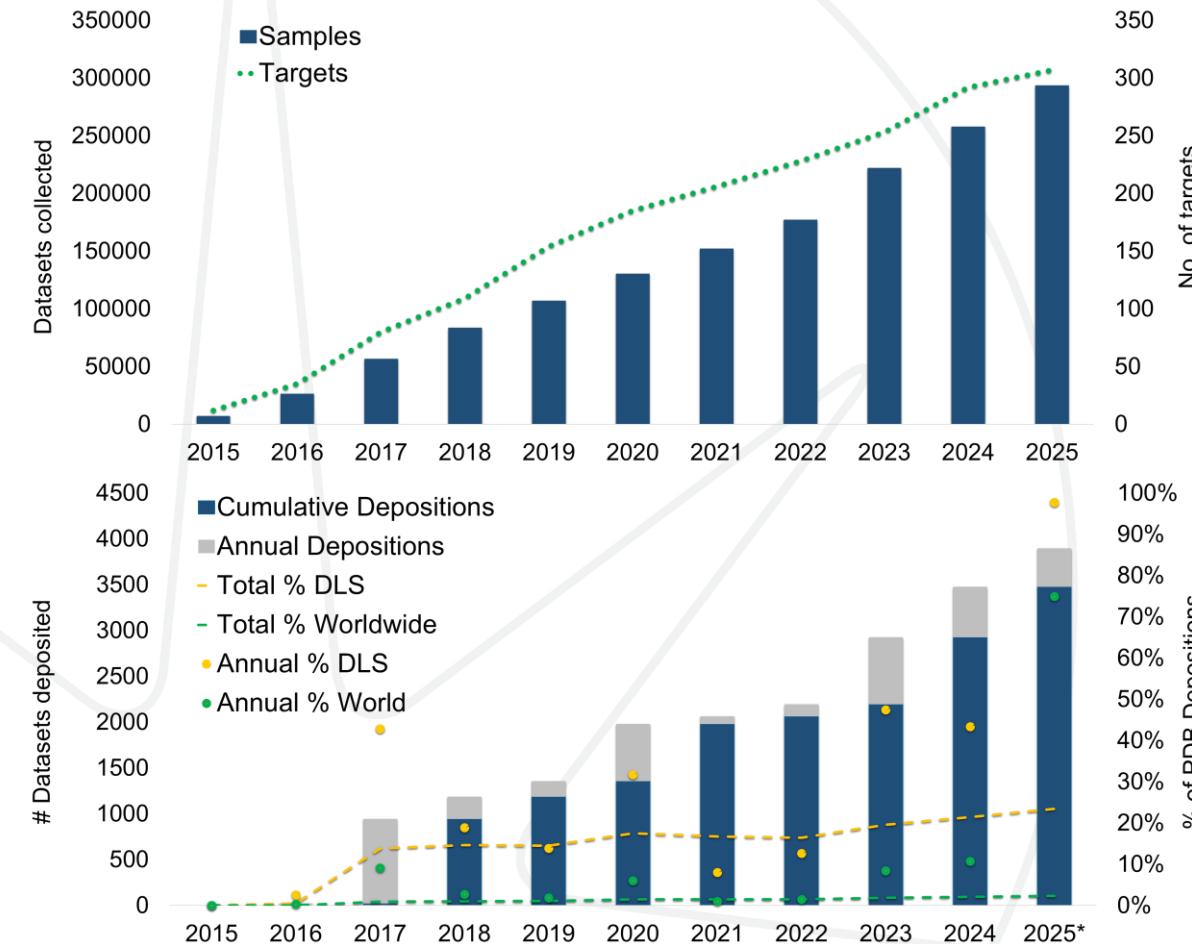
Structure-Based Drug Design is key enabling technology for lead optimization:

- 156 hit-to-clinical campaigns published in J. Med. Chem. between 2018-2021
- 65% reported use of **Structure-Based Drug Design as key enabling technology**
- **Increased to 100% when starting with fragments**

doi.org/10.1021/acs.jmedchem.3c02070
doi.org/10.1021/acs.jmedchem.3c00521
doi.org/10.1021/acs.jmedchem.5c02894



