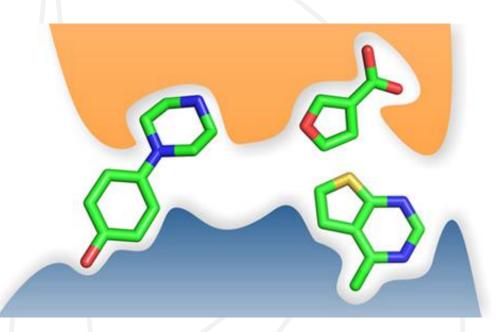


Accessing Crystallographic Fragment Screening at XChem

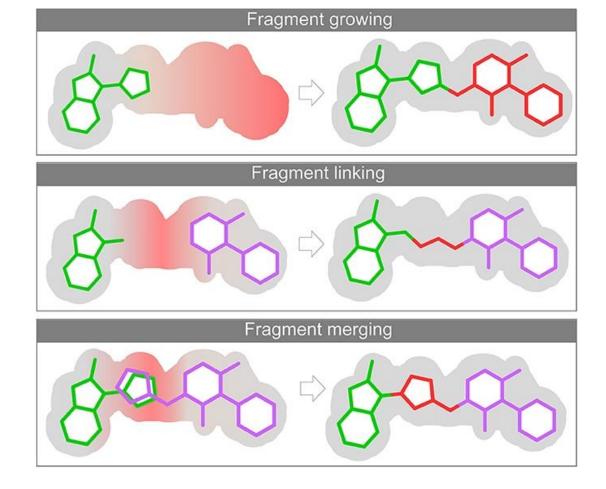
Slides adapted from Charlie Tomlinson Beamline Scientist (XChem) charlie.tomlinson@diamond.ac.uk

Fragment-Based Drug Discovery





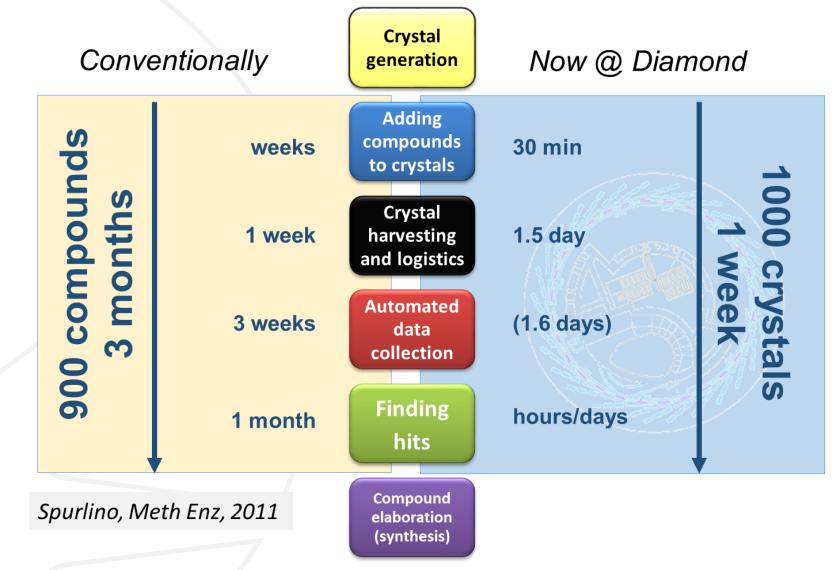
- Libraries typically 500-1000 compounds
- Molecular weight < 250 Da
- Affinities typically in mM- μM range BUT compounds are very efficient
- Usually identified by biophysical methods
- Iterative optimisation driven by structure-based methods





