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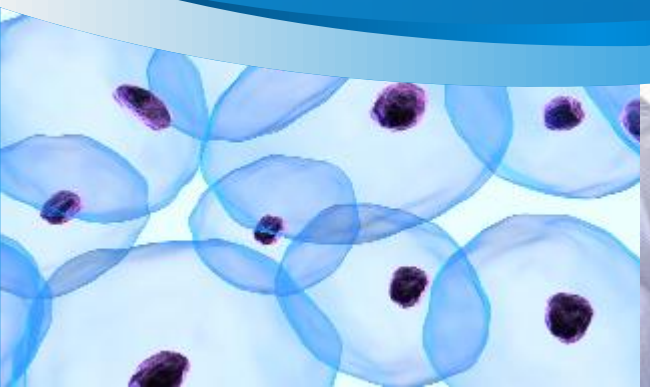
WuXi AppTec

a WuXi AppTec company

Fragment-based Drug Discovery

at

WuXi AppTec´s HitS




Advantages of FBDD

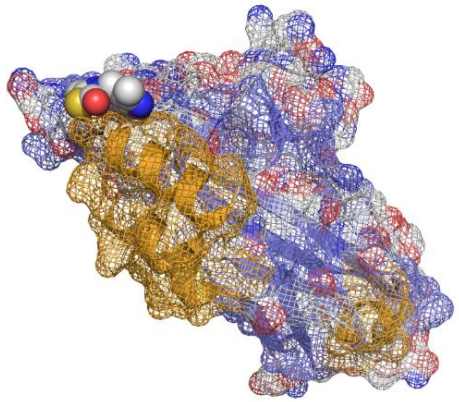
High hit rates (3-10%)

Efficient sampling of chemical space

a diverse set of 1000 fragments represents its chemical space about as effectively as would 10 trillion diverse drug-sized molecules

Ideally suited for targeting PPIs

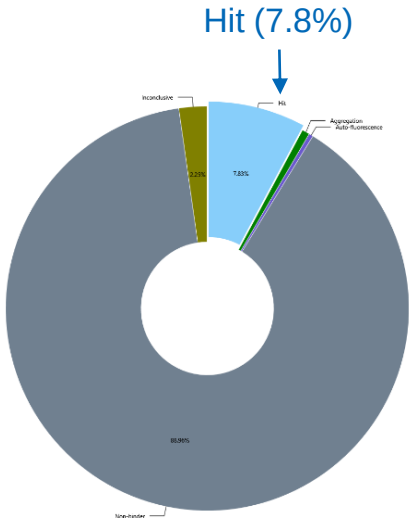
they can bind to small pockets available on the protein surface



Predictor of protein druggability

Obtaining high hit rates is an excellent predictor that high-affinity, small molecule ligands can be identified.

Low hit rates (< 0.1%) strongly suggest an undruggable pocket.



Often unique binding profiles

high-quality interactions between fragment and target

Small-molecule binding

Fragment binding

Chemical optimization

ability to optimize pharmacokinetics profile simultaneously with potency as fragment hit grows to clinical candidate.