10 Years of XChem



- Routine users since 2015
- > 300 academic projects
 - >300k datasets (~30k in 2025)
 - ~50k liganded structures
 - ~4k models deposited in PDB
 - >400 depositions in 2025 to date
- Completed ~200 industrial campaigns

Applied Research

PERSPECTIVE | Open Access |

Accelerating Drug Discovery With High-Throughput Crystallographic Fragment Screening and Structural Enablement

CFS at Diamond: XChem



Crystal imaging and ranking

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Achieving Efficient Fragment Screening at XChem Facility at Diamond Light Source

DOI: [10.3791/62414](https://doi.org/10.3791/62414) · May 29th, 2021

Alice Douangamath^{1,2}, Ailsa Powell^{1,2}, Daren Fearon^{1,2}, Patrick M. Collins^{1,2}, Romain Talon^{1,2,3}, Tobias Krojer^{3,4}, Rachael Skyner^{1,2}, Jose Brandao-Neto^{1,2}, Louise Dunnett^{1,2}, Alexandre Dias^{1,2}, Anthony Aimon^{1,2,3}, Nicholas M. Pearce^{1,3}, Conor Wild^{3,5}, Tyler Gorrie-Stone¹, Frank von Delft^{1,2,3,4,6}

¹Diamond Light Source Ltd, Harwell Science and Innovation Campus, ²Research Complex at Harwell, Harwell Science and Innovation Campus, ³Structural Genomics Consortium, University of Oxford, ⁴Centre for Medicines Discovery, University of Oxford, ⁵Oxford Protein Informatics Group, Department of Statistics, Oxford University, ⁶Department of Biochemistry, University of Johannesburg

* These authors contributed equally

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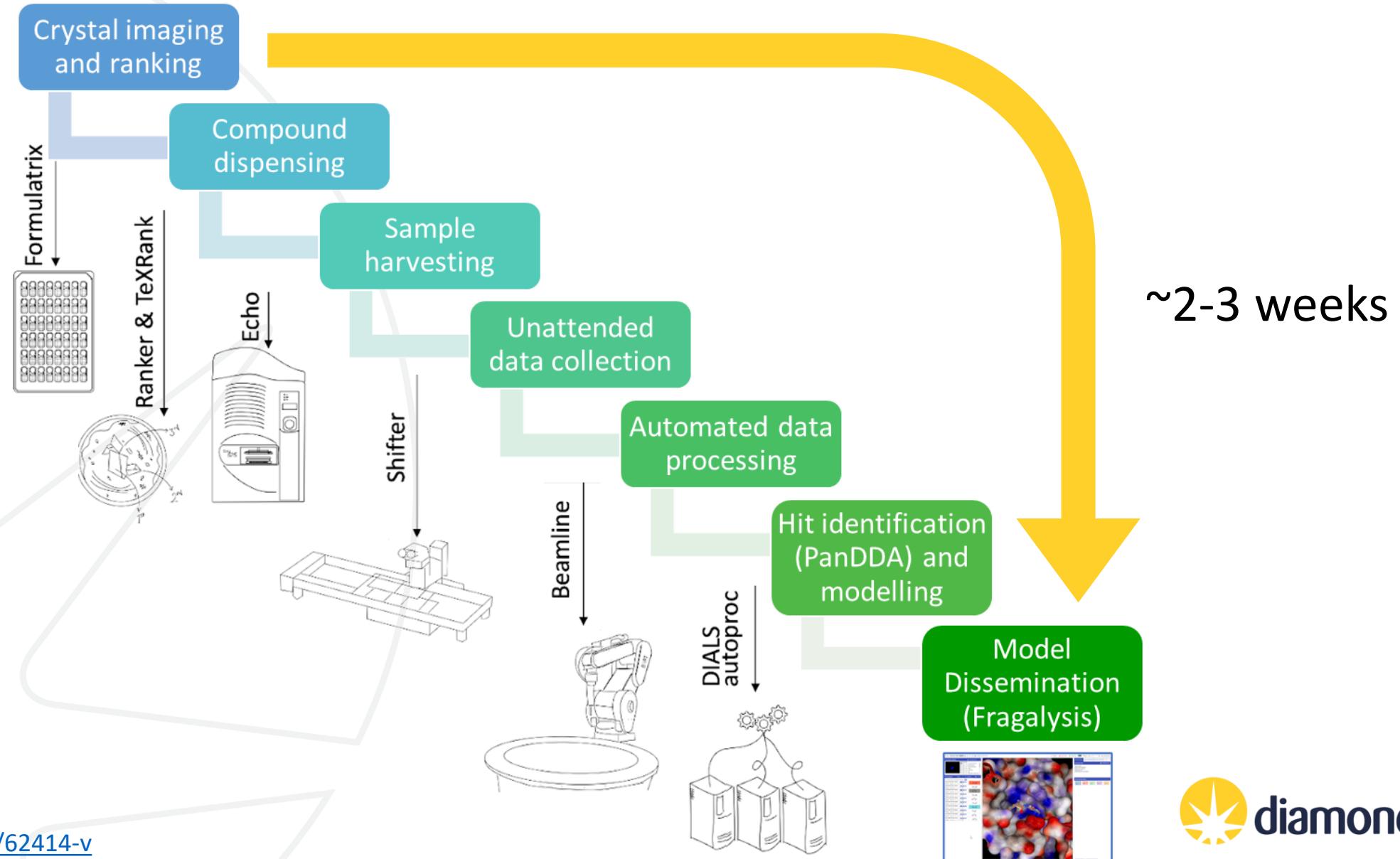