Fragment screening at Diamond: XChem



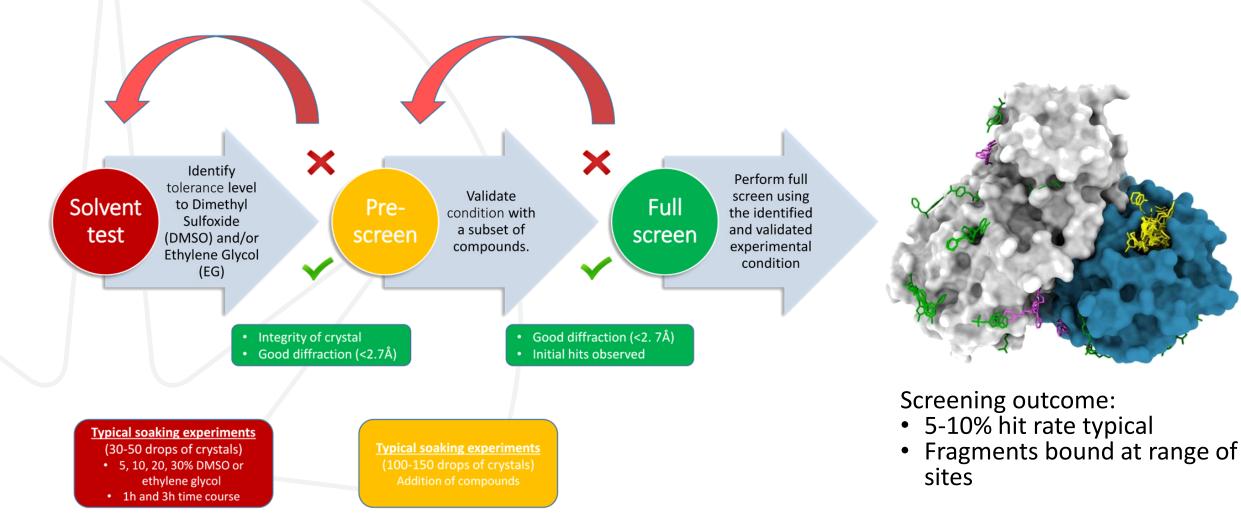




https://doi.org/10.1016/b978-0-12-381274-2.00013-3

XChem screening experiment



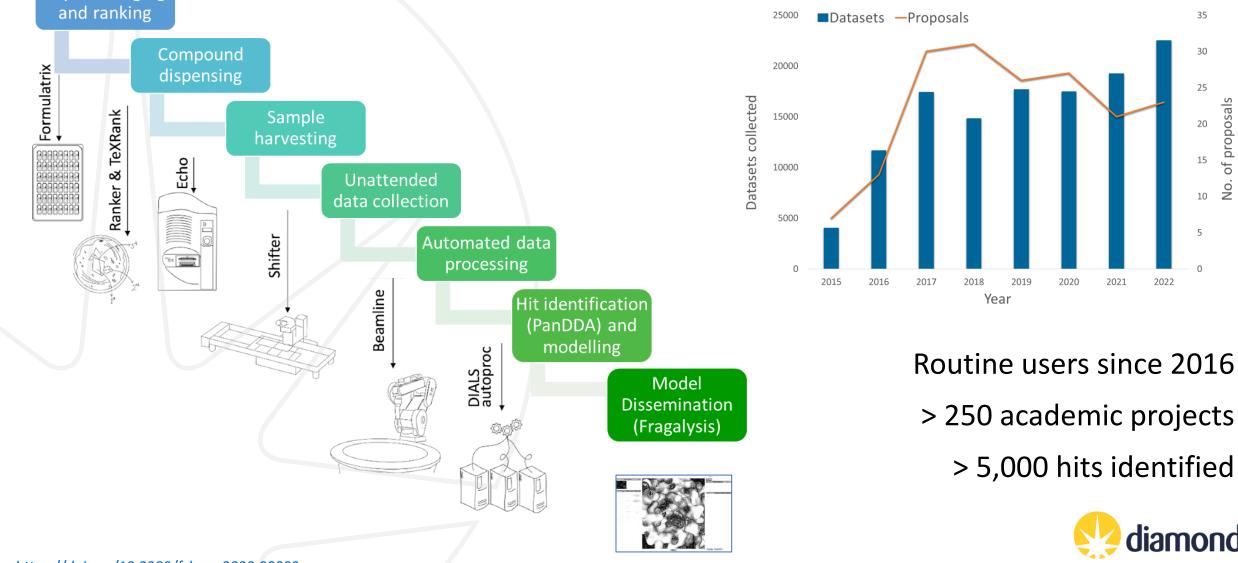




https://dx.doi.org/10.3791/62414

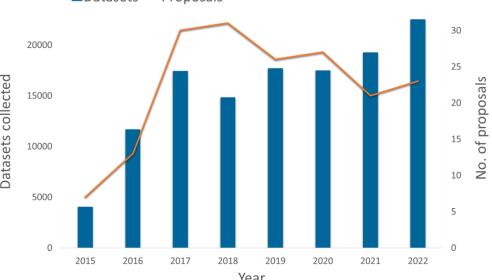
Crystal imaging

Fragment screening at Diamond: XChem





35



> 250 academic projects > 5,000 hits identified



Data dissemination: Fragalysis



12) Chat | Microsoft Teams X 🔕 Mpro: Fragalysis

- -> C 🔒 fragalysis.diamond.ac.uk/viewer/react/preview/target/Mpm

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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 <u>charlie.tomlinson@diamond.ac.uk</u> or <u>daren.fearon@diamond.ac.uk</u>
- Industrial/proprietary access:
 - Contact <u>alexandre.dias@diamond.ac.uk</u> or <u>ailsa.powell@diamond.ac.uk</u>





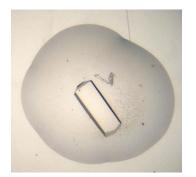


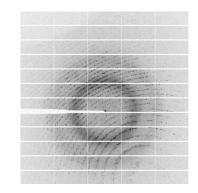
"XChem ready" crystal systems

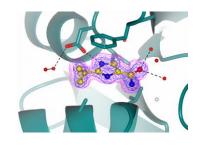
- Optimised growth in >50% drops in SWISSCI 3-drop plates
- Crystals are chunky and comfortable to harvest
- Diffract to high resolution (<2.5 Å) consistently
- Tolerate high solvent (DMSO) concentrations
- Don't require complicated cryoprotection
- Don't grow skin on the drop or stick to the plate

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



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

doi: 10.20944/preprints201809.0383.v1

XChem/i04-1 Team



Dr Daren Fearon Senior Beamline Scientist (XChem)



Jose Brandao-Neto Senior Beamline Scientist (I04-1)



Dr Jasmin Aschenbrenner PDRA - Antiviral research

Professor Frank von Delft

Principal Beamline Scientist



XCHE

Dr Kutu Nidamarthi **Beamline Scientist** (MX)

Diamond

Fragment

Screening



Dr Charlie Tomlinson Beamline Scientist (XChem)



Dr Louise Dunnett **Beamline Scientist** (104-1)



Dr Blake Balcomb PDRA - Antiviral research



Dr Elliot Nelson Senior support scientist (MX)



Dr Warren Thompson PDRA - Chemistry Assisted Robotics



Dr Alex Dias Senior Industrial Liaison Scientist (XChem)



Conor Wild PDRA - PanDDA 2



Dr Ailsa Powell Senior Industrial Liaison Scientist (XChem)





Peter Marples Research Technician



Isabel Barker Research Technician (Industrial)



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



Dr Ryan Lithgo PDRA - Antiviral research



