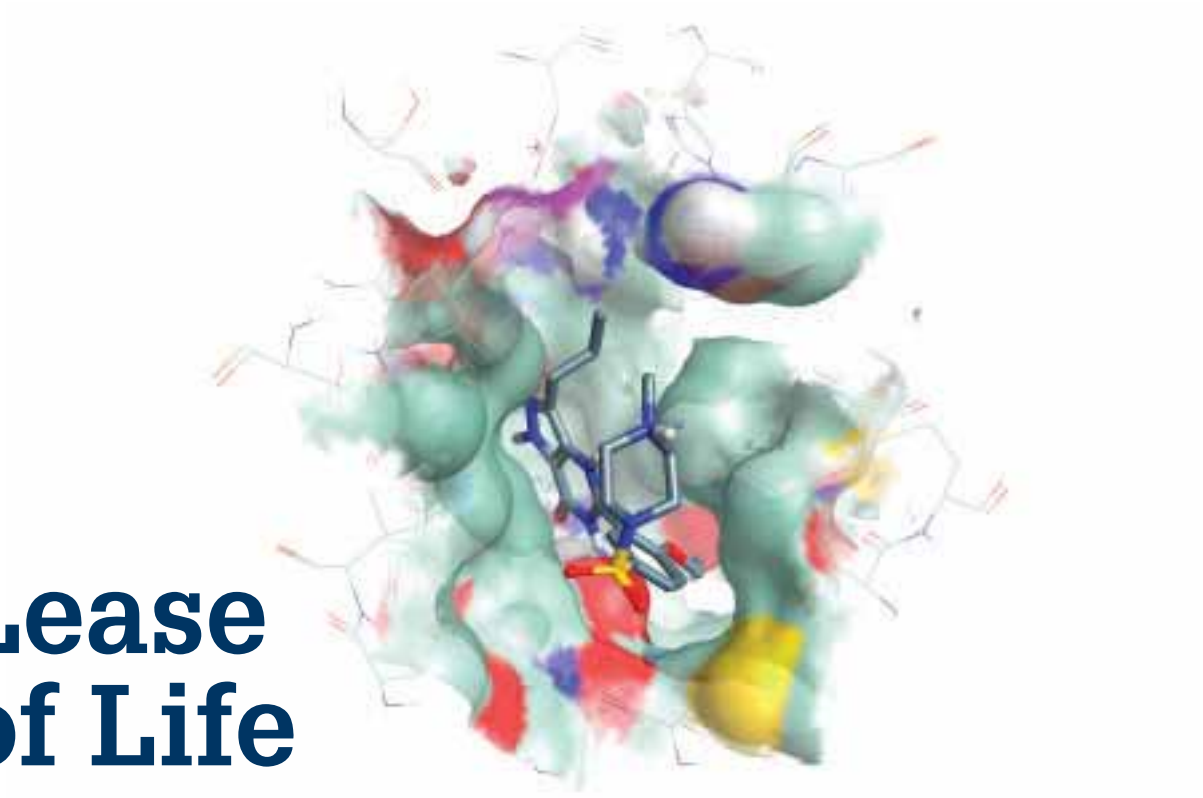

Images: © Re-Pharm

Lease of Life

By combining pharmacological expertise with computational chemistry tools, it is possible to create a rapid route to identifying new activity and intellectual property for existing pharmaceutical compounds. Building on existing understanding, fast development of potential substances can lead to earlier patient access

Robert Scoffin and
Alan Rothaul at Re-Pharm

Drug repurposing – the positioning of an existing drug for a new medical use – has many advantages over *ab initio* drug discovery, including a shorter time to market and a more predictable development pathway. When a drug is repurposed for an alternate use, developers can build on the existing understanding of safety and kinetics already established in the original use of the drug. This reduces the risk of failure and often allows for more rapid development, resulting in reduced costs, an efficient path to approval and, ultimately, to earlier access by the patient population.

Image (above): Sildenafil in the active site of human phosphodiesterase 5, as rendered in Forge. An example of compound reprofiling from hypertension to erectile dysfunction

Where to Start

Like all drug discovery processes, there is an art to choosing the right projects. The starting point for a repositioning project is the identification of a commercially interesting target with clear, unmet medical need. This has to be combined with some sort of pharmacological clue that would result in a viable treatment. For repurposing projects, this clue could come from a number of sources, including:

- Drugs that work but are not viable as therapies due to issues with safety, kinetics, delivery methods or other late-stage development difficulties
- A commercially marketed drug with reported side-effects that may be in themselves of therapeutic value
- Reported off-label use, when a drug is being commonly prescribed for a condition other than that for which it was developed

Any of these situations may point to a promising repurposing opportunity. However, the existence of sufficient evidence to indicate a potential for repurposing often means that it would be extremely difficult, or impossible, to gain any intellectual property (IP) rights. Therefore, only the current patent holder would be able to make a business case for undertaking repurposing work on such a compound.