<https://dx.doi.org/10.3791/62414-v>

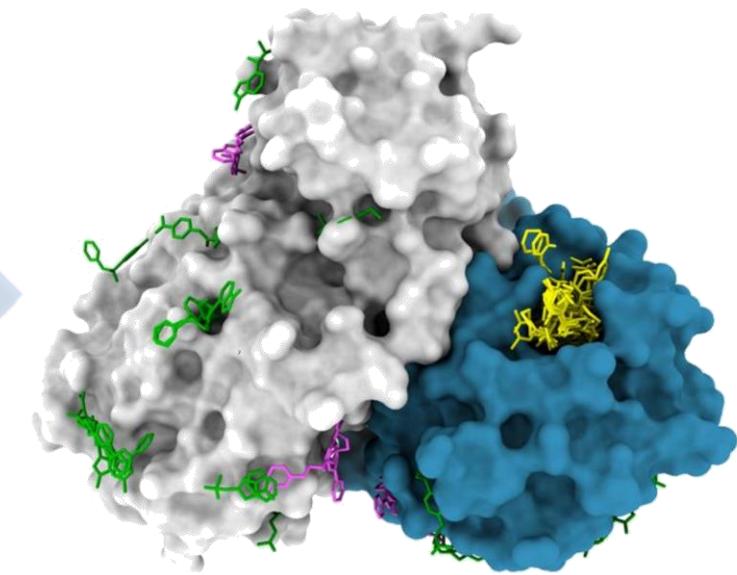
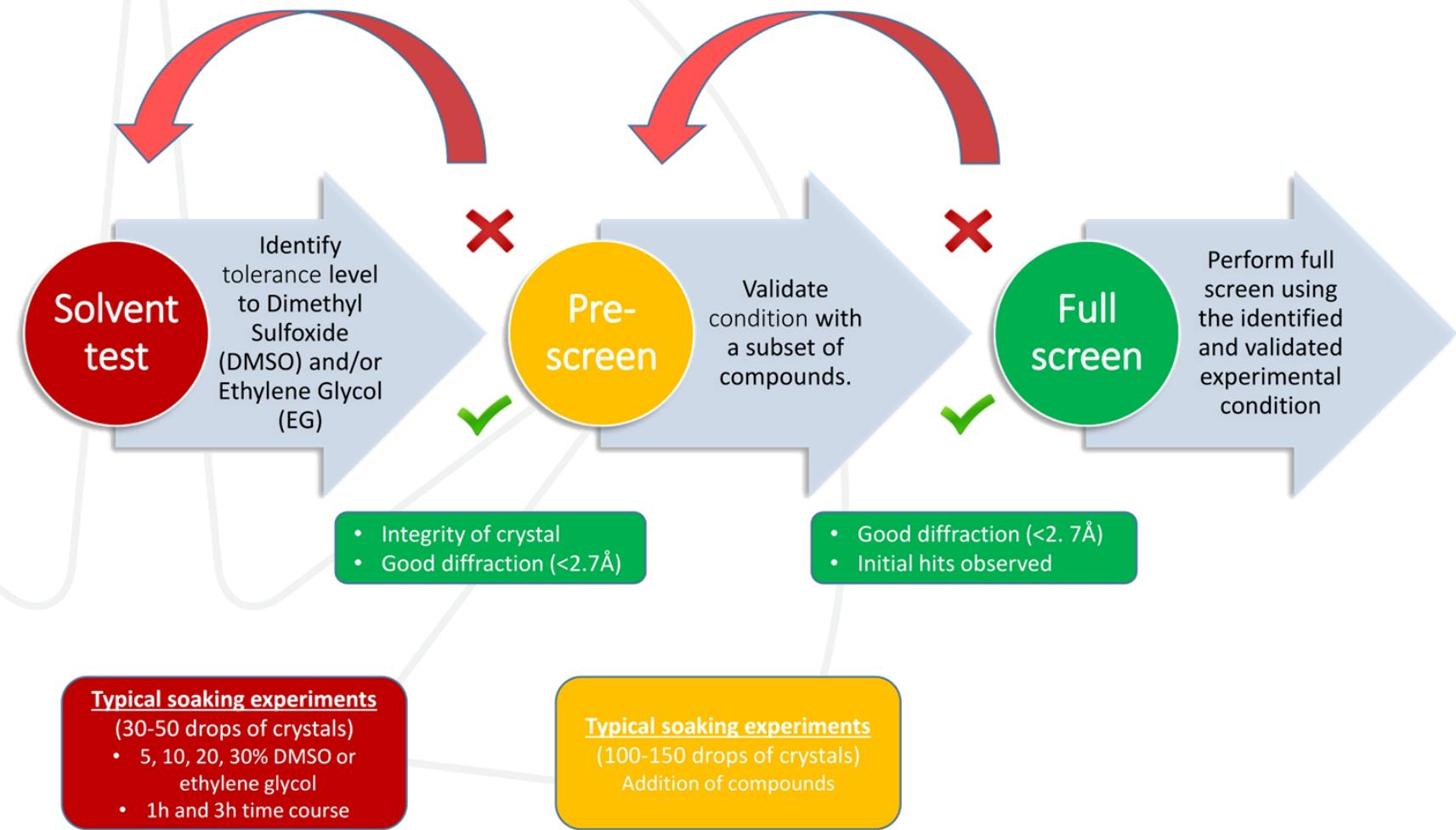
Dissemination
(Fragalysis)



CFS at Diamond: XChem



XChem Workflow



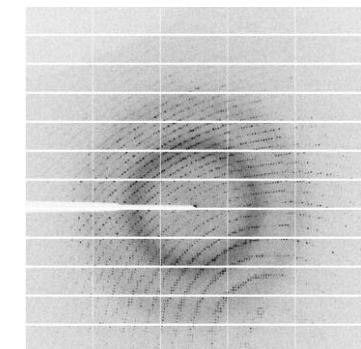
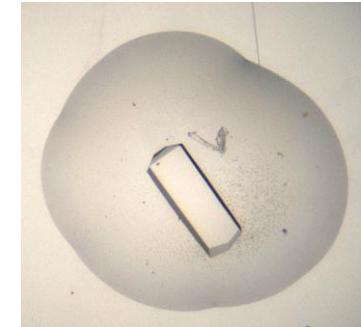
Screening outcome:

