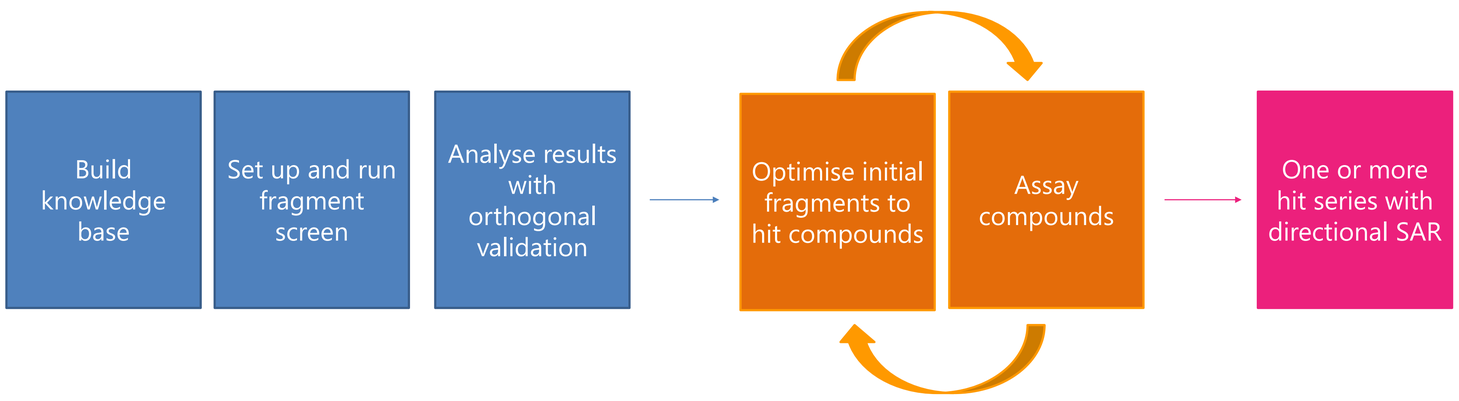
Designing a fragment library: the Domainex approach

Introduction

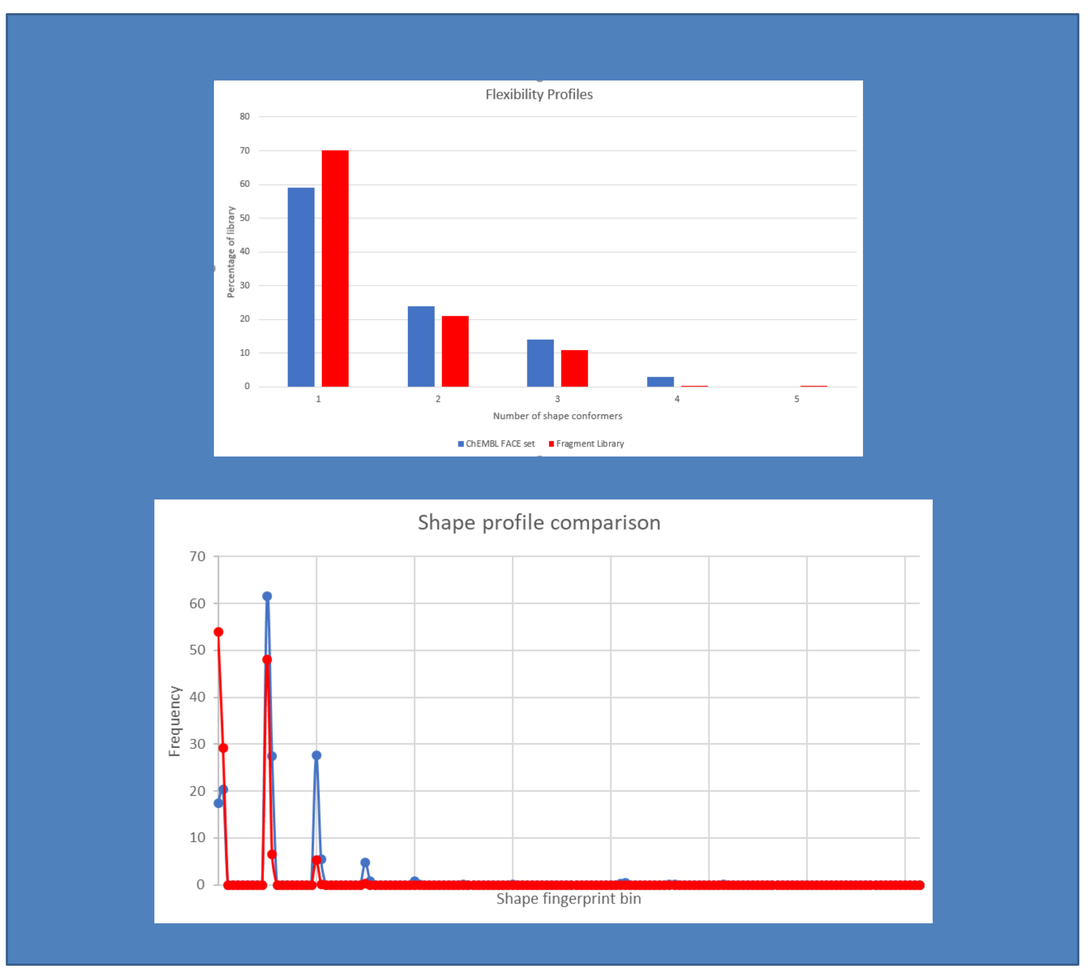
- Fragment screening is a well established approach to underpin the development of ligand efficient hit compounds for progression into drug discovery projects. Compounds resulting from optimisation of fragment starting points are now in clinical use.[1]
- Key to the success of a fragment screening approach is the quality of the underlying fragment library. Domainex have developed the *FragmentBuilder* approach to identifying fragment hits via Microscale Thermophoresis (MST) screening, with orthogonal validation using a range of techniques including X-ray crystallography, DSF and NMR screening.

