Accessing Crystallographic Fragment Screening at XChem

Slides adapted from
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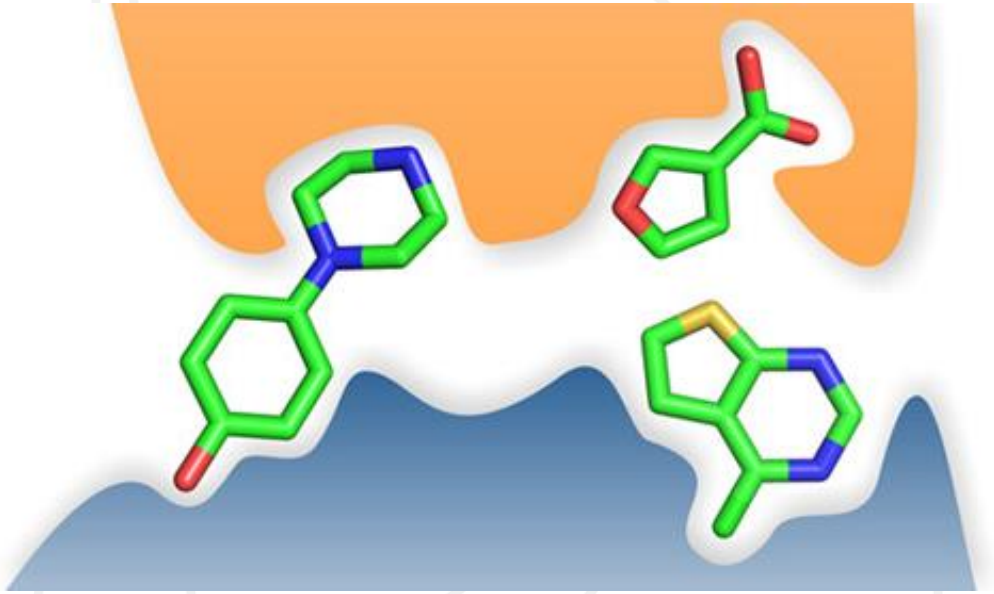
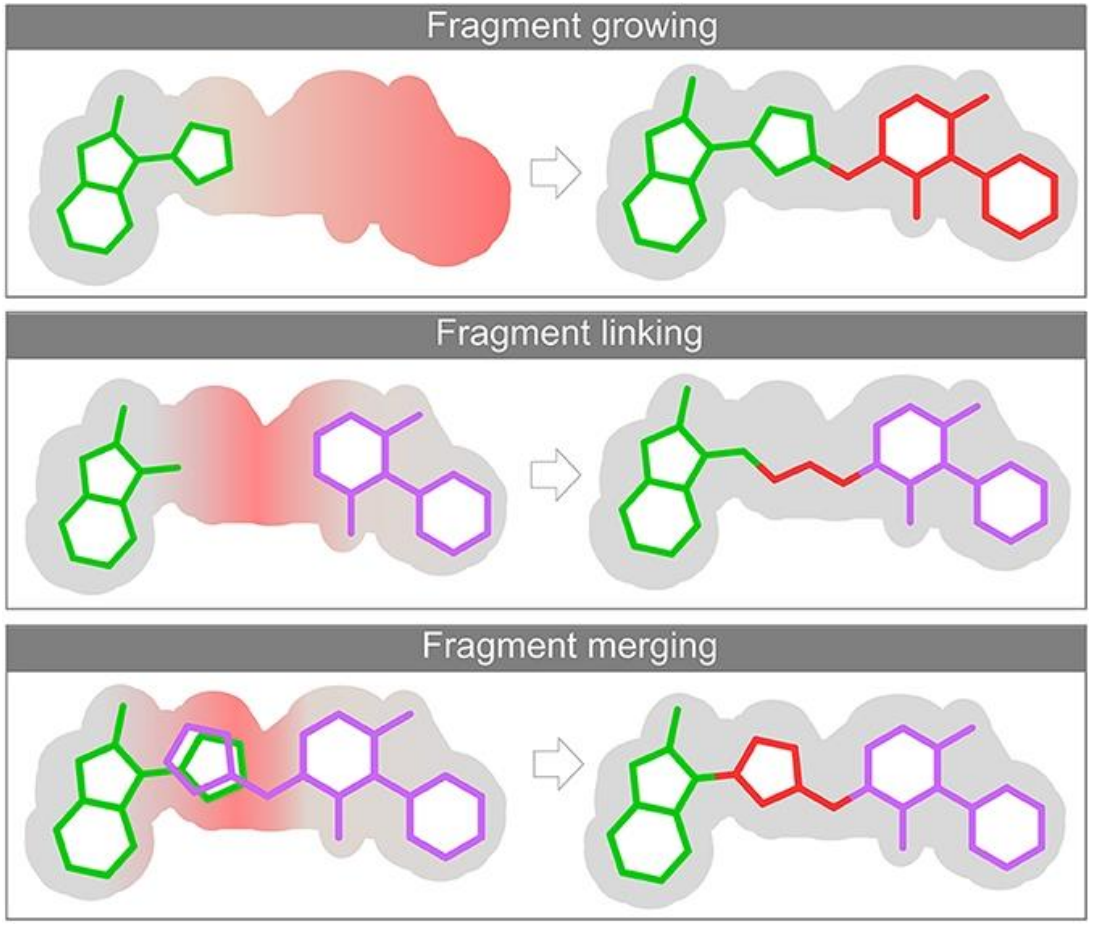
Fragment-Based Drug Discovery