WuXi Fragment Library

Diverse collection of about 3100 fragments

Key pharmacophores

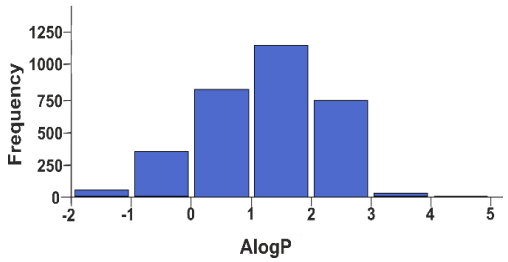
Synthetically accessible

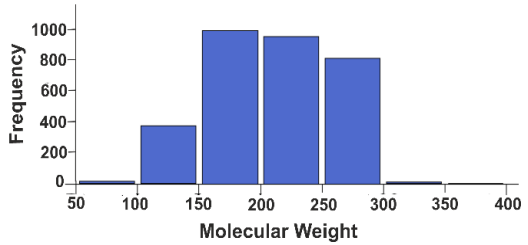
PAINS, REOS, SMART filter

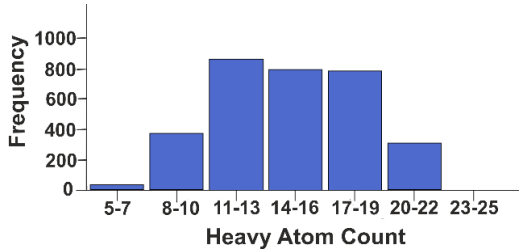
Appropriate complexity

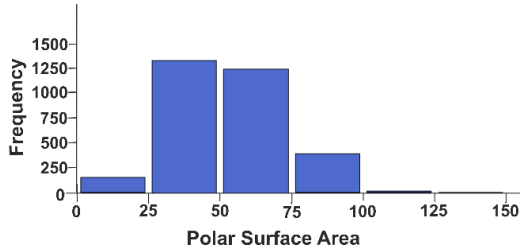
“Rule-of-three” compliant

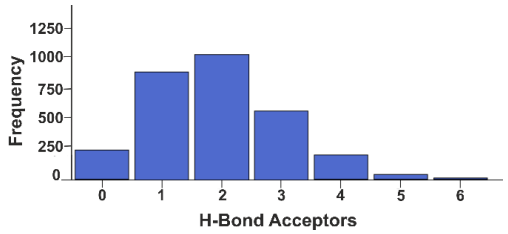
Physicochemical properties of fragment library

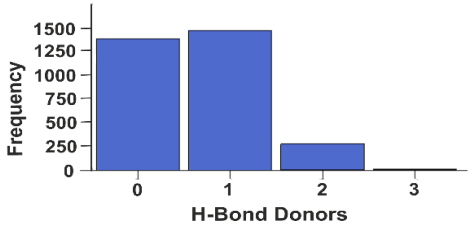


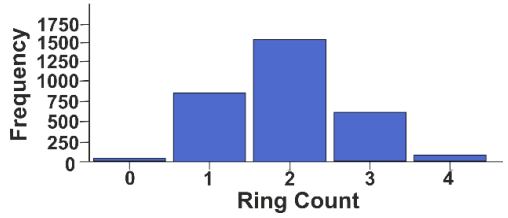


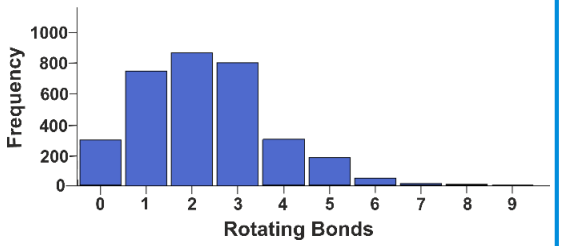






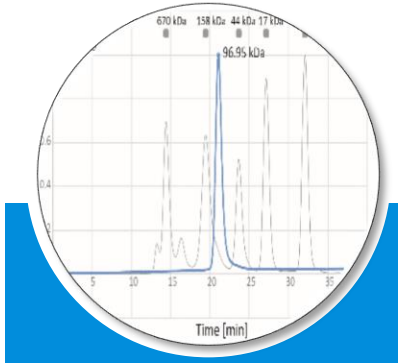




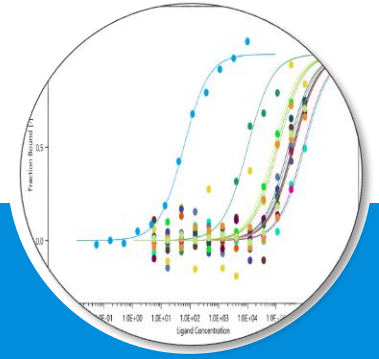


TRIC, MST & SPR based FBDD Workflow (3100 fragments)

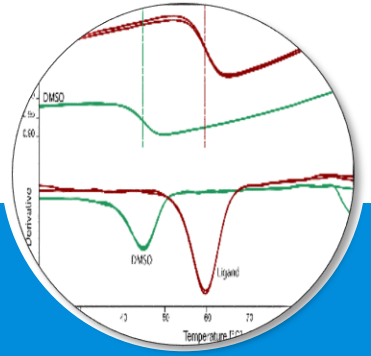
Protein – Fragment Screening – Hit Confirmation – Structure Generation – Fragment Growth



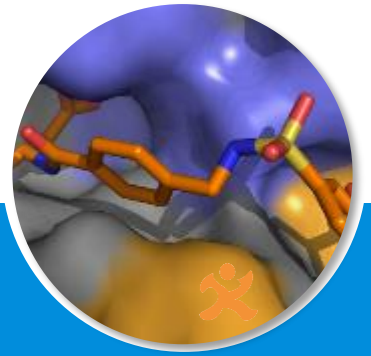
- Protein production
- Assay development



- Single-dose screen
- K_d determination (hit validation)



- Thermal shift (nanoDSF)
- Kinetics (e.g., SPR)
- Binding (e.g., MST)
- Thermodynamics (e.g. ITC)



