Opportunity knocks

Does every cloud have a silver lining? Dr Phil Jones, Chief Scientific Officer, BioAscent Discovery, outlines the opportunities for lead generation and the acquisition of compound screening libraries.

By Phil Jones

About the author:
Dr Phil Jones has over 30 years medicinal chemistry and drug discovery experience from Roche, Organon, Schering-Plough, Merck and the University of Dundee. He was a member of the Research Leadership Council at Schering-Plough. Numerous clinical candidates resulted from groups for which he was responsible. He has led the European Screening Centre team at Biocity Scotland, Newhouse for the past five years which plays a key role in delivering validated hit series for SMEs and academics through the IMI funded European Lead Factory. He is a co-author on over 70 scientific papers and patents.

The discovery of novel medicines is a complex but vital endeavour. The range of approaches being used to identify those new medicines is ever widening with, for instance, new modalities creating opportunities to utilise new modes of action for therapeutic gain[1]. However, small molecules will remain a key pillar to drug discovery[2]. Small molecules have an outstanding track record of delivering therapeutic benefit across a range of disease areas and whilst the route to their discovery and proof-of-benefit is long and time-consuming, the successes in improving the quality of life of patients are remarkable. The journeys to such molecules start with a therapeutic biological rationale but rapidly require chemical matter to create a viable starting point for optimisation. The quality of that chemical matter is key to determining the trajectory of success of the project. High quality leads frequently advance more quickly to and through lead optimisation and prove more robust to failure in clinical development. Therefore, the selection of a high-quality starting point is a decision with long-lasting and potentially high-value consequences.

Not surprisingly, much effort has been focussed on methods to identify these starting points. Essentially there are two strategies: knowledge-based approaches and screening-based approaches although these methods are not discrete but form a continuum.

For screening-based approaches there have been, and continue to be, different tactics to reduce or increase the size of the initial screening library to be searched: think fragment libraries (approx. 1000 members) and DNA-encoded libraries (many millions) representing different ends of this spectrum. Likewise, the application of knowledge to reduce the amount of testing required to find a starting point has employed a range of successful tactics including using enzyme substrates to guide the design of inhibitors and endogenous ligands to do likewise for receptor modulators. The use of biostructures to direct the properties and selection of leads is an attractive approach. Of course, knowledge-based approaches include utilising the primary and indeed patent literature as sources of lead compounds remembering Sir James Black, winner of the 1988 Nobel Prize in Physiology and Medicine who famously stated that, "The most fruitful basis for the discovery of a new drug is to start with an old drug". The application of computational methods eg virtual screening[3] and most recently including AI provides new ways to apply knowledge for the selection of libraries or leads[4].

Whilst the author would argue that high quality leads are so valuable that it is worth employing several lead generation methods in parallel to achieve this goal, frequently pragmatic considerations reduce the options. Focussing on high throughput screening (HTS), the requirements for a successful screen are considerable. They include: a well-curated compound library held in a secure facility which maximises the lifetime of the precious library components; extensive infrastructure capable of developing/miniaturising the assay and then testing >100,000 compounds in the initial screen of the library; a logistics infrastructure to enable follow-up sample handling and an expert and experienced team to perform the activities above. In addition, the triage of the initially identified actives to high quality hits requires a range of further techniques including biochemical and biophysical screening and analytical and medicinal chemistry to avoid the inevitable interference compounds[5]. Accessing such facilities and expertise is often restricted to major pharma companies which have the resources to invest in establishing this infrastructure and developing this expertise, although a small number of CROs (including BioAscent) have the necessary infrastructure, library and (perhaps most importantly) expertise. However, since 2013 academic groups and small companies have been able to benefit from access to the European Lead Factory (ELF) established with funding from the Innovative Medicines Initiative[6]. The ELF has established a bespoke high-quality compound library of over 500,000 compounds sourced from contributing pharma companies and specialist chemistry SMEs. A screening infrastructure has been established – the European Screening Centre – with expertise in compound logistics, protein production, assay development, high throughput screening, biophysical screening, biochemical and biostructural characterisation, IT, scientific collaborations, medicinal chemistry through a group of commercial and non-commercial groups including BioAscent Discovery, Lygature, Pivot Park Screening Centre and the Universities of Dundee and Oxford. The ELF partners have prosecuted over 180 high-throughput screens and provided high quality lead series for multiple academic and commercial collaborators[7,8]. Some of these hit series have subsequently been developed to clinical studies[9].