A far more desirable starting point for a repurposing project is the uncovering of new scientific information: either the discovery or elucidation of a new target, or a better understanding of the mechanism of action of a pathway. This opens up the possibility of repurposing existing compounds for a novel target, bringing far more potential for securing clear IP.

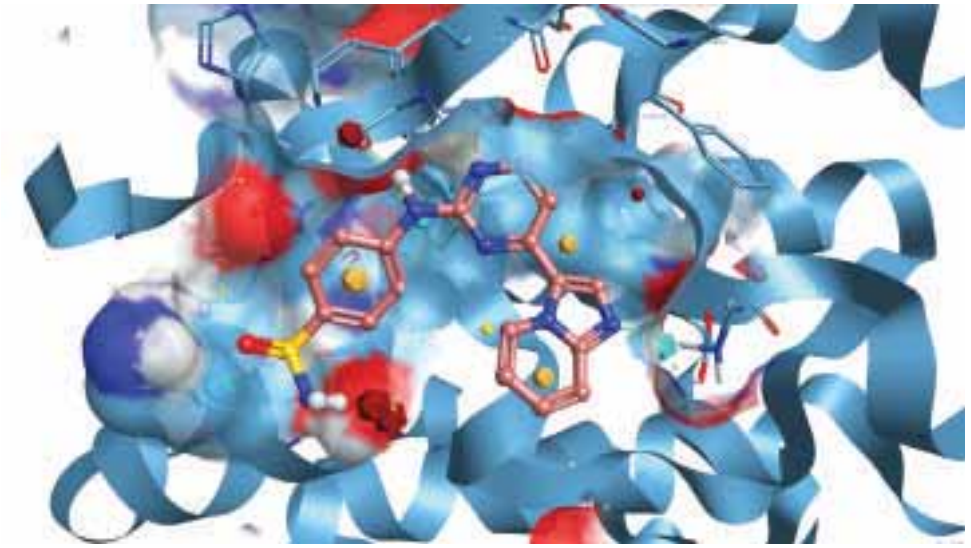

Figure 1: A ligand in a protein binding site displayed in Forge. Knowledge of the protein structure and ligand position are the ideal ingredients for building a successful pharmacophore

Timely Triaging

Successful repurposing projects have to act fast. The point of repurposing is to save time and money in order to get a drug to market as quickly as possible. One of the keys to rapid identification of repurposed compounds is to have a timely triaging process in place for both the targets and the candidate compounds.

Once a potential target has been identified, it is important to qualify it in terms of how easy it is to perform an assay on it. The ideal target will have a quick and meaningful biological assay available to confirm the activity of a repurposed candidate. Targets that cannot easily be assayed will not be suitable for a repurposing project.

When it comes to finding and testing candidate compounds, traditional drug discovery methods take months or even years. This length of time is clearly not economically viable when considering repurposing.

Computational Screening

Computational chemistry software makes it possible to rapidly identify and evaluate all of the possible matches between a target and existing drug compound.

Firstly, a computational template is developed which represents the characteristics that any candidate compound must possess. This template is also known as a pharmacophore. The success of the whole screening process relies on building a sufficiently accurate pharmacophore against which to score potential compounds. This is not a process that is automated by software; it requires the skills of a chemist with experience in drug discovery and computational chemistry.

If the target is well-characterised, the pharmacophore can be built from an X-ray crystallographic structure. Alternatively, it can be constructed by analysing and comparing known ligands. If possible, both of these methods will be used in combination. The ideal pharmacophore includes the essential steric and electrostatic characteristics of any compound that is likely to bind with the target.

The next stage is to compare the pharmacophore against each compound in a database of marketed drugs and late-stage clinical pipeline compounds. The software Forge can be used to codify the electrostatics and compound shapes in a way that makes it computationally viable to search databases of thousands of compounds to find new chemical series with similar biological activity.

The way in which the modelling software handles the electrostatic, steric and hydrophobic characteristics of the molecules determines how accurately the biological activity can be evaluated. Forge depends on the XED force field to make realistic comparisons of biological activity and, therefore, to return candidates with a high chance of success (1,2).

Comparison between structures and the pharmacophore is an automated process, but it is computationally intensive. On average, each comparison takes between seconds and minutes to compute. Databases work from several thousand

Reprofiling Case Study

A recent study aimed to identify novel anti-inflammatory activity for an existing compound. The starting point for this project was a new enzyme target that had been identified. Beginning with an assessment of the target, it was decided that it had good commercial and pharmacological potential. As a result, a search was launched for an existing drug that could be repurposed against it.

There were several known ligands and a crystal structure available, allowing the Forge software to build a pharmacophore. The same program was then able to screen the pharmacophore against a database of thousands of existing drugs, in order to pinpoint those that were likely to be active against the new enzyme target.

The results were evaluated and tested, and RP0217 was identified as an effective new anti-inflammatory agent. RP0217 is an existing drug that is widely prescribed for non-inflammatory conditions. The identification of this novel activity creates the opportunity to develop new non-steroidal approaches for the treatment of a variety of disease indications.
In addition, RP0217 has been demonstrated to boost the activity of existing steroids, and has the potential to be used in combination to achieve effective anti-inflammatory activity, while avoiding the serious unwanted aspects of high-dose steroid therapy.