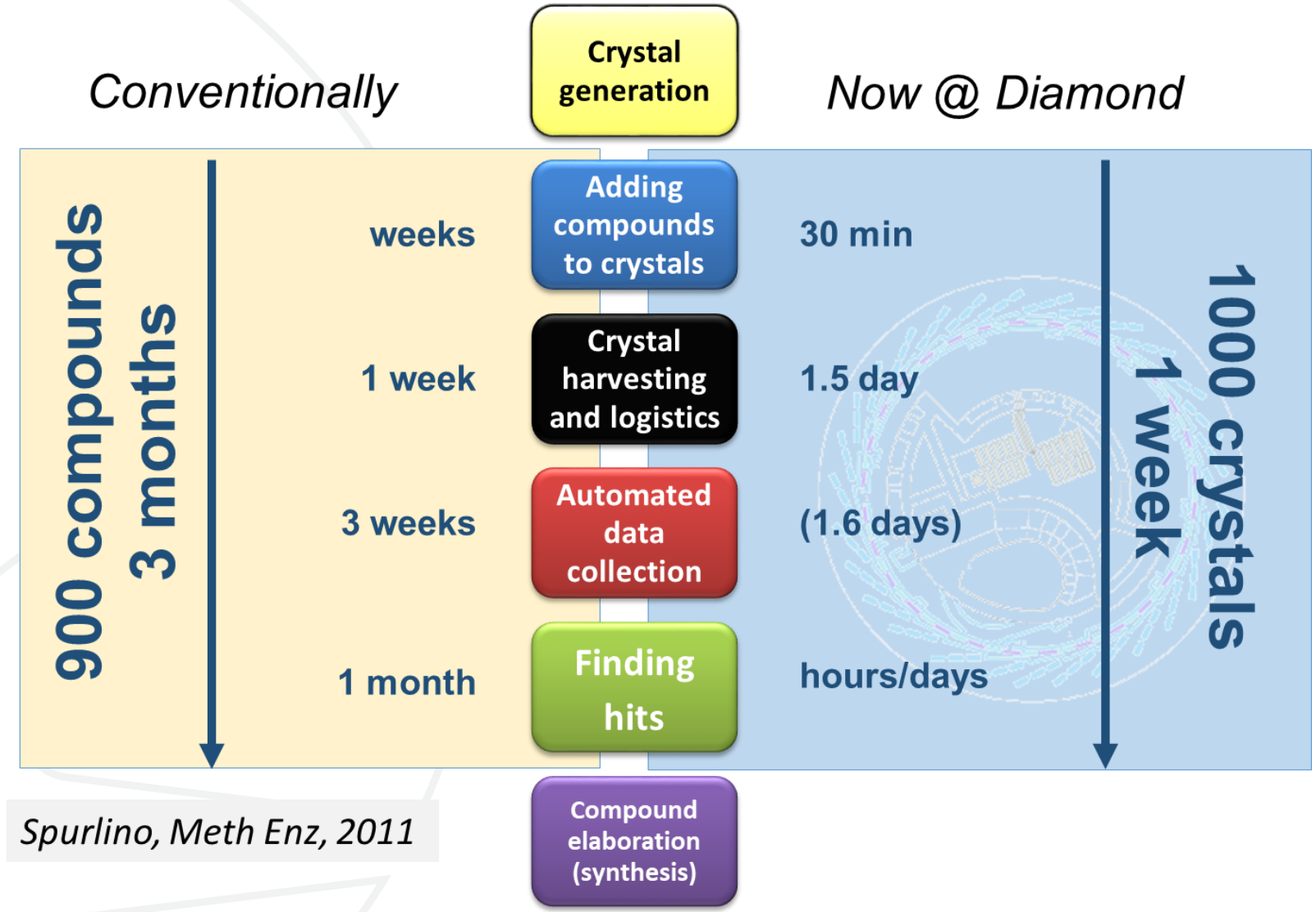




- Libraries typically 500-1000 compounds
- Molecular weight < 250 Da
- Affinities typically in mM-µM range **BUT** compounds are very efficient
- Usually identified by biophysical methods
- Iterative optimisation driven by structure-based methods