- 5-10% hit rate typical
- Fragments bound at range of sites

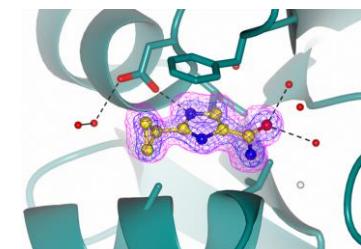
Ideal “XChem ready” crystal systems



- Grow reproducibly (>50% drops) in SWISSCI 3-drop plates
- Consistently diffract to high resolution (<2.5 Å)
- Tolerate high solvent concentrations
- Don't require complicated cryoprotection
- Crystals are chunky, rather than needles
- Don't stick to the plate
- Don't grow skin on the drop



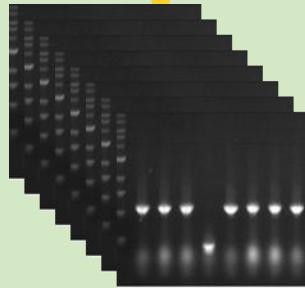
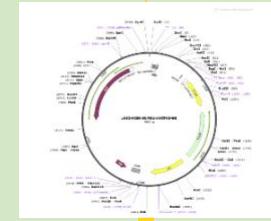
But non-ideal crystals are feasible!



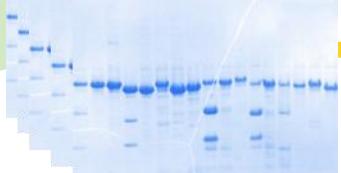
Cloning & small-scale exp.

- Boundary truncations
- Mutations, epitopes
- Expression tags
- AI designs

Multiple designs

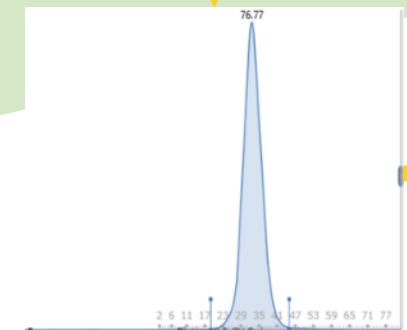
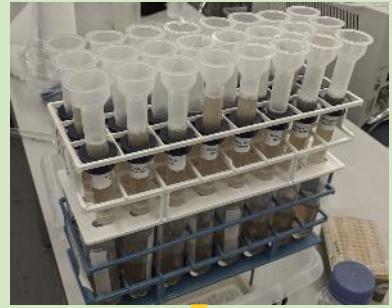


1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17



Scale-up to 1L cultures

- Parallel expression (in bags)
- Parallel purifications



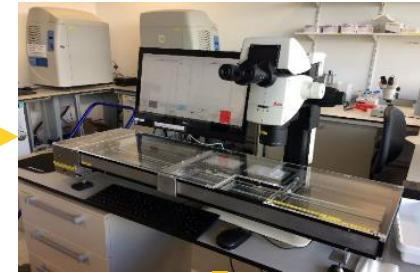
Exhaustive crystal trials

- Multiple screens
- **Seeding**
- Varying drop ratios
- Incubation temperature
- Image over multiple days



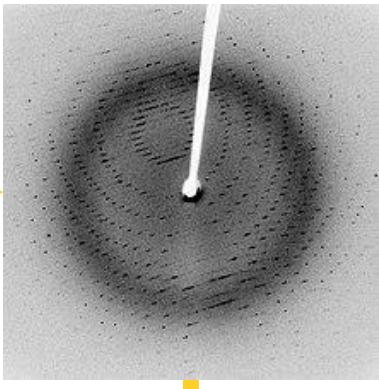
Mounting and data collection

- Test all crystals!
- *In situ* data collection
- Unattended Data Collection



Evaluating crystals:

- Good resolution and quality metrics
- Different crystal forms
- Accessible binding sites

