Interview with Harren Jhoti

How Astex built a business on fragment-based discovery

In biotech, there is often a long chain connecting an original invention with a commercial outcome. The chain can consist of multiple collaborations between the start-up and other businesses until an inflection point is reached and the project moves on, or in the absence of money, the business collapses. Not every business history is that stark. But in cases where businesses fail, there is a usually a reason. Conversely, businesses that succeed often have an identifiable asset or strategy.

Astex Pharmaceuticals (UK) is an example of a resilient biotech. Since its founding in 1999, it has powered ahead with projects based on its fragment-based drug discovery platform – all the while negotiating collaborations with large pharma companies. In 2013, it negotiated a takeover by the Otsuka Group of Japan giving it a larger operating arena but keeping its autonomy as a subsidiary. Astex has changed its name three times since 1999 but kept its home base for drug discovery in Cambridge, UK. The company's chief executive and co-founder, Harren Jhoti, continues to lead the Cambridge operation while also attending global strategy meetings run by Otsuka.

Dr Jhoti is a structural biologist with a strong interest in rational drug design. Before co-founding Astex he was head of structural biology and bioinformatics at GlaxoWellcome, predecessor to GSK, and before this, a post-doctoral scientist at Oxford University. He started Astex to implement a concept in drug discovery which he pioneered called fragment-based drug discovery. Fragment-based discovery is a subset of structure-based drug discovery, where the three-dimensional structure of a target protein is identified in order to design a compound that can interact with that protein and become a drug. Fragment-based drug discovery takes that science one step further by working with much smaller compounds.

In an interview Dr Jhoti explained how, by working with academic and industry collaborators, Astex used fragment-based discovery to identify multiple new compounds of which three have been approved for the market. The most well-known is Kisqali, a breast cancer drug originating from a collaboration with Novartis that started in 2005. Kisqali was approved in the US in 2017 and now is one of Novartis' best-selling products. In the third quarter of this year it generated sales of $562 million.

The two other products are Balversa for urothelial carcinoma, approved in 2019. This originated from a 2008 collaboration between Astex and Janssen Pharmaceuticals. And – most recently – Truqap, a breast cancer drug approved in the US on 17 November. This originates from a drug discovery collaboration between Astex and AstraZeneca Plc that started in 2005.

The lock and key

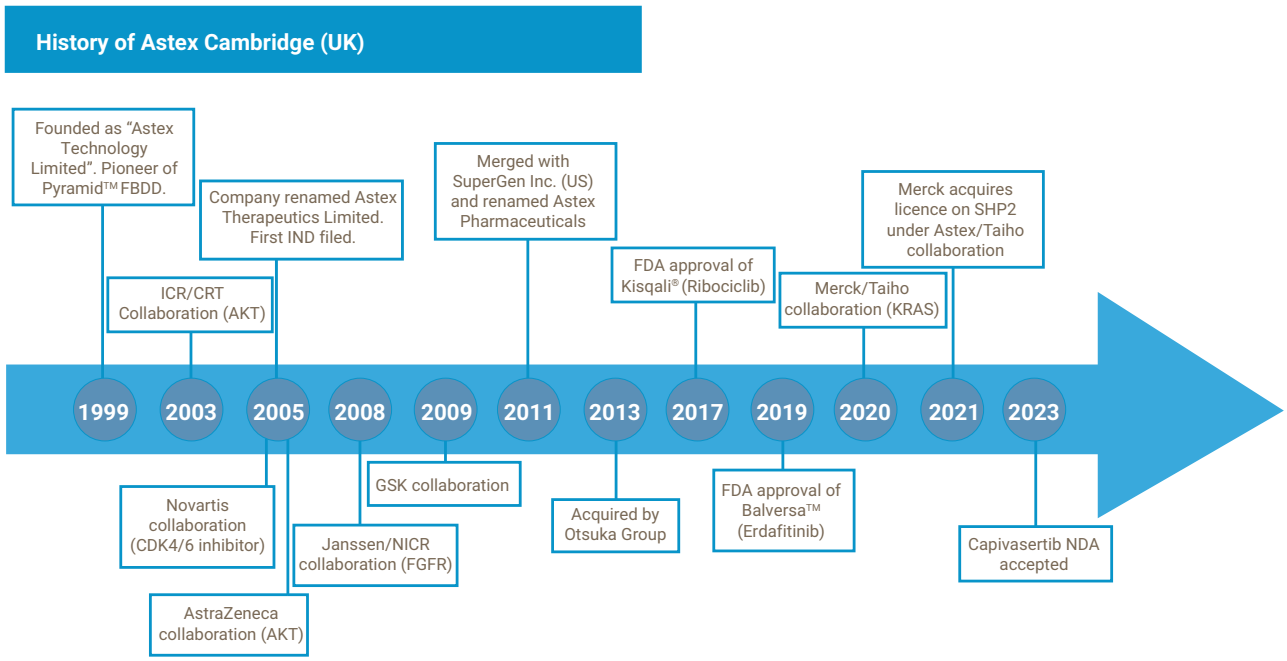
In the interview, Dr Jhoti described fragment-based discovery as being similar to fitting a key to a lock. To begin with, the compounds are very small. Whereas a compound investigated using structure-based discovery might have a molecular weight of 300 to 400, ones used in fragment-based discovery are one-third of that size. "The analogy we give is the lock and key. If you imagine a key which had, let's say 10 teeth, for that key to fit that lock it has to get every one of those teeth absolutely right. It just needs to have one of those teeth out [of place] and the lock does not open. But if you could fragment that key, just say to those individual teeth, you are then able to have a much higher chance of finding the bits that fit perfectly, and avoiding the fact that there is one which would not fit at all," Dr Jhoti said.