https://doi.org/10.1021/bi3005126

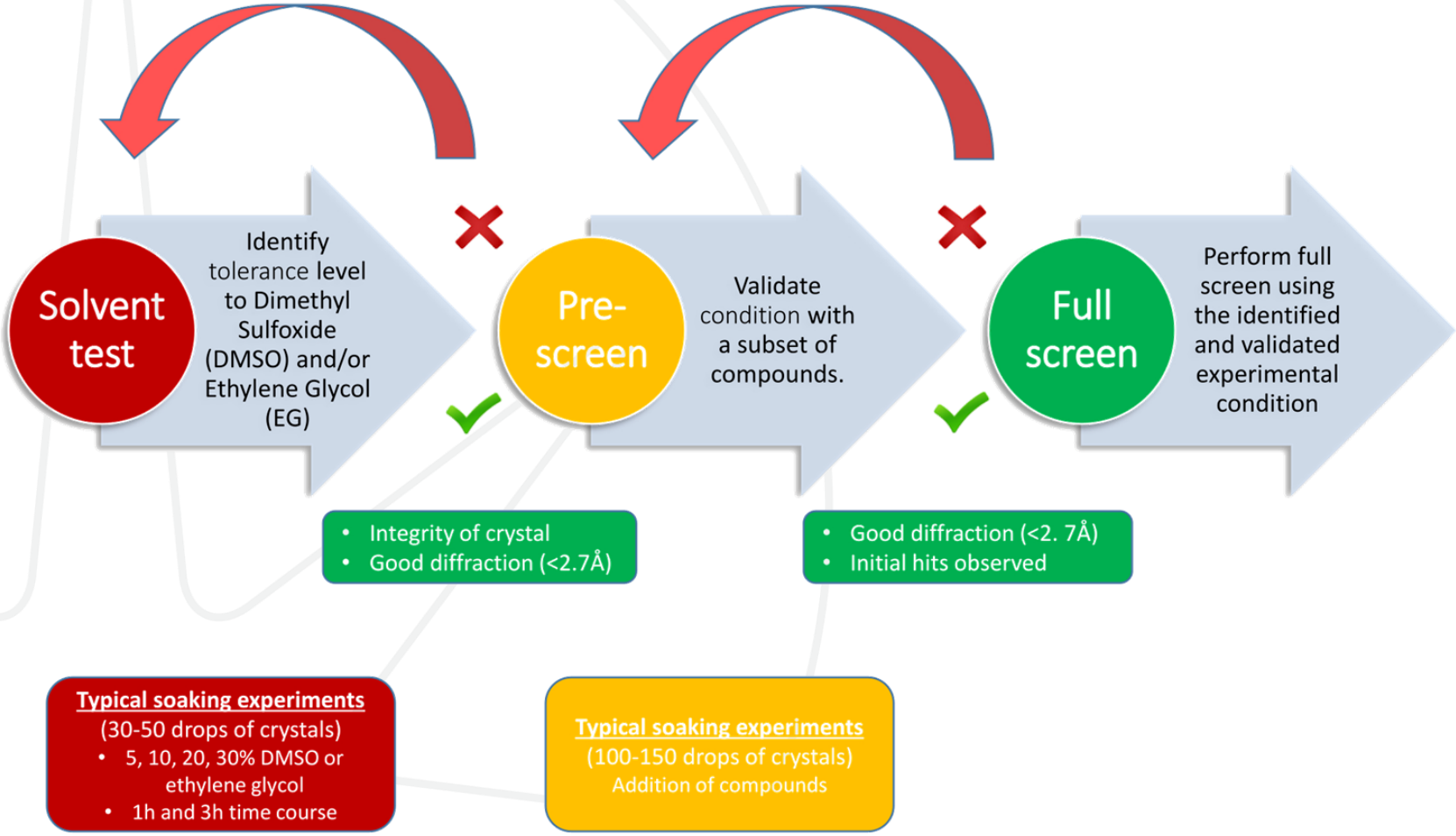
Fragment screening at Diamond: XChem

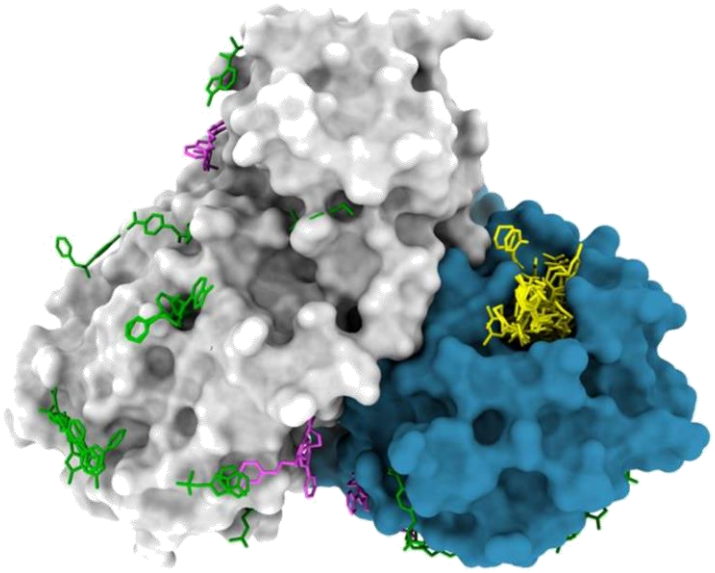


Spurlino, Meth Enz, 2011

https://doi.org/10.1016/b978-0-12-381274-2.00013-3

XChem screening experiment

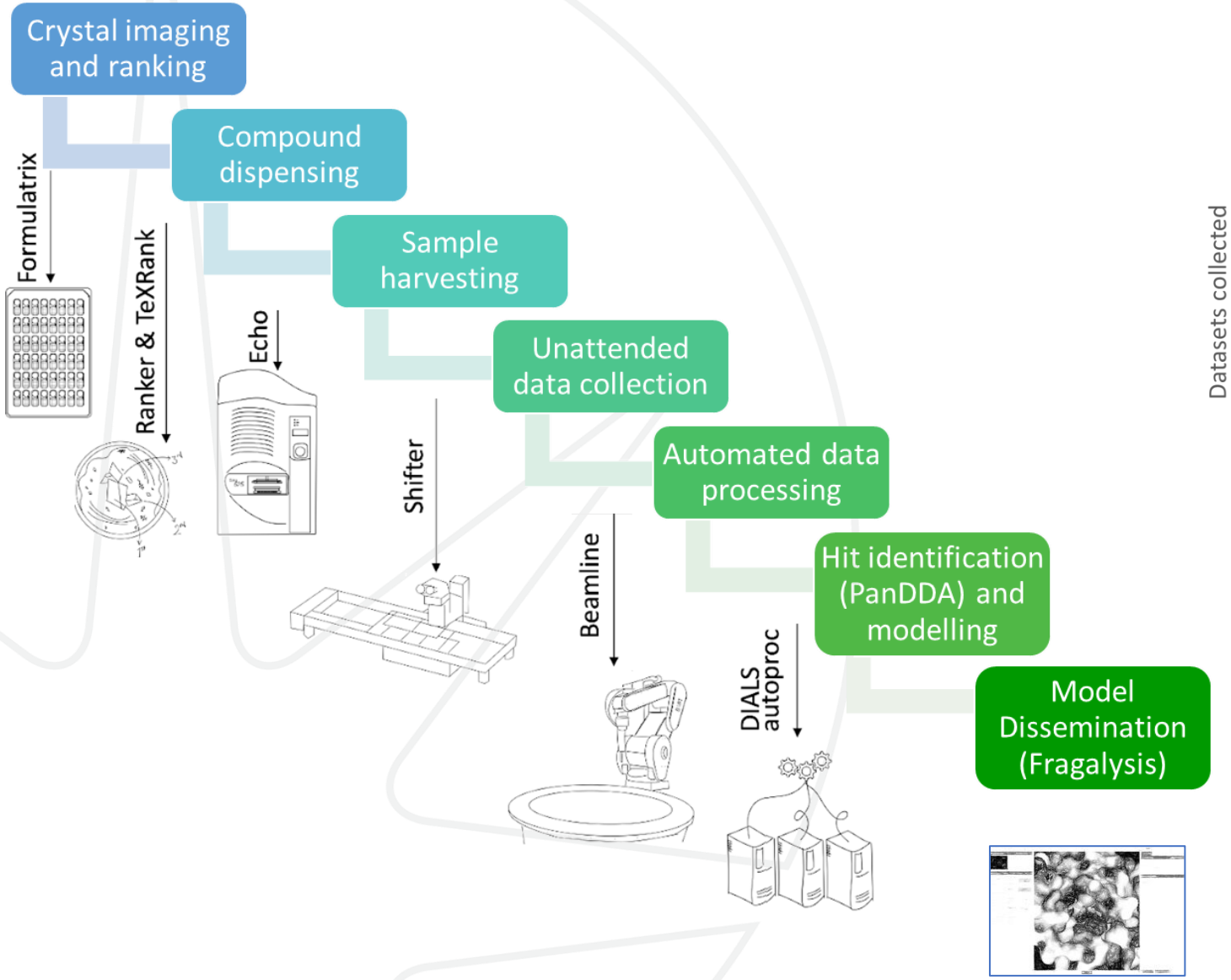


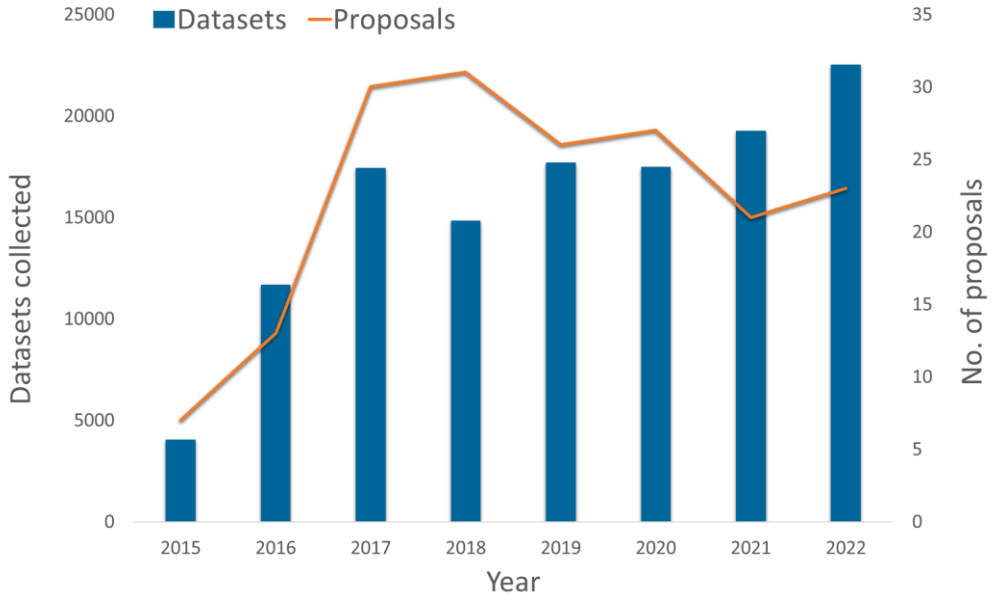


Screening outcome:
- 5-10% hit rate typical
- Fragments bound at range of sites

https://dx.doi.org/10.3791/62414

Fragment screening at Diamond: XChem





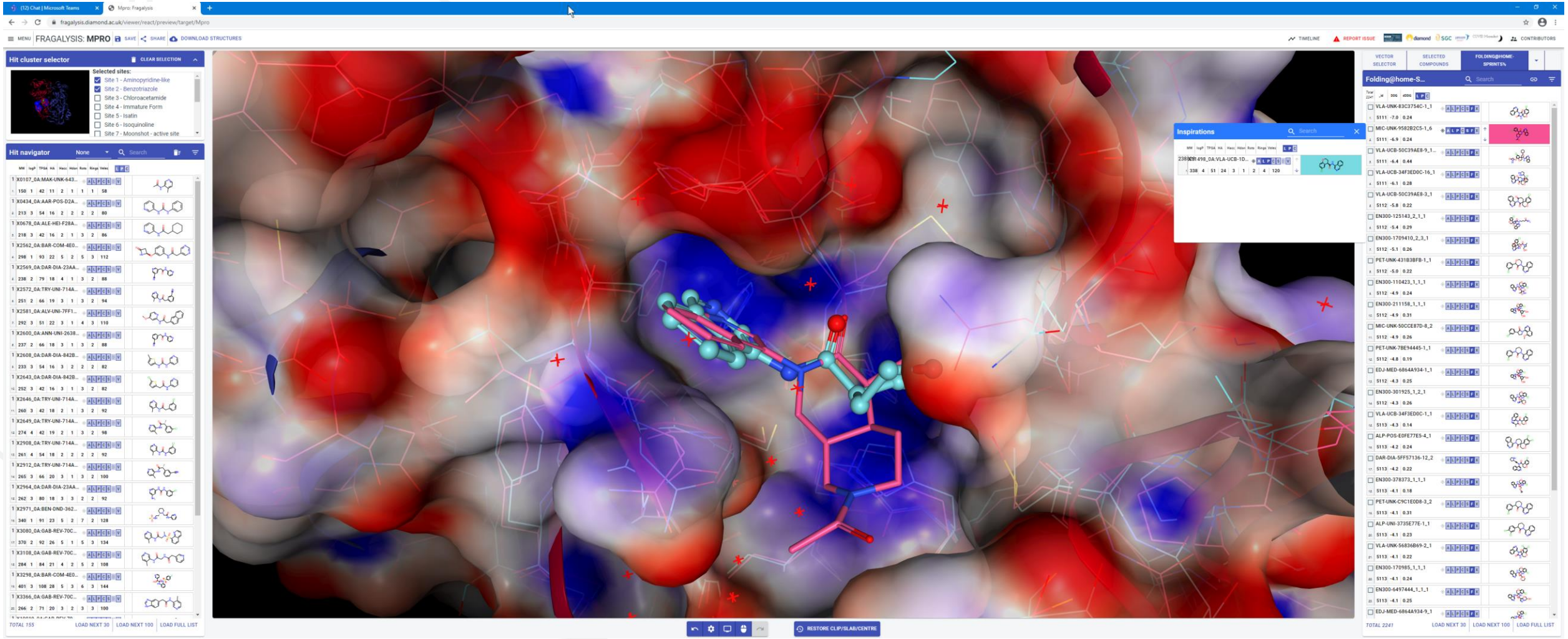
Routine users since 2016

> 250 academic projects

> 5,000 hits identified