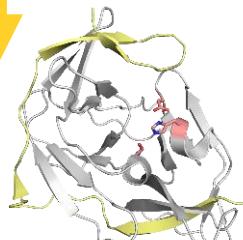


Output: XChem ready crystals

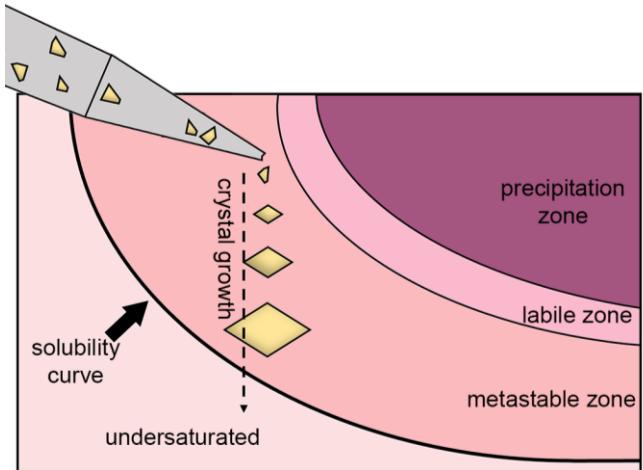
Suitable
crystal
form

vs.

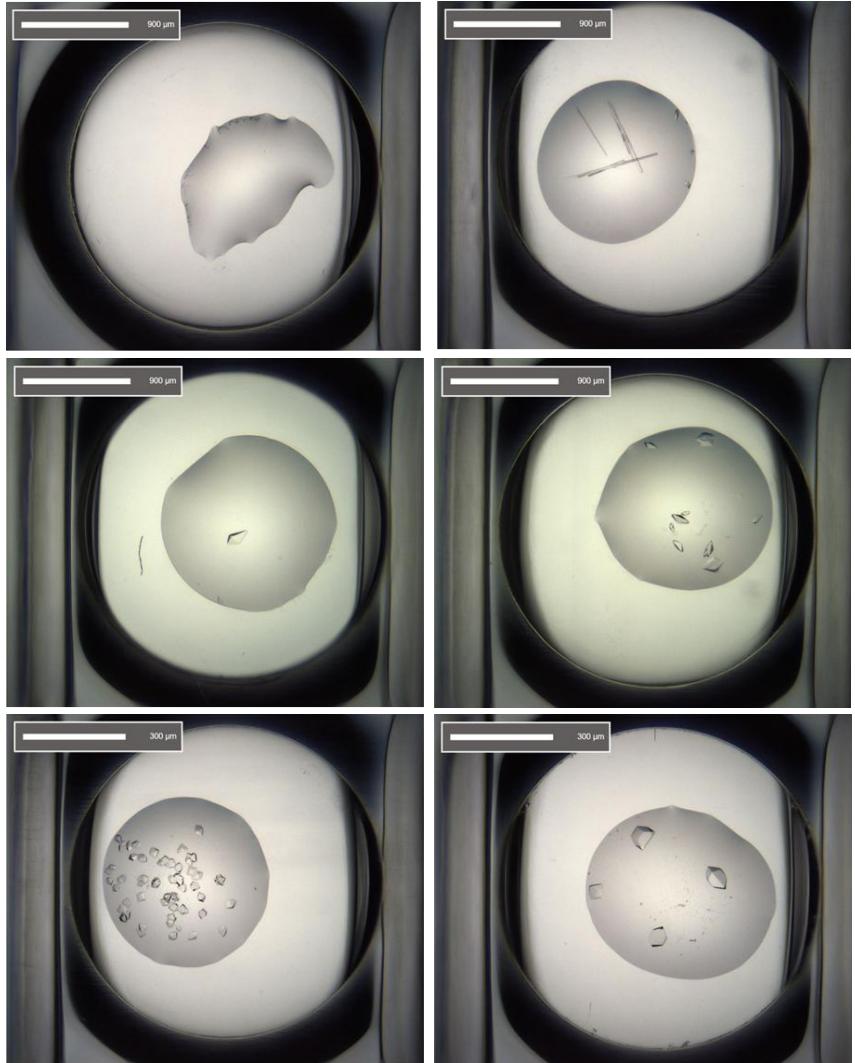
Not fit
for purpose



Crystal seeding enables CFS



- Decouples nucleation from crystal growth
- Can help to:
 - Improve/standardise crystal quality
 - Increase reproducibility
 - Speed up crystallisation
 - Remove problematic buffer components
 - Identify (more) useful crystal forms
 - Aid co-crystallisation



