Fragment-based approaches to drug discovery

We talk to the CSO of Astex Therapeutics, a company with a novel approach to drug discovery which it uses to identify its own drug candidates as well as in collaborative drug discovery projects with major pharmaceutical companies.

Drug discovery and development company Astex Therapeutics recently obtained FDA approval for its IND application for the clinical development of its proprietary cancer treatment AT9283, just one example of a drug candidate discovered and developed internally using the company's fragment-based drug discovery platform, Pyramid™.

This is Astex's second IND approval in less than 12 months - the company's lead compound, AT7519, is already in Phase I trials in the USA and in the UK. An initial Phase I study on AT9283 in haematological cancers will be conducted at one of the world's leading oncology centres in the USA, and the company plans to initiate additional studies in North America and Europe in patients with solid tumours during the second half of the year.

"We are delighted both to have been given the go-ahead by the regulatory authorities to advance AT9283 into clinical development, and to be working with some of the world's leading cancer experts on our clinical programme. We are now putting the final preparations in place to begin this first clinical trial of AT9283 in the coming weeks," comments Dr Harren Jhoti, chief scientific officer of Astex. "This second IND underscores the productivity of our fragment-based discovery engine. In addition to AT9283, we have a number of other unpartnered programmes also progressing towards the clinic and we are well on the way to meeting our corporate goal of generating at least one IND per year from our proprietary platform."

AT9283 is an inhibitor of mitosis and is the second most progressed drug candidate in the Astex portfolio of novel, molecularly-targeted cancer drugs. AT9283 is a potent inhibitor of the Aurora A and B kinases and has been shown to arrest tumour growth in a range of tumour models. Aurora A and B are over-expressed in many human tumours and are believed to be excellent targets for anti-cancer therapy.

Integrated discovery engine

Astex's position in fragment-based drug discovery derives from its integrated discovery engine, Pyramid™. High-throughput X-ray crystallography and other biophysical techniques are used to identify drug fragments bound to target proteins and to transform the fragments, using efficient medicinal chemistry, into potent, selective drug candidates. Pyramid™ has been successfully applied across a wide variety of therapeutic targets, including those regarded as 'intractable' by the pharmaceutical industry, resulting in lead compounds for the potential treatment of cancer, inflammation and Alzheimer's disease.

Astex Therapeutics was founded in 1999 by Jhoti, then at GlaxoWellcome, and Professors Tom Blundell and Chris Abell of Cambridge University who were interested in looking at solutions to problems regarding the efficiency of combinatorial chemistry programmes. The concept of a fragment-based approach to drug discovery was first discussed in the scientific literature in the early 1980s from a theoretical point of view, but by the mid-1990s it looked very promising as a practical approach to addressing some of these problems.

"The first challenge for the company was to build a high-throughput X-ray crystallography platform. The company was successful in obtaining venture capital backing in the form of an early loan to fund some proof of principle work and has gone on to raise more than £51 million in two funding rounds in 2001 and 2003 which were among the largest financing rounds in the European biotech sector in those years. This funding has allowed it to develop its Pyramid™ technology for identifying and subsequently modifying fragments into drug candidates. Astex has swiftly expanded to the point where it now employs about 100 people, and now has its first drug candidate derived from a fragment in clinical trials, being the first biotech to achieve this milestone."

MEET HARREN JHOTI OF ASTEX

Harren Jhoti co-founded Astex Therapeutics in 1999 and is the company's Chief Scientific Officer. He previously led the Structural Biology and Bioinformatics groups at GlaxoWellcome (1991-1999), applying protein structure analysis to drug discovery and was involved in structure-based drug design projects aimed at a variety of therapeutic targets. He received his PhD in Protein Crystallography from Birkbeck College, University of London.

Consistent business model

Jhoti emphasises that the company's business model has been consistent from the start: "Other companies have used X-ray crystallography to examine structural genomics, but we have focused on using protein structres to enable us to perform fragment chemistry. Our approach is to identify leads against drug targets both in house and as part of strategic collaborations with pharma companies. For example in our agreements with AstraZeneca, Schering AG and Boehringer Ingelheim, we use our approach to come up with novel lead compounds and in return we receive upfront fees, funding to cover our research and development expenses and milestone payments and royalties on future product sales as opposed to the fee-for-service model used by companies in the drug discovery service sector.

