Institution: University of Cambridge		
Unit of Assessment: 8		
Title of case study: Fragment-Based Drug Discovery		
Period when the underpinning research was undertaken: 01/01/2000 - present		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s): Professor Chris Abell	**Role(s) (e.g. job title):** Professor	**Period(s) employed by submitting HEI:** 1984-2020
Period when the claimed impact occurred: 01/08/2013-31/07/2020		
Is this case study continued from a case study submitted in 2014? Y		

1. Summary of the impact

The application of X-ray crystallography to the screening of small molecule fragments for protein binding was developed in the Departments of Chemistry and Biochemistry at the University of Cambridge and this work led to the fragment-based drug discovery approach implemented at Astex. Astex have used these methods in collaborations that have led to the discovery of new highly successful anti-cancer drugs that were launched in 2017 (Kisqali® for breast cancer) and in 2019 (Balversa™ for urothelial cancer). The fragment-based approach is now used by most major pharmaceutical companies, and over 40 compounds discovered using fragments have reached clinical trials. Astex currently employs 140 people and has a turnover of GBP72,000,000.

2. Underpinning research

Professor Chris Abell is one of the pioneers in the use of small molecules (fragments) in drug discovery. In collaboration with Professor Tom Blundell in the Department of Biochemistry and Astex, Abell has tackled a series of fundamental scientific questions that underpin the process of fragment-based drug discovery, leading to methodology that is now used throughout the pharmaceutical industry.

Fragment-based drug discovery (FBDD). The idea behind FBDD is that a library of hundreds of small fragments (molecular weight < 300 Da) can be used to explore chemical space more efficiently than a million-compound library of larger drug-like molecules. Professors Abell and Blundell and Dr Jhoti at Astex realised that high throughput X-ray crystallography could provide a powerful method for determining high-resolution three-dimensional structures of fragments bound to protein targets. If multiple crystals of target proteins are screened with a small fragment library, any small molecules that bind can not only be identified, but their position and orientation in the binding site can also be defined at high resolution. The structures of any hits could then be iteratively elaborated into potent inhibitors. A team of post-docs working in the Blundell and Abell laboratories set out to explore this idea by soaking single protein crystals in concentrated DMSO solutions of fragments. By March 2001, the proof of principle experiments were in place, and the use of X-ray crystallography to carry out fragment screening for drug discovery was described in two highly influential papers published in 2002.[R1,R2] Based on these results, Astex raised GBP28,000,000 in investments in 2001 and established their first research laboratory on the Cambridge Science Park. Abell and Blundell have collaborated closely with Astex over many years working on solutions to some of the challenges in the practical implementation of X-ray based FBDD.

Fragment Linking. Early work on FBDD at Astex focused on fragment growing, and almost all targets that had been tackled were protein kinases. In the fragment growing approach, functional groups are appended to a single fragment in the hope of picking up additional interactions with protein side-chains in the binding site. Fragment linking is potentially much more powerful. If two different fragments can be identified that bind to the same protein pocket but at to two distinct locations, it should be possible to obtain very high affinity ligands

in a straightforward manner by covalently connecting the two fragments. A collaboration between Astex and the Abell laboratory in the Department of Chemistry identified two fragments that bound to different sites in thrombin and demonstrated for the first time how fragments could be effectively linked to obtain a high affinity ligand.[R3] The thrombin ligand showed that FBDD was not restricted to kinases and significantly expanded the range of targets. As part of an Abell and Blundell collaboration targeting tuberculosis using FBDD, a comparative analysis established the relative merits of fragment linking and fragment growing in the rapid development of enzyme inhibitors.[R4] This system was then used to developed an NMR approach to identify the most promising fragment linking strategy using inter-fragment NOEs.[R5] These new fragment linking approaches have been highly influential in the way Astex now implement FBDD.

3. References to the research

[R1] Blundell, T. L.; Abell, C.; Cleasby, A.; Hartshorn, M. J.; Tickle, I. J.; Parasini, E.; Jhoti, H. High-throughput X-ray Crystallography for Drug Discovery. Drug Design: Cutting Edge Approaches. Darren Flower, Ed. Royal Society Chemistry **2002**, 53–59.

[R2] Blundell, T. L.; Jhoti, H.; Abell, C. High-throughput Crystallography for Lead Discovery in Drug Design. *Nature Reviews Drug Discovery* **2002**, *1*, 45–54. (this review article published new crystal structures of the first fragments bound to proteins)

[R3] Howard, N.; Abell, C.; Blakemore, W.; Carr, R.; Chessari, G.; Congreve, M.; Howard, S.; Jhoti, H.; Murray, C. W.; Seavers, L. C. A.; van Montfort, R. L. M. Application of Fragment Screening and Fragment Linking to the Discovery of Novel Thrombin Inhibitors. *J. Med. Chem.* **2006**, *49*, 1346–1355.

[R4] Hung, A. W.; Silvestre, H. L.; Wen, S.; Ciulli, A.; Blundell, T. L.; Abell, C. Application of Fragment Growing and Fragment Linking to the Discovery of Novel Inhibitors of Mycobacterium Tuberculosis Pantothenate Synthetase. *Angew. Chem. Int. Ed.* **2009**, *48*, 8452–8456.