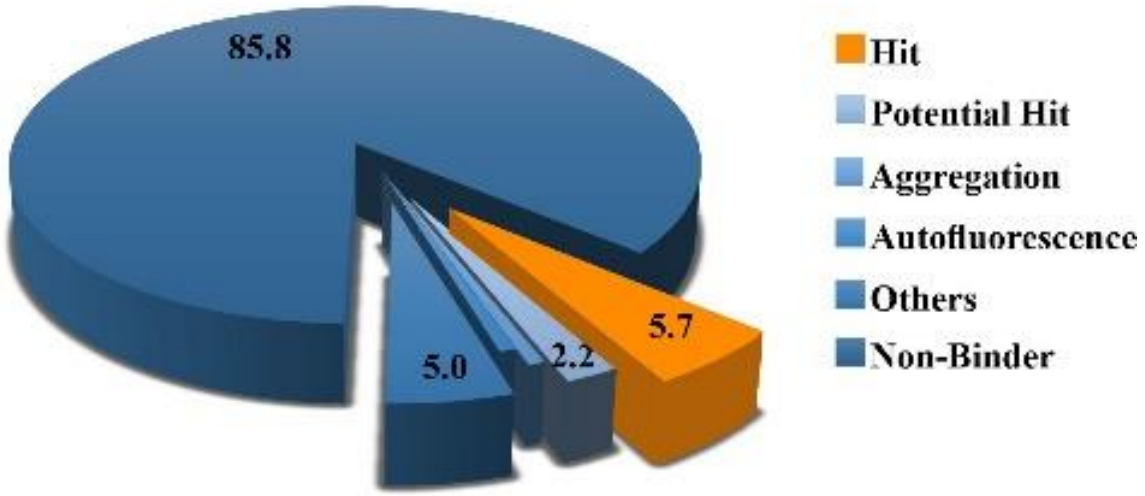
- Crystallography
- NMR

- *In silico* fragment growth
- SAR by catalogue
- MedChem
- Fragment-to-IND development

Faster with high-speed fragment screening

From the fragment library to the list of hits within few hours

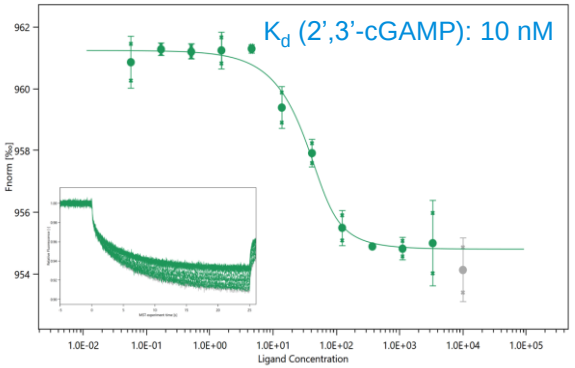
Dianthus NT.23PicoDuo
384 data points within 30 min



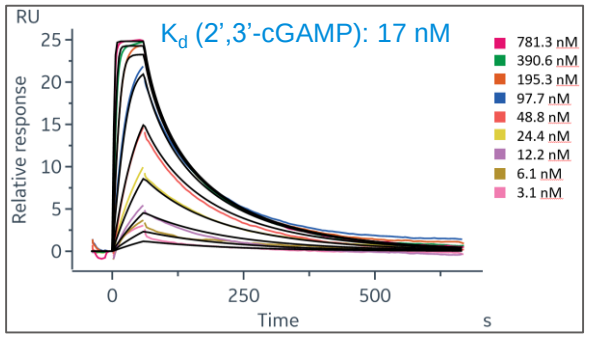
Case Study: STING

Biophysical toolbox for STING fragment screening

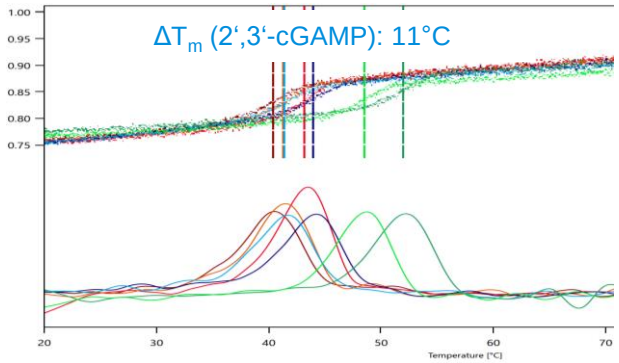
Screening
MST and TRIC



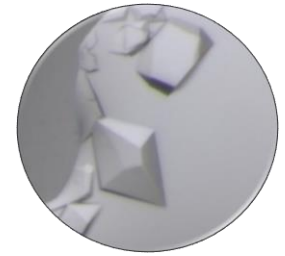
Hit Confirmation
Surface Plasmon Resonance (SPR)



