The advantages of outsourcing computational chemistry (Part 2)

With the increasing pressure to drive efficiencies in the drug discovery process, innovative approaches using computational chemistry are delivering proven results, particularly in the areas of lead identification and optimisation. However, maintaining an in-house team is often a luxury and there is an increasing trend to outsource computational chemistry in order to benefit from the advantages it delivers in terms of insight into the biological activity and interactions of molecules across a range of target classes, enabling the identification of new candidates that would otherwise have been overlooked.

According to Martin Slater, director of consulting at Cresset BioMolecular Discovery, there are two main factors driving the current increasing trend in outsourcing computational chemistry: first, a trend to outsource across the discovery spectrum. "The increasing fragmentation of the drug discovery business has brought an increase in companies that can move quickly to offer tailored research often through the use of on-demand services from consultants," he says. "At the same time, computational chemistry has become a more integral and accepted part of the drug discovery process. For example, 3D computational molecular design is now an essential part of the medicinal chemists' toolkit. Cresset has always provided consultancy alongside its software, but over the past few years there has been a steady growth in demand for consultancy services.

"The main reason to outsource computational chemistry to a company like Cresset is that we bring expert scientific knowledge, experience and methods to bear on projects for maximum scientific return. The other reason is that using our services is very cost-effective – there is no need for to go to the expense of hiring and training in-house computational chemists that may not be put to use full-time."

The second factor driving the increase in computational chemistry outsourcing is that Big pharma companies are seeking to reduce their R&D costs as many key patents are due to expire over the coming years.

"As IP space is becoming more crowded and regulatory requirements more stringent, these companies are keen to reduce risk and overheads in every way possible. Outsourcing computational chemistry can play a part in the drive to get maximum ROI on every R&D dollar spent," says Slater.

Examining the widest target class range

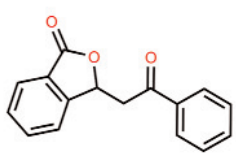
Because Cresset's technology can work with or without a structure of the target protein, it can be used on the widest range of target classes. This can simplify matters when starting a consulting project when the structure of the target protein is not known. For example, an active compound may be unusable due to off-target activity or patent conflicts. Therefore, the goal is to modify the compound to avoid the undesirable effects while keeping the biology the same. Cresset can characterise the molecule according to its field activity, then look for compounds with new chemistry that have the same activity, which are often from a different structural class.

Another example would be where a pharmaceutical company may wish to find an inhibitor for a natural substrate or peptide. Cresset can apply its software to mimic the chemical properties of the recognition sequence in order to find a small-molecule inhibitor. The company has also worked on projects where the potential starting point has been large protein-protein interactions, including antibodies, however, these are more difficult to manage computationally.

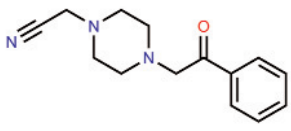
Contracted work

In addition to project-based work, Cresset offers a high-flexibility model of working termed 'CompChem on Demand', in which pharmaceutical companies buy the number of days they need and then contact Cresset to work for them anytime within the next year. Slater says this model is often accessed by companies to help overcome obstacles on particular projects, and that it often leads to establishing longer-term collaborations:

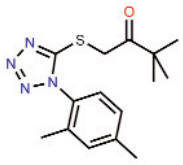
"Of course, different clients prefer different consulting models and we try to be as flexible as we can to meet our customers' needs," he says. "We even rent out our software on a per project basis. The scientists get access to state-of-the-art software tools, but only pay for what they need. This model is particularly popular with contract research organisations, since it makes it easy to bill clients for product usage.



IC_{50} 470nM
Similar patents filed by Incyte



IC_{50} 1100nM
Similar patents filed by AstraZeneca



IC_{50} 170nM
Client filed patent

Three of the most active compounds, illustrating the diverse chemotypes that field screening is designed to find.

"In general Cresset does not benefit from downstream royalties on projects, although we have carried out some more collaborative drug discovery programmes, particularly with charity and academic partners, in which we have retained some IP rights. In the majority of cases, though, we offer a very simple fee-for-service model in answering very specific questions and addressing key issues in the discovery and early development phases of a new drug."

