WuXi AppTec

WuXi Biology

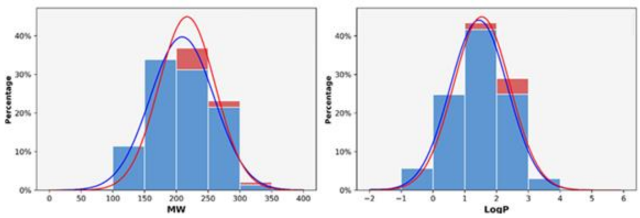
Fragment-based Drug Discovery

WuXi AppTec has been providing series of screening approaches from biophysical, biochemical, mass spectrometry and structure biology platforms. Together with our well-seasoned synthetic and medicinal chemistry platform, WuXi AppTec incorporates different techniques into a integrated fragment-based drug discovery.

Selecting the Library

Conventional fragment library (>4600)

- Balanced design involved RO3, structural diversity and lead-oriented filters.
- 855 fragments with fluorine as a subset suitable for NMR screen.
- Good solubility and stability based on local program.
- Easy to re-synthesize or purchase from vendors.
- High quality with strict QC standards.

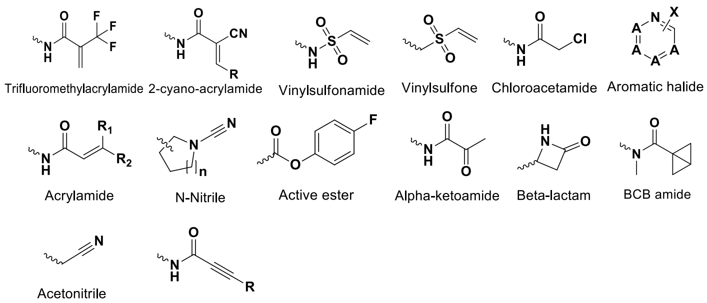


WuXi AppTec fragment library

Commercial fragment library

Covalent fragment library (>2500)

- Covalent fragments with 9 types of warheads targeting different amino acids (Cys/Lys/Tyr/Ser).



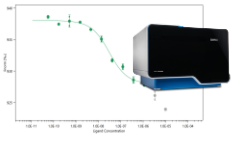
Trifluoromethylacrylamide, 2-cyano-acrylamide, Vinylsulfonamide, Vinylsulfone, Chloroacetamide, Aromatic halide, Acrylamide, N-Nitrile, Active ester, Alpha-ketoamide, Beta-lactam, BCB amide, Acetonitrile, Ynamide

Warhead type	Target Amino Acid			
	Cys	Lys	Tyr	Ser
Activated Alkene	√	√	√	√
Active ArX	√	√		
Alkyl Halide	√	√	√	√
Activated Alkyne	√	√	√	
Activated CN	√	√		√
Active ester		√		
Ketoamide	√			√
Beta-lactam	√	√		√
Strain Release Motif	√			

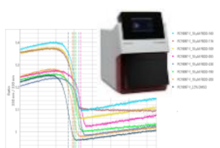
And Combining it With an Optimal Screening Approach