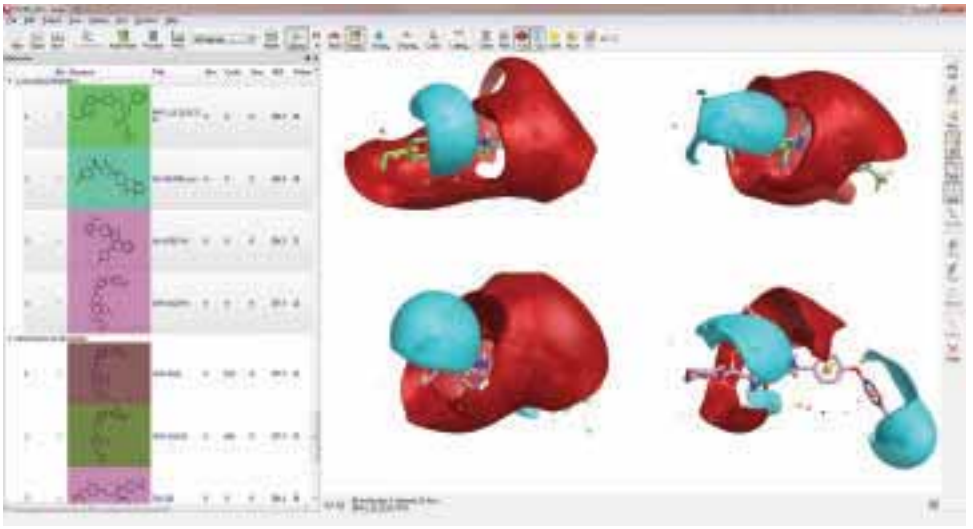

Figure 2: Forge illustrates similarities between molecules allowing for the identification of reprofiling opportunities. The handling of electrostatics based on the XED force field reveals the similarities between structurally diverse compounds

structures of known drugs and close-to-market pipeline compounds, so a full search may take up to a day to complete.

Finally, the hits from the database search are scored and returned in order of priority. The automatic scoring function is based on the similarity between the compound and the pharmacophore, and can be adjusted to give priority to different features. Even so, evaluation of compounds is ultimately a human task.

Advancing Compounds

Each potential hit must be manually reviewed and evaluated to produce a shortlist of prioritised compounds for testing. The results have to be evaluated for:

- Activity against the target
- The IP position and potential freedom to operate
- Compound selectivity, including absorption, distribution, metabolism and excretion, in addition to toxicity risks

All of the compounds that are identified for testing already have some known history. This is always considered when assessing how easy it will be to develop a candidate and when predicting future market opportunities.

One of the key concerns in repurposing is the IP position of any potential compound. In order for it to be possible to develop leads, they have to be clear of prior art. Repurposing of existing compounds means that substance of matter patents are usually not feasible. This leaves traditional use patents and, possibly, formulation patents as avenues to gain an IP position.

Attaining a second medical use patent on an existing compound is a difficult, and somewhat specialised, task. It requires very careful, and usually narrow, definitions of the compound of interest and the therapeutic indication being targeted. There also needs to be sufficient biological data to validate the surprising discovery of new activity.

Once the results have been evaluated *in silico* and *in cerebro*, the best compound is validated in further confirmation and secondary screens in order to assess how suitable it is for development. The most viable repurposing targets will possess an *in vitro* or simple *in vivo* screen that can be used in low-throughput mode to assess a small number of candidate compounds. This can be done sequentially or in parallel with small batches – the key being to find activity quickly and economically.

References

1. Low CMR and Vinter JG, Rationalizing the activities of diverse cholecystokinin 2 receptor antagonists using molecular field points, *J Med Chem* (51): pp565-573, 2008
2. Cheeseright T, Mackey M, Rose S and Vinter A, Molecular field extrema as descriptors of biological activity: Definition and validation, *J Chem Inf Model* (46): pp665-676, 2006

About the authors

Dr Robert Scoffin is the co-founder and Chief Executive Officer (CEO) of Re-Pharm, an early-stage drug discovery and development company dedicated to compound reprofiling. Robert has extensive experience in the fields of cheminformatics and molecular modelling, and has held positions at Oxford Molecular, Amedis and CambridgeSoft. He is also the CEO of Cresset. **Email: rob@re-pharm.com**

Dr Alan Rothaul is the co-founder and Chief Scientific Officer of Re-Pharm. A pharmacologist by training, Alan has a strong track record in drug discovery and development, with particular expertise in preclinical biology, preclinical and clinical pharmacology, and toxicology. He was a co-founder of the reprofiling company Serentis Ltd and has held positions at Arakis Ltd, Celltech-Chiroscience, British Biotechnology and Smith Kline & French. **Email: alan@re-pharm.com**