[R5] Sledz, P.; Silvestre, H. L.; Hung, A. W.; Ciulli, A.; Blundell, T. L.; Abell, C. Optimisation of the Interligand Overhauser Effect for Fragment Linking: Application to Inhibitor Discovery against Mycobacterium Tuberculosis Pantothenate Synthetase. *J. Am. Chem. Soc.* **2010**, *132*, 4544–4545.

All research outputs have been published in peer-reviewed journals.

4. Details of the impact

The FBDD approach pioneered by Abell, Blundell and Astex has led to the widespread adoption of this technology throughout the pharmaceutical industry, changing the way that drug discovery is carried out. The approach has become so embedded in the industry that there are now dedicated FBDD groups within most major pharmaceutical companies, including GSK, AZ, Merck, Roche, Novartis, Pfizer, Abbvie, BM, and Bayer. By 2018, over 40 compounds were or had been in clinical development due to the uptake of this technology.[E1]

Astex. The company (named sequentially Astex Technology, Astex Therapeutics, and Astex Pharmaceuticals) was originally founded by Professors Abell and Blundell and Dr Jhoti to exploit FBDD using X-ray crystallography. Astex continues to be a world-leader in FBDD with a strong proprietary clinical pipeline targeting cancer and diseases of the CNS. Astex became a member of the Otsuka Group in October 2013 (acquired for USD886,000,000),[E2] and currently employs 140 people with a turnover in 2018 of GBP72,200,000.[E3] Both Abell and Blundell maintain close involvement through consultancy and as members of the Scientific Advisory Board.[E3] This strong interaction

ensures a continuing dynamic exchange of ideas between the Abell and Blundell laboratories in the Departments of Chemistry and Biochemistry and Astex. The original 2002 papers by Abell, Blundell and Jhoti set the manifesto for how Astex would implement FBDD using X-ray crystallography.[R1,R2] There followed years in which the process was continuously refined for drug discovery and applied to a range of targets. The objective was to identify an important target and produce preclinical candidates that were then partnered with major pharmaceutical companies who took them through clinical trials to market. This has led to two drugs being taken to market, as detailed below, along with another three currently in clinical trials.[E4]

Kisqali®. In 2017, Astex's first drug (variously called Kisqali®, Ribociclib, LEE011) was launched by Novartis.[E5] Kisqali® is an inihibitor of the cyclin-dependent kinases CDK4/6 and is used in combination with another drug Letrozole as a first-line treatment of an advanced form of breast cancer called hormone receptor positive, human epidermal growth factor receptor-2 negative, HR+/HER2-. Kisqali® was discovered as part of a collaboration between Astex and Novartis, and a key step was the determination of the crystal structure of CDK4 by scientists at Astex. The compound was taken through preclinical and clinical development by Novartis, and gained approval for commercialization in 75 countries [E5] including approval by the US Food and Drug Administration (FDA) (March 2017) and by the European Medicines Agency (EMA) (August 2017).[E5] Sales of Kisqali® for the 2019 financial year were USD480,000,000.[E6] In June 2019 Novartis published clinical trial data showing a significant increase in survival rate for patients treated with Kisqali® and Letrozole. Survival rates at 42 months were 70.2% for the Kisqali combination therapy compared to 46.0% for endocrine therapy alone.[E7]

Balversa™. Another Astex clinical candidate (called Erdafitinib or Balversa™) was so successful in Phase 2 clinical trials that it was granted Breakthrough Therapy Designation by the US FDA in March 2018 for the treatment of metastatic urothelial cancer, the sixth most common type of cancer in the USA.[E8] This designation led to rapid review and approval of the drug for marketing in the USA in April 2019.[E5] Erdafitinib was discovered using FBDD by Astex as part of a collaboration with Janssen to identify novel, small molecule inhibitors of Fibroblast Growth Factor Receptor (FGFR) kinase. Janssen was responsible for the clinical development and commercialisation of Erdafitinib,[E8] which is the first FGFR kinase inhibitor to be approved by the FDA.[E5]

5. Sources to corroborate the impact

[E1] Practical Fragments – Blog for Fragment-based Drug Design Practitioners 06.10.2018. "Fragments in the clinic: 2018 edition".

[E2] Nature Biotechnology - Otsuka Pharmaceutical Acquisition 08.11.2013. "Otsuka snaps up cancer drugmaker Astex"

[E3] Letter from Dr David Rees, CSO of Astex 27.01.20

[E4] Astex website – drugs in clinical trials

[E5] Approvals for Kisqali® and Balversa™

[E6] Novartis – Kisqali Sales 2019

[E7] Novartis – Kisqali 01.06.2019. "Novartis Kisqali significantly extends life in women with HR+/HER2- advanced breast cancer in MONALEESA-7 trial"

[E8] Bloomberg – FDA approval for Balversa 12.04.2019. "Astex Pharmaceuticals Celebrates as Second New Cancer Drug Receives US Marketing Approval"