

Fragment-Based Drug Discovery

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Fragment-based drug discovery (FBDD), while still a relatively new approach, has been so successful for identifying ligands for protein targets that it is already widely regarded as representing a sea-change in drug discovery techniques. The strategy involves identifying small (typically <300 Da), low-affinity ligands ('fragments') and combining or expanding these to produce larger, higher-affinity ligands. The major advantage of FBDD over more traditional high-throughput screening is that FBDD provides a more rapid and effective means of identifying ligands for a protein target. Because there are fewer possible fragment-sized molecules than lead- or drug-sized molecules, FBDD samples chemical space far more efficiently than traditional approaches and therefore requires far fewer compounds to be tested to identify suitable hits as starting points for development. Furthermore, fragment-based screening typically provides more 'developable' compounds than traditional drug discovery approaches, which optimise a medium- to high-affinity hit. Most importantly, fragment methods produce lead candidates with physicochemical properties (described by Lipinski's 'rule of five') that are likely to result in orally bioavailable compounds.

FBDD also has the capability of developing inhibitors of protein–protein interactions (PPIs), about which the pharmaceutical industry has had major reservations in the past as drug targets; that skepticism, however, is gradually being eroded as blockers of such interactions progress to the clinic. Indeed, the recent approval of vemurafenib, a B-Raf(V600E) inhibitor developed by Plexxikon for late-stage melanoma, validates FBDD as an approach to support the development of clinically useful drugs.^[1] Moreover, the Practical Fragments blog (<http://practicalfragments.blogspot.com.au/2013/01/fragments-in-clinic-2013-edition.html>), hosted by Dan Erlanson, lists 25 fragment-derived compounds in various stages of clinical evaluation, and that number is likely to be an underestimate.

The ingredients of a successful fragment-based drug discovery program are a stable biomolecular target that can be produced in milligram quantities, a well-constructed fragment library, one or more biophysical screening methods, and access to medicinal chemistry expertise to develop promising hits. It helps to have a high-resolution structure of the target, determined by either X-ray crystallography or NMR spectroscopy. As all of these are accessible in an academic research environment, and do not require access to sophisticated robotic platforms or dedicated assay development, there is enormous interest in FBDD within the academic community in Australasia and elsewhere. As a reflection of this, a two-day workshop 'Fragment-Based Drug Design Down Under' was run at the Monash Institute of Pharmaceutical Sciences, Parkville, in November 2012, attracting over 100 participants. This Special Issue of the *Australian Journal of Chemistry* captures the spirit of this workshop and highlights some of the work being pursued in Australia in this rapidly developing area.

Fragment screens can be undertaken with commercially available libraries, although most practitioners prefer to create their own. Issues related to constructing a purpose-built fragment library are described in the articles by Doak et al.^[2] and Francis et al.^[3] The article by Jonathan Baell and colleagues^[4] outlines some of the chemical properties to be wary of in both fragment-based drug discovery and high-throughput screening, as encapsulated in his concept of PAINS.

Screening is mostly undertaken using biophysical techniques, as conventional biochemical methods are often not sufficiently sensitive to identify the modest (often mM) affinity of fragments for the target protein. Many such techniques are used to identify fragment hits, each with its own strengths and weaknesses, and it is advisable to employ at least two orthogonal methods to eliminate false positives. Mass spectrometry



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approaches are described here by Poulsen,^[5] thermal shift assays by McMahon et al.^[6] and surface plasmon resonance, isothermal titration calorimetry and X-ray crystallography by Dolezal et al.^[7] The importance of recognising aggregating fragments that can lead to false positives in screening undertaken by saturation-transfer difference NMR, which is a widely-used method, is discussed by Vom et al.^[8]

Headey et al.^[9] give an example of how NMR can be used to guide the optimization of fragments in the absence of an atomic resolution structure of the protein target. Examples of applications of FBDD to specific targets are provided in the articles by Lim et al. on a malaria surface protein^[10] and Chhabra et al. on an enzyme from *Staphylococcus aureus*.^[11] This Special Issue concludes with an optimistic overview by Martin Drysdale of the future for FBDD,^[12] which also highlights some exciting new developments that promise to further enhance the power of this approach, including the introduction of three-dimensionality into fragment libraries.^[13] This field offers many exciting opportunities for the chemistry community; we hope you share the enthusiasm of the authors for the prospects it offers to produce new biological tools and eventually new therapeutics.

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