New Drugs from Old

Exploring the chemical space around existing drug molecules provides a lower-risk, lower-cost strategy for the discovery of new chemical entities.

Sir James Black, winner of the 1988 Nobel Prize in Physiology and Medicine, famously stated that: “The most fruitful basis for the discovery of a new drug is to start with an old drug.” Disillusioned with HTS, and struggling to bring new chemical entities to market, many companies are turning back to Sir James’s wisdom. They are finding unexploited potential in the chemical space around existing drugs, which is yielding therapeutic and business returns.

In commerce, the first to market with a product or service does not always end up as the market leader. Innovators are vulnerable to fast followers, who seize the new idea and adapt and improve it, often opening up new markets in the process. The followers avoid a lot of the risk to which the innovator was exposed and, furthermore, can take advantage of the experience gained by their rivals. So this applies in pharmaceutical discovery too.

Once a drug has been discovered, companies work very hard to make sure its full potential is exploited. This may involve reformulating the active compound to improve delivery methods, or determining whether the compound may be active in different therapeutic areas. Interestingly, scientists also take known drugs as starting points for making structural changes. Searching the chemical space around an active compound has proven to be a fruitful strategy and a growing number of companies have taken this approach as their business model, reflecting the growing trend to ‘start with what you know’.

Re-Using Existing Drugs

Re-using existing drugs is the lowest risk approach that a company can take to developing their drug portfolio and exploiting their existing intellectual property. The most common approach is to reformulate an existing drug; in fact, pharmaceutical companies are continually working on reformulations of their drug portfolio. New formulations may increase patient convenience by improving the delivery method or increasing the half-life so that less frequent doses are required.

AstraZeneca developed Nexium by making process changes to the production of their existing proton pump inhibitor, omeprazole, by selecting only the structure with a single enantiomer. Nexium was the second highest-selling pharmaceutical product in the US in 2011.

Another straightforward way to re-use an existing drug is to combine it with another drug to find synergies. GlaxoSmithKline’s Advair, with US sales of $4.7 billion in 2010, was the result of combining the two pre-existing asthma treatments, salmeterol and fluticasone.

The third main way to re-use an existing drug is to re-purpose it in a new therapeutic area. Many companies look for alternative indications for their own drugs in order to extend the market and the patent life for a compound. Literature searches can reveal side effects or off-label usage of drugs that point to applications against a new target.

For example, Johnson and Johnson’s anticonvulsant drug, topiramate, was originally approved by the FDA in 1996 as a treatment for epilepsy. It is now most frequently prescribed as a treatment for migraine, for which it was approved in 2004.

Melior Discovery’s business model is built on finding new applications for known drug-like compounds. They use a set of in vivo assays across a range of broad indications to look for activity in other therapeutic areas. They can produce a complete pharmacological profile of a compound in about 10 weeks. However, this is ultimately a slow way of analysing the large number of compounds that have made it through to Phase 3 trials.

A more efficient approach can be to use computational techniques to analyse the activity profile of an...
This method is used to build up the pharmacophore – a template of field patterns that a compound is likely to have to be active against a particular protein target. This pharmacophore is then used to search databases of compounds to find matches. It can also be used to evaluate drug candidates that result from a literature search or other discovery methods.

Using Pharmacophores to Find New Targets for Existing Drugs

Pharmacophores are a computational method of expressing the activity profiles of molecules. They can be used to search for other compounds with similar activity profiles that may give an indication of new targets against which compounds may be active.

Traditionally, computational chemists analysed the relationship between a compound’s chemical structure and its known activity. Statistical analysis led to the development of a quantitative structure activity relationship (QSAR) model that could be used predictively on potential drug-like molecules to give an estimate of their likely activity.

However, as can be seen in Figure 1, biological activity is not always directly related to chemical structure. An improved computational approach uses the molecular fields of a compound to analyse the way it interacts with a protein target. The field pattern at the active site gives a ‘protein’s eye’ view of the compound. This goes much further than the 2D chemical structure of the compound in describing the actual biological interactions taking place.

Often, there are a number of compounds that are known to be active against a particular target. This makes it possible to gain more information by looking at the consistent patterns of interaction to determine the most important interaction sites for the protein.

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Finding New Chemical Entities Based on Existing Drugs

An approach that has yielded some of the greatest rewards is to take existing drugs or drug-like compounds as the starting point for the discovery of new chemical entities (NCEs).

This approach is largely computationally based and involves searching the chemical space around existing compounds by making structural changes to come up with an NCE. The aim is to find a new compound that not only retains the activity of the parent compound, but also shows some improvement, either in terms of improved activity or a reduction in side effects. The fact that the resulting compound will have a similar chemistry to a known active significantly increases the likelihood of activity and therefore return on R&D spend.

The FDA requires that new licensed drugs must not only fulfil their function safely, but also fulfil it better than existing licensed drugs.

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Figure 2: The power of scaffold hopping to explore new chemical space while retaining biological activity. Pfizer’s sildenafil (left), Bayer’s vardenafil (centre), and a known PDE5 active reported by Novartis (1) (right) have different scaffolds yet express similar field patterns.

Scaffold Hopping

Scaffold hopping is an ideal approach to making changes to an existing compound. Computational field technology is used to find biologically equivalent replacements for key moieties in the molecule. The activity profile of the new compound can be compared with the starting point or with a pharmacophore. It is an extremely effective method of exploring new chemical space.

This approach is well validated. Bayer’s Levitra (vardenafil) was created by altering Pfizer’s Viagra (sildenafil) molecule. The small chemical change involved a substitution of the nitrogen positions in a fused ring, which was not covered by Pfizer’s patent. Computational analysis of the field patterns of the two compounds shows that this structural change had only a subtle effect on the molecule’s field pattern.

The analysis of field patterns around new scaffolds can also be extended to other chemical series. For example, as shown in Figure 2, the Novartis PDE5 compound (1) shows a similar field pattern to Levitra and Viagra. This comparison of field patterns around potential new scaffolds can prove valuable in informing chemistry decisions.

Fragment Swapping

Redx Pharma Ltd takes an alternative approach to securing new intellectual property by preparing compounds that are one or more oxidation state removed from known drugs. The structural similarity of these compounds to their well-characterised parent drugs lowers their overall risk profile and reduces development times. Redx has an ongoing collaboration with Cresset BioMolecular Discovery Ltd to perform computational screening of the new analogues to prioritise them for synthesis.

Under their collaboration, Cresset carries out a field point analysis of the proposed compounds and prioritises them based on their field similarity to known active drugs. Cresset’s software tools are used to provide binding hypotheses and predictions of the likely biological similarity for sets of molecules in various lead series.

Redx’s anti-viral project started with the known anti-flu compounds zanamivir, oseltamivir and peramivir. Their chemists proposed modifications and then Cresset’s consultants scored the results and the best candidates were synthesised. They found good correlation between the predicted field similarities and the inhibition of neuraminidase.

Conclusion

Many companies have come to know the truth of Sir James’ statement and have used old drugs as the starting point for finding new drugs. Companies are continually looking to maximise the potential of their existing drug portfolio by reformulating drugs and looking for new applications in new therapeutic areas. Other companies are finding that exploring the chemical space around existing drugs is a rewarding way of discovering new chemical entities. Computational chemistry is powering research in this area, providing insight into biological activity through field technology software to identify the most promising candidates and optimise potential hits in a number of therapeutic areas.

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Reference


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