SPR

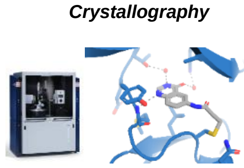
MST



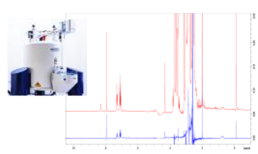
NanoDSF



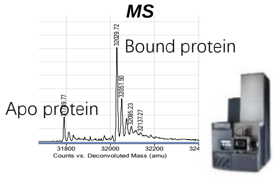
Crystallography



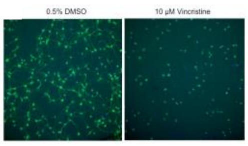
NMR



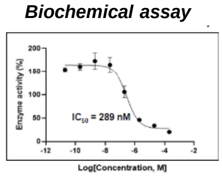
MS



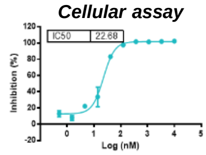
High content imaging



Biochemical assay



Cellular assay

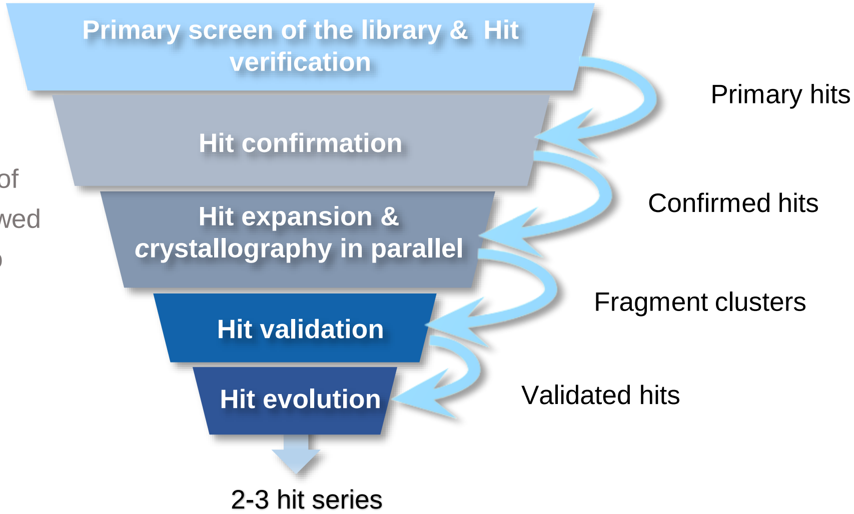


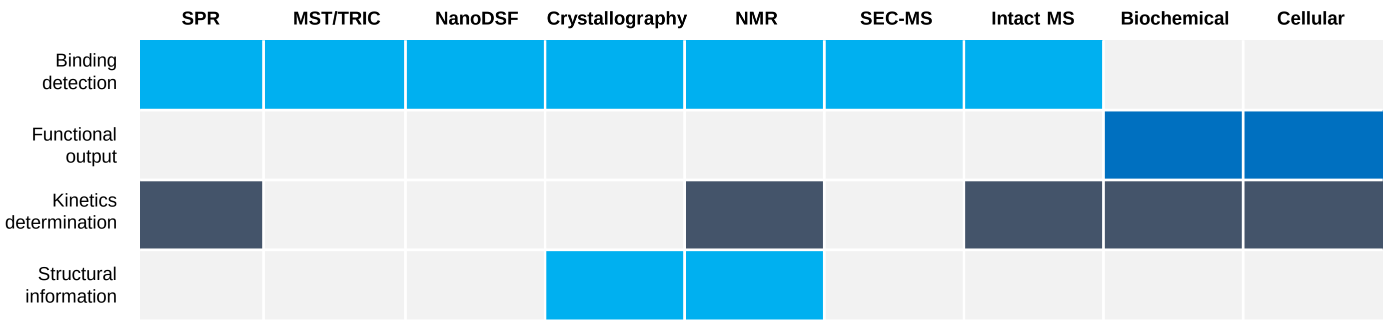
KRASG12C mutation cells

Target Categories: RNA, Helicases, Kinases, E3 Ligases, Transcription Factors, Oncology&inflammation tagrets

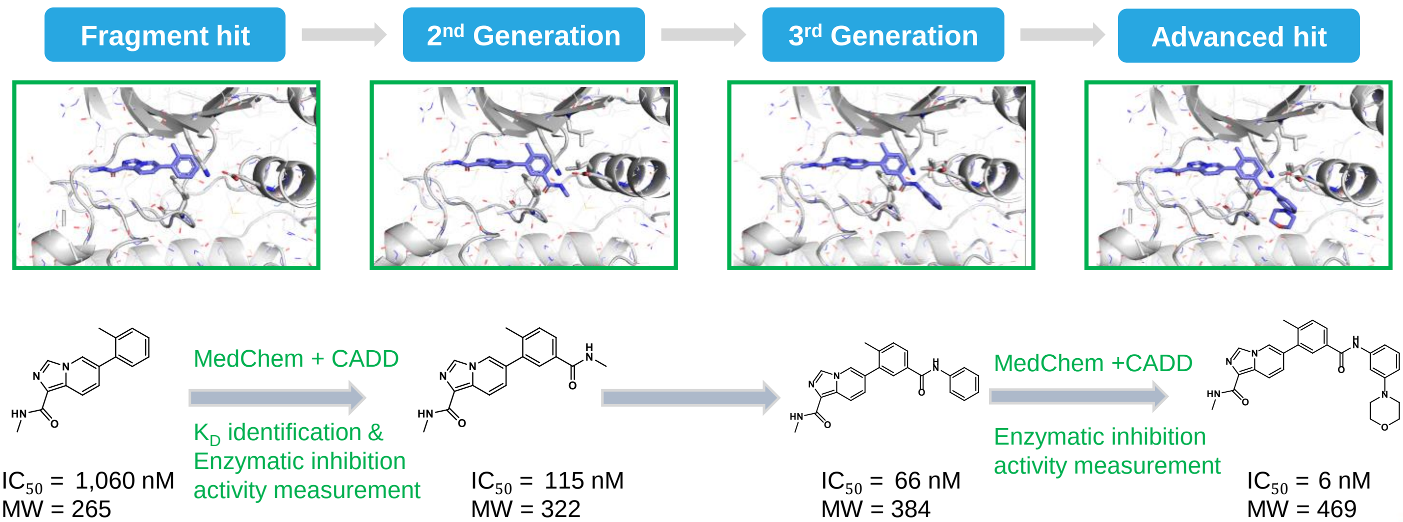
Typical FBDD Workflow

The success of FBDD relies on valid screening of carefully curated collection of low MW and complexity fragments, followed by rational medicinal chemistry design to progress fragment hits to lead-like compounds





From Fragment to Lead Compound



IC_{50} = 1,060 nM
MW = 265
LE = 0.41

IC_{50} = 115 nM
MW = 322
LE = 0.39

IC_{50} = 66 nM
MW = 384
LE = 0.34

IC_{50} = 6 nM
MW = 469
LE = 0.32

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