Hit Confirmation
nanoDSF



X-ray
crystallography

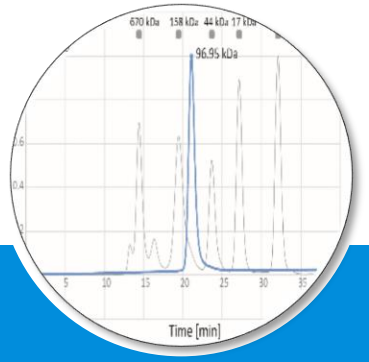


STING study in numbers

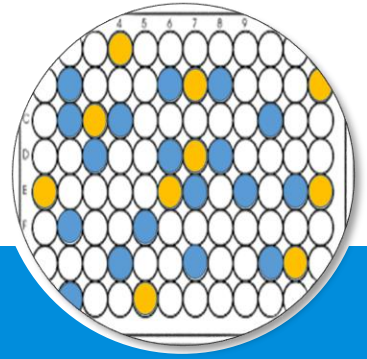
2600	3	66	10 – 500 µM	66
fragments	orthogonal assays	binders	affinity	in crystallization

Crystallography-based FBDD Workflow (few 10 - 100 fragments)

Protein – Library Selection – Soaking – Structure Generation – Fragment Growth

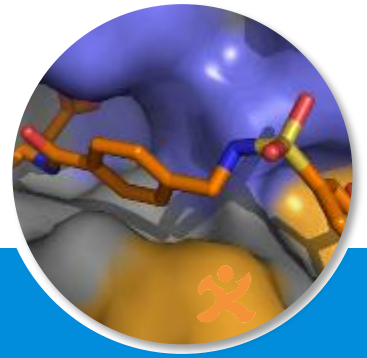


- Crystal Grade Protein production



- Library selection (any provider)

- Identification of crystallization conditions
- DMSO tolerance test
- Fragment soaking
- Data collection



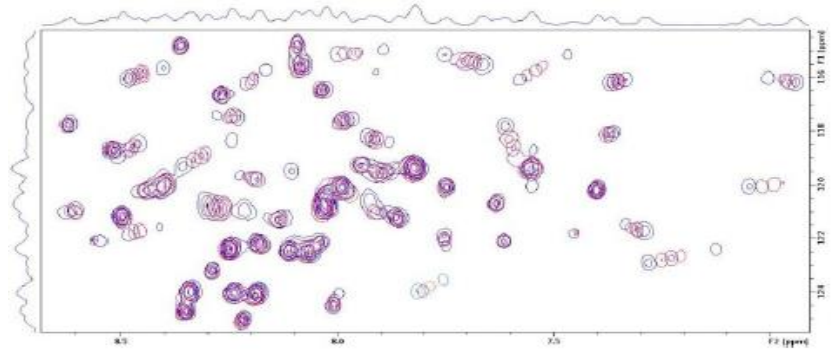
- Automated data processing
- Auto-refinement pipeline and PanDAA
- Manual refinement of chosen hits

- *In silico* fragment growth
- SAR by catalogue
- MedChem
- Fragment-to-IND development

NMR-based Fragment Screening (1500 fragments)

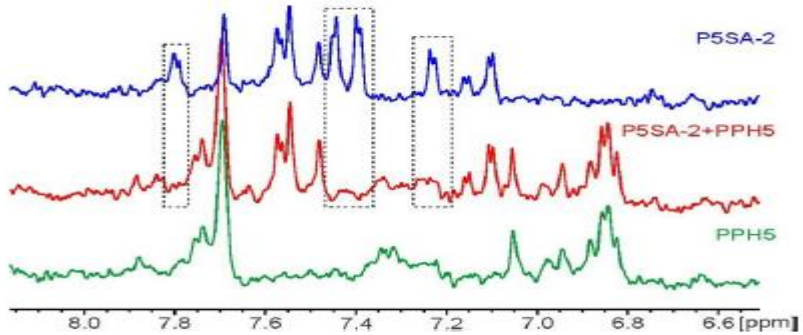
Ligand *vs.* Protein based

Protein- based



- Usually 2D HSQC
- Requires isotope labeling
- Typically > 100 mg protein required
- Delivers SAR information
- Very low false positive/negative probability
- Easy to implement and interpret the data

Ligand-based



- Usually fast 1D experiments
- No labelling needed
- Typically 10 mg protein required
- Prone to false positives/negatives and unspecific binding
- More difficult implementation and data analysis

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