Astex Pharmaceuticals
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Astex targets CNS with fragment-based approach

Building on success in the oncology field, Astex Pharmaceuticals is applying its fragment-based drug discovery (FBDD) platform to new neurodegenerative disease targets.

With eight small-molecule targeted therapies discovered and advanced into clinical trials in eight years, FBDD pioneer Astex Pharmaceuticals has an established track record in productive lead discovery, primarily in oncology. Now the company is planning to replicate that success in neurodegenerative diseases—an area where Astex believes its proprietary Pyramid platform technology could offer distinct advantages.

"The Pyramid platform is agnostic in terms of targets, so we are trying to recreate some of the success we have had in oncology by looking at particular central nervous system (CNS) targets where we feel we can add most value," said Jeremy Carmichael, VP of corporate development and head of business development at Astex. "We are optimizing the chances of success by focusing on targets that are amenable to our approach and where there is potential to identify those patients who might benefit from a new targeted treatment."

Founded in 1999, Astex became a wholly owned subsidiary of Otsuka Pharmaceutical Co. Ltd. (Tokyo, Japan) in 2013. It now operates from two sites, with drug discovery research headquartered in Cambridge, UK, and clinical development based in Pleasanton, California, USA. The company's internal research programs have delivered a robust clinical portfolio of oncology drugs, including guadecitabine, a small-molecule next-generation DNA-hypomethylating agent currently being clinically tested for the treatment of acute myelogenous leukemia and solid tumors.

Astex has also enjoyed success with a number of partnered products and programs in collaboration with major pharmaceutical companies. Four partner-funded clinical compounds that resulted from early partnerships with Astex are now under active clinical development. These include ribociclib (LEE011), an inhibitor of cyclin-dependent kinase 4 and 6 that is currently in phase 3 development for hormone-receptor-positive, HER2-negative advanced breast cancer (Novartis), and lanabecestat (AZD3293), a β-secretase (BACE) inhibitor in phase 3 development for Alzheimer's disease (AstraZeneca/Lilly).

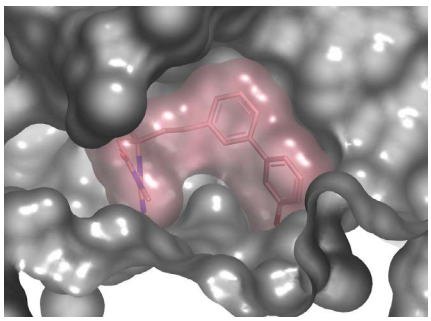

Figure 1: Representation of a BACE inhibitor discovered using FBDD[3].

Backed by Otsuka, which has a well-established franchise in CNS drug discovery and development that includes Abilify (aripiprazole) and newly approved Rexulti (brexpiprazole), Astex is now working on joint projects with Otsuka scientists and is also exploring new collaborations with academic centers, disease charities and industry as it starts to build its CNS portfolio.

Rational molecule design

FBDD with Pyramid can offer advantages compared with high-throughput screening (HTS) for CNS drugs, which must overcome the challenge of crossing the blood–brain barrier. The Pyramid platform integrates biophysical techniques, such as X-ray crystallography, nuclear magnetic resonance spectroscopy and calorimetry, with fragment library design and a range of computational methodologies. This combination of approaches makes it possible to gain a detailed understanding of fragment binding to the target protein at an atomic level, which supports an efficient chemistry optimization process[1,2] (**Fig. 1**).

Unlike HTS, FBDD with Pyramid starts with very small, low-molecular-weight drug fragments, so there is potential to keep the overall complexity and molecular weight of each drug candidate low. "From these small 'bits of molecules' or starting points, you can design molecules that interact optimally with the protein target—to either inhibit or activate it—by adding only essential atoms to improve affinity and control physicochemical parameters," said Lee Dawson, VP and head of CNS at Astex. "This allows us to design molecules rationally, so that they have a better chance of getting into the brain and are optimized to hit targets that we hope will have an effect on the ongoing disease pathology in neurodegenerative disease."

Astex is looking at the underlying molecular processes of neurodegenerative diseases to identify targets and biomarkers for efficacy and patient stratification. Informed by the latest genetics research, the search for targets is concentrating on those areas of biology that could make individuals more prone to develop neurodegenerative disease. Mitochondrial quality control, proteostasis and neuroinflammation are some of the common neuropathological mechanisms that could yield new targets.

A range of neurodegenerative diseases will be investigated, including dementia, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis and frontotemporal dementia. The research will also include orphan CNS diseases with a clear genetic association, as well as epigenetic targets.

'Open innovation' approach

The developing CNS portfolio will be strengthened through 'open innovation' alliances with a range of global partners. "We are working with academics, biotechs and charities in a collaborative manner to develop the biology in neurodegenerative diseases," said Dawson. "The goals are to find novel targets in the space that will work with our technology, and then use our technology to identify small-molecule ligands to validate the biology and ultimately develop new drugs."

For example, Astex recently joined the Dementia Consortium, a charity–private partnership set up between Alzheimer's Research UK, MRC Technology and five pharmaceutical companies. The consortium provides drug discovery resources, project management, industry expertise and funding to support collaborative target validation of potential novel drug targets from academia and SMEs (small and medium-sized enterprises).

With its world-leading FBDD expertise and resource capabilities, Astex is able to work on projects at a much earlier stage than many pharmaceutical or biotechnology companies, which often require *in vivo* proof of concept. "We will consider a collaboration opportunity as soon as there is some indication or evidence that the target is involved in a particular disease," said Carmichael. "In some cases, we can also help to fund or co-fund development."

The company has a pragmatic approach to business models, with risk-sharing drug discovery and development models open to discussion. Partners can also benefit from Astex's reputation for publishing high-quality science with its collaborators.

Ultimately, the company is aiming to find novel therapeutics for clearly defined neurodegenerative disease populations by working with partners that have clear synergies with Astex.

1. Jhoti, H. *et al. Nat. Rev. Drug Discov.* **12**, 644–645 (2013).
2. Davies, T.G. *et al. J. Med. Chem.* **59**, 3991–4006 (2016).
3. Edwards, P.D. *et al. J. Med. Chem.* **50**, 5912–5925 (2007).

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