The main problem is that the affinity of these fragments to the target protein is very, very weak. "You can't detect fragments in a bio-assay. What you have to then revert to is trying to detect the fragment by using a bio-physical technology such as X-ray crystallography," he said. The idea of using X-ray crystallography to screen for fragments of compounds and detect binding with a target instead of a more established technique like nuclear magnetic resonance (NMR) was new. "When we set up Astex we said that's [NMR] an okay approach but the quality of information that you get from NMR is significantly inferior from what you can get from an X-ray decision. And that's because you don't really get a picture of how the fragment binds to the protein," he said. In lodging this critique "most people thought we were completely bonkers," he added.

Was the decision to proceed with X-ray crystallography based on logic or hope? "90% logic, 10% hope," Dr Jhoti said, adding that he had seen evidence of very low affinity sugar molecules binding to proteins. "So that was our bet. We would try to transform X-ray crystallography into a high-throughput technique."

In recent years, Astex has evolved its basket of screening technologies to add NMR as an option, and also include an entirely new technique – cryo-electron microscopy, or Cryo-EM. Cryo-EM is a way to determine the three-dimensional structure of a protein without the need for that protein to be crystallised. It is a technology co-developed by three scientists, Jacques Dubochet, Joachim Frank and Richard Henderson, who won the Nobel Prize in Chemistry in 2017 for their work. Dr Henderson, a UK molecular biologist and biophysicist, was cited by the Nobel Committee for Chemistry for "using an electron microscope to generate a three-dimensional image of a protein at atomic resolution."

At the time of the award, Astex and four other pharmaceutical companies (AstraZeneca, GSK, Heptares and UCB) were already evaluating Cryo-EM as an industrial technique under a partnership led by FEI Company, a US service company which supports microscope technology. Currently, Astex uses Cryo-EM for about 20-30% of its drug discovery work, with X-ray crystallography remaining the foundation of its platform. "We were one of the first to set this up in an industrial setting," Dr Jhoti said.



The commercial dimension

By 2010, Astex had secured several large collaborations based on its technology but it was still dependent on venture capital. "We had done these deals, raised significant amounts of venture capital from VCs but there comes a time when the VCs say 'that's it'…We were getting chunky upfronts, $30 to $40 million, to keep the company going. But of course that is not an exit. We looked around about doing a deal in London, but that was just about the time of the financial crisis, so we had to hunker down," Dr Jhoti recalled.

Then, at one of the annual Jefferies Healthcare conferences in London, Astex was approached by the chief executive of SuperGen Inc, a US oncology company, about a possible merger. SuperGen was listed on Nasdaq and had revenue from Dacogen, a treatment for adults with newly diagnosed acute myeloid leukaemia, but they wanted a discovery engine. "They had very strong clinical development and regulatory operations but they wanted a front end, a discovery [engine]. They also wanted to change their name. They wanted to rebrand themselves," Dr Jhoti said. From Astex's side, there was the attraction of becoming a listed company. The transaction, completed in 2011, took the form of a takeover by SuperGen of Astex. The merged company was named Astex Pharmaceuticals with two distinct units, Astex Pharmaceuticals (UK) and Astex Pharmaceuticals (US).

This was only the start of the expansion. Now a listed company, the next question to arise was whether Astex Pharmaceuticals was being correctly valued. The Astex management team huddled with its investment advisors and concluded that the company could do better. Among the potential buyers of the newly merged Astex Pharmaceuticals was Otsuka Holdings Co Ltd, one of Japan's largest pharmaceutical groups. Otsuka is a conglomerate and owns Taiho Pharmaceutical and its subsidiary Taiho Oncology. When discussions began about a possible takeover of Astex by Otsuka, the Japanese company did not have a fragment-based drug discovery engine. "That was one of the key reasons for buying us," Dr Jhoti said.

Otsuka did make an offer, and the final amount, at $8.50 per share in cash, represented a 48% premium to Astex's average closing stock price for the prior 30 days. This gave a deal value of approximately $886 million. The deal was closed on 5 September 2013.

Now, 10 years later, Dr Jhoti remains CEO of Astex Pharmaceuticals (UK) and a member of the board of directors of Astex Pharmaceuticals (US).

Operationally independant

Who makes decisions affecting Astex (UK)? "We need to keep them [Otsuka] informed, but operationally we are independent," Dr Jhoti said. An example is a recent drug discovery collaboration signed with Merck & Co Inc which will attempt to identify small molecule drug candidates targeting p53, a tumour suppressor protein and one of the most difficult targets in oncology. This is based on research that has been underway at Astex for some time and will be conducted by the Cambridge, UK-based company.

This interview was conducted and written by the *MedNous* editor.