Establishing “XChem ready” systems



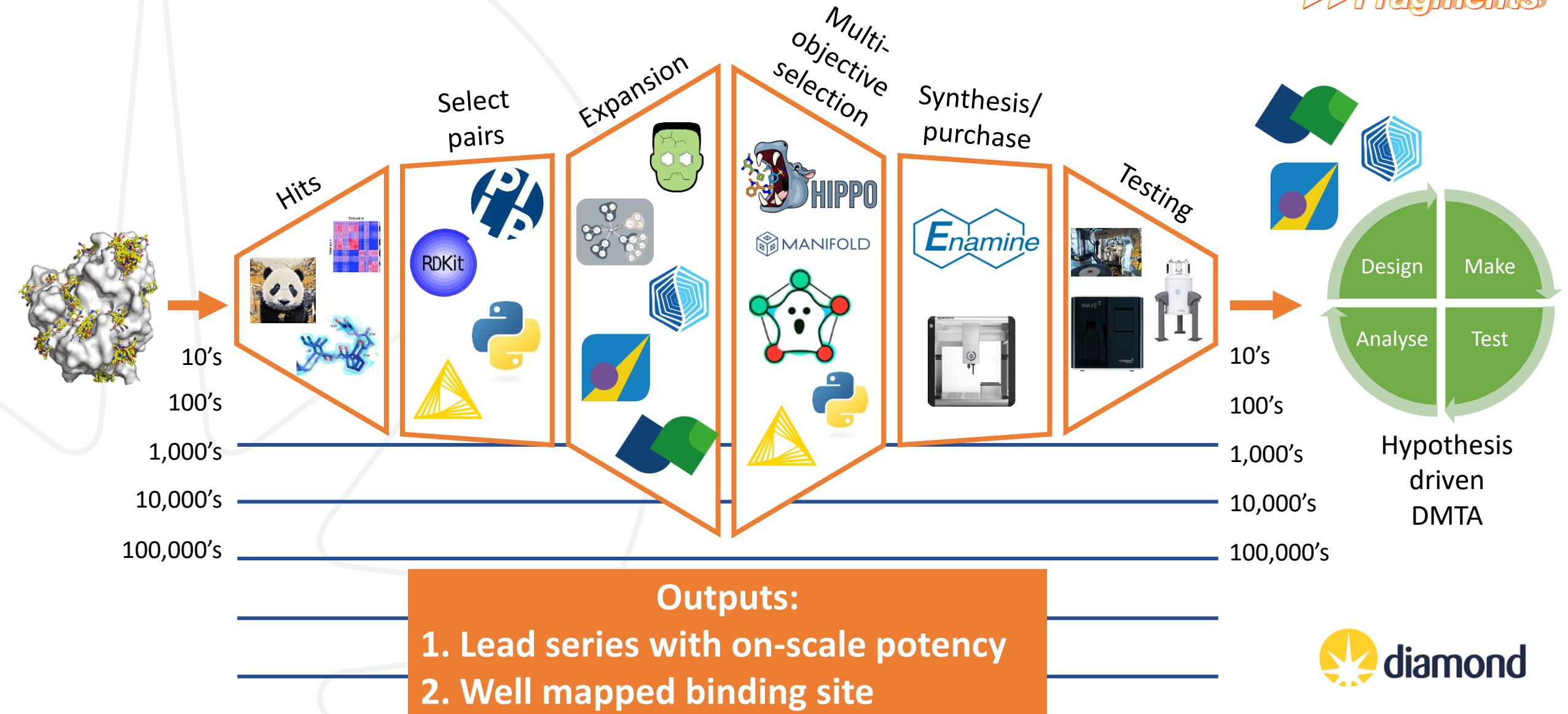
- Get the right protein for crystallisation
- Identify multiple crystal forms/crystallisation conditions
 - PEG preferable over high salt conditions
 - Be aware of pH and volatile solvents
- Establish robust seeding protocol
- Run QC for your protein batches and crystal trays
- Determine transferability of crystallisation trays and life span of crystals
- When conditions established, keep things consistent

Implementing Lessons to Enable Progression

Fast Forward Fragments (FFF)