Fragment Builder



Domainex Fragment Library

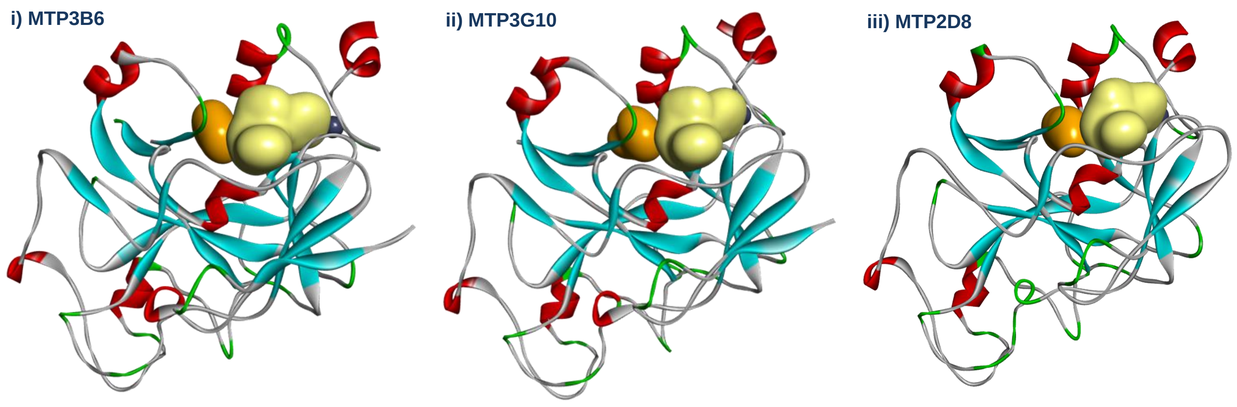
- Domainex, in collaboration with SpiroChem, offers a library of >1000 fragments for biochemical assay, all of which have experimentally measured solubility and QC validation. The fragment library is 'Rule of 3' compliant.[2]
- Numerous studies suggest the importance in having fragments in a library that cover a range of 3D shapes and one popular way to infer this is via the fraction of sp3 atoms in each fragment (Fsp3). AbbVie, in particular,[3] have demonstrated the importance of covering the full range of Fsp3 space, with a particularly important range being 0.4-0.7 in their analysis of available screening data.
- In addition, an ideal fragment library should balance closely mimicking known bioactive space – with potential for rapid expansion of initial hits using SAR by catalogue – with a degree of novelty. An analysis of fragment compounds in ChEMBL, using the shape based fingerprint method,[4] illustrates the need to control compound flexibility during fragment library design.



Case Study: G9a

- The lysine methyltransferase G9a is an important therapeutic target with potential utility in the treatment of cancer.
- A subset of the Domainex fragment library was screened against G9a with a hit rate of 5.3%, identifying fragments with high ligand efficiencies.
- MST allows rapid false-positive identification by highlighting compounds that induce protein aggregation or cause fluorescent effects.
- Fragment hits were further validated using X-ray crystallography. The crystal structures of three of the hit fragments complexed to G9a are shown in the right hand panel. This data enabled an SBDD program for this target.

H) In-house G9a-Fragment structures (Orange –Fragment, Yellow –SAM)



Summary

- Domainex has developed the *FragmentBuilder* approach, which has demonstrated success in identifying fragments suitable for progression into drug discovery projects.
- Quality of the fragment screening library is key. Domainex, in collaboration with SpiroChem, offers a fragment library with 'Rule of 3' compliant property profiles and measured solubility.
- An ideal library covers chemical and bio-active space whilst also providing novelty. It includes compounds with a range of Fsp3 values. The collaboration between Domainex and SpiroChem has resulted in a fragment library which balances these criteria and which can produce hits amenable to rapid optimisation.

Services/Contact

Domainex welcomes interest from any potential collaborators, industrial or academic. If you would like to learn more about applying our drug-discovery platform to other targets, please contact: **tom.mander@domainex.co.uk**
www.domainex.co.uk

References
[1] Erlanson *et al, NRDD*,15, 605, (2016); [2] Rees *et al, NRDD*, 3, 660, (2004); [3] Cox, AbbVie Inc, "Important aspects of fragment screening collection design", Cresset UGM, 2017; [4] Richardson *et al, BMCL*,25(10),2089,(2015)