https://doi.org/10.3389/fchem.2020.00093

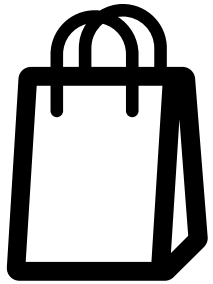
Data dissemination: Fragalysis



https://fragalysis.diamond.ac.uk/viewer/react/projects/708/503

XChem access modes

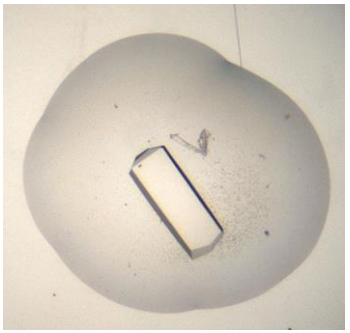
- 6 Monthly proposal calls
  - April – September 2024 access – apply by September 2023
- Standard academic access - covers a single target with three levels of experiments:
  - Tier 1: Exploratory projects of 200-300
  - Tier 2: Full screen of up to 1200 fragments
  - Tier 3: Follow-up support – batches of 200-300 compounds
- 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 to organise and provide logistical support
- Academic Access
  - In first instance - contact charlie.tomlinson@diamond.ac.uk or daren.fearon@diamond.ac.uk
- Industrial/proprietary access:
  - Contact alexandre.dias@diamond.ac.uk or ailsa.powell@diamond.ac.uk

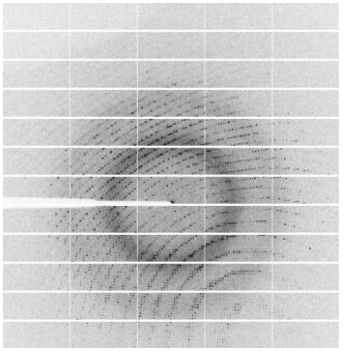


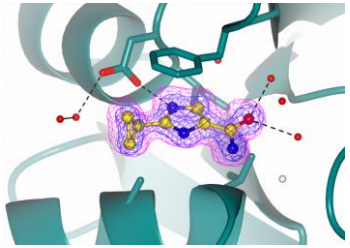
https://www.diamond.ac.uk/Instruments/Mx/Fragment-Screening/XChem-Applications.html
https://www.diamond.ac.uk/industry/Techniques-Available/Integrated-Structural-Biology/Fragment-Screening---XChem.html

"XChem ready" crystal systems

- Optimised growth in >50% drops in SWISSCI 3-drop plates
- Crystals are chunky and comfortable to harvest
- Diffract to high resolution (<2.5 Å) consistently
- Tolerate high solvent (DMSO) concentrations
- Don't require complicated cryoprotection
- Don't grow skin on the drop or stick to the plate







But non-ideal crystals are still welcome!

https://www.diamond.ac.uk/Instruments/Mx/Fragment-Screening/Troubleshooting-Tips-Tricks/Crystallisation-And-SamplePrep.html

doi: 10.20944/preprints201809.0383.v1

Preparing “XChem ready” systems

- Explore multiple protein constructs and protein engineering
- Identify multiple crystallisation conditions/crystal forms
  - PEG preferable over high salt conditions
  - Be aware of pH and volatile solvents
- Run QC for your protein batches and crystal trays
- **Establish robust seeding protocol**
- Determine crystal solvent tolerance and life span of crystals
- Test transferability of crystallisation/trays between locations
- When robustness established, keep things consistent
- Speak to the XChem team

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XChem/i04-1 Team

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Research Technician (Industrial)

http://www.diamond.ac.uk/Beamlines/Mx/Fragment-Screening.html