"We selected our own targets from the very beginning to build

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Fragment growth illustrated using an Astex discovery programme on a kinase enzyme. (a) The starting fragment is shown in yellow (potency >1mM). (b) A compound (potency ~ 50μM), displayed in orange, that was derived from the first chemistry iteration on the starting fragment (shown in yellow). (c) A subsequent lead molecule is shown in red (potency ~ 300nM) superimposed on the earlier fragments. All binding modes are taken from actual protein-ligand crystal structures.

our internal pipeline of oncology compounds. As little as three or four years ago, Big Pharma didn't recognise fragment approaches as being viable but now they are becoming much more interested," he says.

High-efficiency binding

Jhoti explains how with the fragment-based approach to drug discovery, it is not actually necessary to do a lot of chemistry: "It's possible to develop a fragment hit with a millimolar affinity to a lead compound with nanomolar affinity by performing only a few iterations and synthesising only about 50 to 100 compounds. Thus less assays are required and this greatly speeds the drug discovery process. For example, our AT7519 compound went from first synthesis to its first trial in patients in less than 18 months, and our other compounds are coming through to the clinic quickly.

"Because of the low potency of the binding of fragments to targets, it's necessary to work with fragments at very high concentrations. Although the fragments bind with low affinity, given that their overall size is very small, typically 150-200 MW, their binding is highly efficient, a term we describe as ligand efficiency. The affinity of the fragment bindings can then be improved in the hits-to-lead stage by adding functionalities to improve potency and introduce good physicochemical properties while aiming to maintain high levels of ligand efficiency. This is very different from the traditional HTS approach and, because the fragment-based technology allows us to keep the overall size of our compounds small, metabolic liabilities can potentially also be minimised," he says.

Strategic alliances and outlicensing

In July 2005, Astex established a new strategic alliance with AstraZeneca to discover, develop and commercialise novel small-molecule inhibitors of the anti-cancer target Protein Kinase B (PKB/Akt) and the two companies also have an agreement relating to the discovery of novel drugs against beta-secretase, a key protein target implicated in the onset of Alzheimer's disease:

"We've completed a number of early-stage deals that have validated the technology and reduced scepticism about its effectiveness, including for example our collaboration with AstraZeneca on Alzheimer's disease, which validated our work in this area. AstraZeneca licensed in the programme and asked us to develop more compounds against beta-secretase, which is regarded as a very important disease target. The PKB collaboration was the third we'd done with AstraZeneca and was on compounds that were at the lead optimisation stage at the time this $270 million deal was completed. This emphasises the value of our fragment-based chemistry approach in terms of creating early-stage deals with significant value. In these projects we deliver leads and in return we obtain research and development funding, milestones and royalties, while AstraZeneca is responsible for performing the downstream development work," says Jhoti.

"Our other main outlicensing deal, which we signed in December 2005, is with Novartis, where we have outlicensed compounds in the cell cycle space for oncology. This was a $520 million topline deal covering a worldwide licence for the development of AT9311, which is at the preclinical stage, and a further option on a worldwide licence for the development of AT7519, which is in Phase I clinical trials. Novartis has provided an upfront payment of $25 million in cash and deferred equity and in return will receive an equity component in Astex at some stage in the future. We believe this is one of the largest deals in European biotech," he says.

"I must emphasise that we're very keen to outlicense compounds at different stages of development. We are confident that we can replenish our pipeline using our fragment discovery engine, which gives us the option to outlicense some of our programmes earlier rather than later. One of our key compounds in development is AT9283, identified as being active against the cancer target aurora kinase. This drug is set to enter the clinical stage of development in coming months.

"Our corporate goal is one IND a year, and we have achieved this since 2005. We anticpate another IND next year. We have been focused on oncology but we are ready to expand into other therapeutic areas, thus increasing the potential for our discovery engine," says Jhoti.

"This is an exciting and fruitful time for companies like ourselves. Big Pharma companies' pipelines are fairly dry and they are willing to pay more for earlier-stage drug candidates to replenish their pipelines, which is good for biotech. They have become much more flexible, which is very good for the pharmaceutical sector all round," he concludes. *sp²*

FURTHER INFORMATION

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