Improving time-to-market

In one recently established collaboration, Isogenica, Biolauncher and Cresset have brought together their individual expertise and capabilities in peptide library screening, computational biology and computational chemistry in order to radically improve the time-to-market for novel therapeutics, and to improve the throughput of converting well-funded discovery biology into active small-molecule chemistry. The opportunity was identified by Biolauncher in its role as both a developer of computational biology expertise and also a consultancy with a track record in bringing together novel technologies to create high-impact end-to-end solutions for difficult drug discovery problems.

"Within the collaboration the partners have distinct roles," explains Slater. "Isogenica's CIS-Display technology is used to generate sets of peptides that bind to a given biological target; Biolauncher's computational biology expertise is used to translate these binding peptide sequences into a proposed set of 3D structures; and Cresset's computational chemistry capabilities are used to transform the proposed peptide structures into a library of small molecules that may be screened against the target for activity."

The collaboration has received funding from the UK Government in the form of a two-year Technology Strategy Board grant, with the goal of further developing the integrated platform, and applying it to a number of validation examples. In parallel, the partners are pursuing commercial relationships with pharmaceutical companies, publically-funded research bodies, patient interest groups, life science charities and academic research groups in order to build a standalone profitable business, which will accelerate drug discovery, release value from the extensive investments made in target biology, and create a pipeline of drug candidates that can be progressed to treat diseases.

The 'natural' way to design and optimise drug candidates

"Our goal is to lower the costs of drug discovery and to accelerate the creation of candidates in order that serious conditions with unmet medical needs can be effectively and efficiently addressed," says Slater.

Looking ahead, he says that Cresset hopes that its applications and services are adopted globally as the natural way to design and optimise drug molecules, while also being utilised by molecular discovery groups in parallel industries. "In a changing drug discovery environment, where collaboration and outsourcing are key, a common molecular design platform utilised by large pharmaceutical companies, biotechs, CROs and service providers can only lead to increased efficiencies in discovery," he says.

He also foresees an increasing role for 'front-end' companies to convert the increasingly large base of biological targets into viable and developable drug development programmes, which would entail the broadening of the company's offering from design of molecules into the synthesis and biological testing of those molecules, which, he says, is a very natural extension of the company's capabilities.

"It is very well known that the pharmaceutical sector has a long-term issue in the effective development and launch of new compounds. Many authors have pointed out the staggering costs associated with the launch of each NCE, and the decreasing efficiency of the discovery process behind those launches. Computational chemistry has the power to help reverse this trend, in allowing much more efficient assessment of the likelihood of compound failure in development.

"Computational methods have also started to be applied in compound reprofiling, which is a short- to medium-term approach to easing the issues of releasing new compounds: re-profiling or repurposing allows for the use of existing molecules to a new therapeutic area, lowering the costs and risks of development. Computational chemistry allows the re-profiling to be done in a low-cost and rational way, leading to major cost and time advantages.

"Through these and other factors computational chemistry consulting is seeing significant growth. The other drivers behind this trend are the wish to outsource computational chemistry to get maximum value for money, and the increasing recognition of the scientific value of computational chemistry expertise for discovery research. In the end though, it's the results that count. Cresset's consultancy team has demonstrated the value of outsourcing computational chemistry by delivering valuable results for many clients, proven in terms of patented scientific discoveries that have led to solid business returns.

"Computational chemistry is not magic, it is science. And scientific tools need scientists to provide intelligent input and interpret the results. It is our expertise and depth of experience that really deliver results for our customers," Slater concludes.

Meet Martin Slater of Cresset Biomolecular Discovery

Dr Martin Slater is Director of Consulting at Cresset Biomolecular Discovery. He studied medicinal chemistry at the University of Huddersfield and the University of Leeds, and spent 14 years in the pharmaceutical 'fee for service' environment at BioFocus in which he supported medicinal chemistry and a diverse range of programmes. He joined Cresset in May 2011 as Director of Consulting for the company's new Professional Services Division.

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