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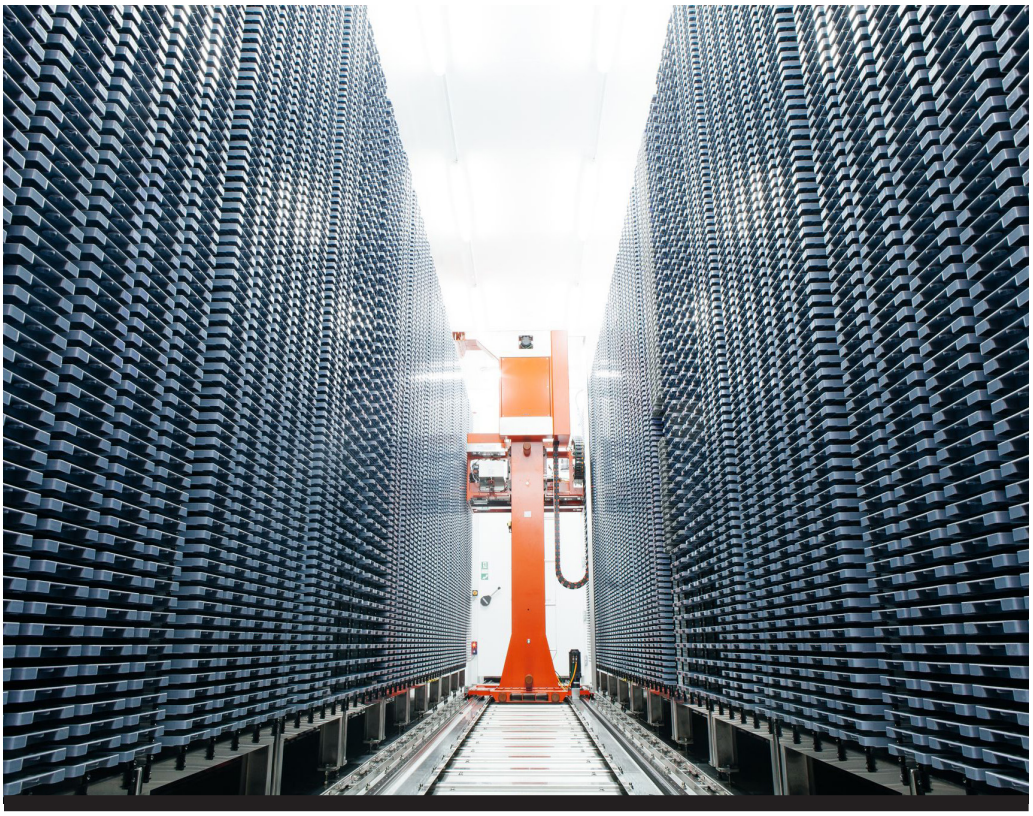
An alternative approach is to use smaller libraries where the choice of compounds screened is guided by knowledge of the target or screening approach. For example, specific structural motifs may be preferred as a consequence of knowing the target class or specific physicochemical properties may be preferred to maximise the chances of success in cell-based assays or if the target resides in a less accessible biocompartment eg beyond the blood-brain barrier[10]. Many of the skills and capabilities required are the same as for screening large numbers of compounds but the infrastructure is more modest due to the reduction in numbers to be tested. Even though the selection of compounds is guided by knowledge the team still must be alive to the risks of false positives and so not reduce the rigour of the triage and analysis of the results that follow[11]. Experience and expertise of the project scientists in the area of hit triaging is key to a successful and efficient outcome and should be taken into account when selecting a partner. Of course, central to the success of this approach is the availability of suitable compounds. There are now many suppliers of such compounds[12], but this choice brings with it new issues. The selection of 100s or 1000s of compounds will likely require computational support and obviously availability of the chemical structures of the compounds in a suitable format for analysis eg SD file is vital. The logistics issues can be daunting with using multiple suppliers given that the formats that compounds will be supplied in, delivery times and availability will vary. Once compounds arrive, they may need to be dissolved, aggregated and formatted into suitable plates to enable testing. Thus, assembling a bespoke compound set for a specific screen requires diligence and time-consuming effort. Specialist companies supporting these activities are available, such as Molport and BioAscent[13].

A compromise between the full HTS and the knowledge-based selection is the iterative screen. Here, the results from an initial screen of a subset of the library are used to guide the selection of a second set. This process can be repeated several times to sample the chemical space of the library whilst only physically testing a fraction of it. To successfully prosecute this approach the methods used above to select a subset of the library need to be repeated several times. The iterative screening approach has the advantage over the knowledge-based screen that the selections are guided by experimentally determined results.

One of the advantages of the large-deck HTS is that HTS has the potential to identify unexpected compounds as hits and potentially provide truly original starting points. By definition, the knowledge-based approach reduces this likelihood as there is a rationale for including all the components in the screening set. The iterative approach potentially combines the advantages of both methods – sampling a wide range of chemical space but with a much-reduced number of compounds. Of course, the iterative approach is highly dependent on the initial selection. It is also highly dependent on access to the required infrastructure as multiple bespoke screening sets are required.

Another consideration to be taken into account is that the compounds selected for any of the approaches above but which do not have the desired properties (realistically most of them) will be surplus to requirements for the project in question and must either be disposed of or stored for the next project (with associated cost) and, of course, the more bespoke the selection procedure the less likely the compounds acquired will be required in future.



Compound management supplied: *Flexible storage systems, like this one at BioAscent, provide the key to efficient large-deck screening as well as focussed approaches.*

Outsourcing is now a central pillar to drug discovery and experts in this area are available to support clients by providing compound libraries to assist in identifying lead compounds. When choosing a partner to provide compound libraries the author would suggest the following criteria are used to assess alternatives:

- Access to chemical structures prior to purchase
- Broad diversity of compounds available
- Rapid access to any selection of the compounds in the library
- Cost
- Storage facilities which maximise the lifetime of samples
- Availability in formats suitable for screening
- Only get what you need to avoid need for subsequent disposal or storage
- Availability of follow-up samples
- Experienced team

Collections such as BioAscent's Compound Cloud satisfy these criteria, combining both a wide range of compounds with expertise to enable cost-effective flexibility in the choice of screening sets.

Selecting the right compounds is a key decision in the success of your small molecule drug discovery project. There are now multiple players in the compound suppliers' field. Selecting the right compounds starts by selecting the right partner, which in turn will impact on the success of your drug discovery project.

> **The most fruitful basis for the discovery of a new drug is to start with an old drug.**

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