►Fragments



Feeding ML Models With Structural Data



- Protein Data Bank (PDB) enabled AlphaFold
 - What could 500,000 structure/affinity pairs do?
- Scalable dataset for training ML models in:
 - Algorithmic fragment merging
 - Ligand binding pose prediction
 - Affinity estimation
- Next generation infrastructure (K04) + data pipelines
→ ML-ready datasets ([OpenBind](#))



www.gov.uk/government/news/uk-to-become-world-leader-in-drug-discovery-as-technology-secretary-heads-for-london-tech-week

<https://openbind.uk/>

nature

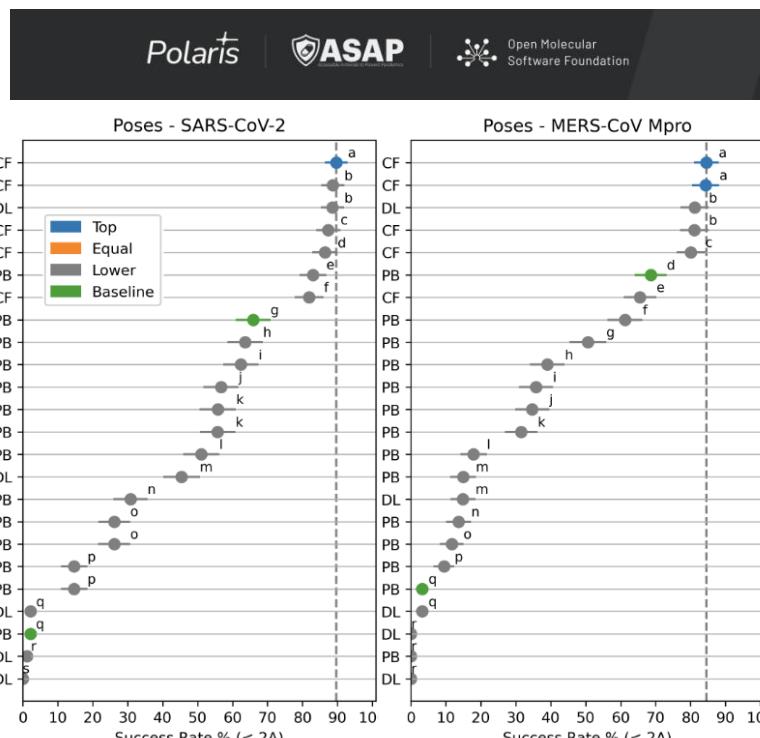
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NEWS | 27 March 2025

AlphaFold is running out of data – so drug firms are building their own version

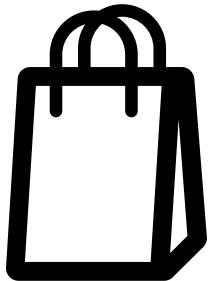
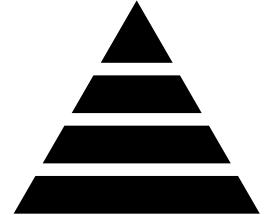
Thousands of 3D protein structures locked up in big-pharma vaults will be used to create a new AI tool that won't be open to academics.



XChem Access Modes



- Standard academic access - covers single target with three levels:
 - Tier 1: Exploratory projects (1 shift; 200-300 datasets)
 - Tier 2: Full screen (4 shifts; up to 1000 fragments)
 - Tier 3: Fast Forward Fragments - Fragment progression
- XChem BAG access - for groups, institutes or collaborations
 - Routinely have crystal systems for evaluation and screening
 - Hit-to-lead infrastructure in place
 - Stringent internal prioritisation process
 - Experienced crystallographers
- Academic access eligible for Instruct-ERIC support
- Proprietary access - contact: industry@diamond.ac.uk



<https://www.diamond.ac.uk/Instruments/Mx/Fragment-Screening/XChem-Applications.html>

<https://www.diamond.ac.uk/industry/Techniques-Available/Integrated-Structural-Biology/Fragment-Screening---XChem.html>





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Megan Lambert



instruct
ERIC



All collaborators and users of XChem facility

Fragment
Screen



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Xiaomin Ni
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