Institution:
University of Cambridge

Unit of Assessment:
UoA5

Title of case study:
Structure-Guided and Fragment-Based Drug Discovery

1. Summary of the impact (indicative maximum 100 words)

In 1999, Tom Blundell (Biochemistry), Chris Abell (Chemistry) and Harren Jhoti cofounded Astex Technology Ltd. to develop an X-ray structure-guided, 'fragment-based' approach to drug discovery. This led to a significant change in how the pharmaceutical industry approached drug discovery. Astex Technology Ltd developed four molecules in house using this approach which have in 2013 reached Phase I/II clinical trials for various tumours. Four further molecules have been taken into phase I through collaborations between Astex and Janssen, Novartis and AZ. In 2011 the company was sold to Supergen for $150 million (ca £100 million), creating Astex Pharmaceuticals, Inc., currently with ~120 employees, and a value of >$500 million (>£320 million).

2. Underpinning research (indicative maximum 500 words)

The underpinning research was conducted in collaboration between Professor Sir Tom Blundell (Sir William Dunn Professor of Biochemistry, Department of Biochemistry, 1996-2009, and now Research Director) and Professor Chris Abell (Professor in Biological Chemistry, since 2002; Department of Chemistry; since 1984) and developed their combined expertise in structural biology and organic chemistry to better understand protein-ligand interactions.

Professor Blundell has had a long-standing interest in structure-guided drug discovery and in the 1980s recognised the importance of characterising the 3D structure of a protein target in order to optimise the drug discovery process. Between his arrival at Cambridge in 1996 (appointed as Sir William Dunn Professor of Biochemistry in 1995) and 1999, Prof Blundell collaborated with various pharmaceutical companies to use structure-guided crystallographic approaches of enzyme-inhibitor complexes to optimise new lead molecules. A study of a series of non-peptidic inhibitors of matrix metalloproteinases (MMP) with improved binding properties (Ref. 1, Section 3) was one example of structure-guided drug discovery in which the 3D structure of a protein target was central to optimising a "hit" compound and developing a "lead". He also collaborated with Chris Abell in defining crystal structures of a series of microbial proteins complexed with small molecules, such as the structure of *E. coli* aspartate decarboxylase, showing an ester intermediate in autocatalytic self-processing of one of the catalytic subunits (Ref. 2, Section 3).

In 1998, Blundell and Abell, together with Dr H Jhoti (at the time working at GSK), suggested a novel approach, which underpinned the formation in May 1999 of the spinout company Astex Technology. The approach was to develop novel therapeutics from very small chemical fragments (MW<300) using high-throughput methods with powerful X-ray sources, together with roboticised data collection, to define at high-resolution complexes of small molecules (fragments). They hypothesised that a library of 300-1,000 small fragments could explore chemical space more efficiently than a million-compound library of larger drug like molecules. The approach, known as fragment-based drug discovery, depended on identifying the positions of fragments bound to the protein by X-ray crystallography and then using knowledge of their positions and the structure of the targets to elaborate these.

Research in the laboratories of Blundell and Abell was funded in the University during 1999-2000 by a grant from Abingworth Ventures via Astex Technology. The research was carried out by two post-doctoral researchers in the Blundell group (Department of Biochemistry; Dr Emil Parasini and Dr Anne Cleasby), in collaboration with a post-doctoral researcher in the Abell group (Department of Chemistry; Dr Martyn Frederickson). Multiple crystals of target proteins (e.g. renin, trypsin) were screened with a small fragment library (including peptides, and molecules such as benzamidine, 4-aminopyridine, cyclohexylamine, histamine, 2-aminoimidazole, 4-aminoimidazole, proflavin, 4-guanidinobutyric acid and cycloheptamine) in 1999. They demonstrated in 1999-2000 that binding of very small molecules (MW less than 300) could be detected and their positions, including

orientation, defined at high resolution by X-ray crystallography. Due to their commercial sensitivity these results were not published until 2002 (Refs 3 and 4, Section 3). In these papers, Blundell and Abell describe the concept of X-ray structure-based fragment screening, and the linking and "growing" of fragments across the binding site using X-ray structures as guides (e.g. Figure 3, Ref. 4, Section 3). The significance of their results enabled Blundell, Abell and Jhoti to raise substantial further funding and develop the spinout company Astex Technology Ltd.

3. References to the research (indicative maximum of six references)

1. G. Pavlovsky, M. G. Williams, Q. Z. Ye, D. F. Ortwine, C. F. Purchase, 2nd, A. D. White, V. Dhanaraj, B. D. Roth, L. L. Johnson, D. Hupe, C. Humblet, and T. L. Blundell. (1999) X-ray structure of human stromelysin catalytic domain complexed with nonpeptide inhibitors: implications for inhibitor selectivity. Protein Sci. 8, 1455-1462 DOI: 10.1110/ps.8.7.1455
2. Albert, A., Dhanaraj, V., Genschel, U., Khan, G., Ramjee, MK., Pulido, R., Sibanda, BL., von Delft, F., Witty, M., Blundell, TL., Smith, AG and Abell, C. (1998) Crystal structure of aspartate decarboxylase at 2.2Å resolution provides evidence for an ester in protein self-processing. Nature Structural Biology 5(4): 289-293 DOI: 10.1038/nsb0498-289
3. Blundell TL, Abell C, Cleasby A, Hartshorn MJ, Tickle IJ, Parasini E and Jhoti. (2002a) High-throughput X-ray crystallography for drug discovery. Drug Design, Cutting Edge Approaches. Ed Darren Flower. Royal Society Chemistry, 53- 59 DOI: 10.1039/9781847550705
4. Blundell, T.L., Jhoti, H. and Abell, C. (2002b). High-Throughput crystallography for lead discovery in drug design. Nature Reviews Drug Discovery. 1, 45-54 DOI: 10.1038/nrd706

Funding:

Holder: Tom Blundell, Department of Biochemistry; Title: Protein Modelling, Building and Macromolecular X-ray Analysis; Sponsor: Warner Lambert; Dates: 19/04/96 - 19/04/01; Value: £216,649

Holder: Tom Blundell, Department of Biochemistry; Title: ROPA grant; Sponsor: BBSRC; Dates: 01/10/96 - 30/09/97; Value: £50,190

Holder: Tom Blundell, Department of Biochemistry; Title: Sponsored Research Agreement; Sponsor: Astex Technology Ltd; Dates: 01/10/99 - 30/09/00; Value: £279,370.00

4. Details of the impact (indicative maximum 750 words)

Impact on Commerce

A spin-out company has been created and established its viability by generating revenue or profits:

On the basis of research carried out in the Blundell and Abell labs on structures of molecules that bind protein targets at high resolution by X-ray crystallography, a spinout company, Astex Technology Ltd, was created in 1999 (Company No. 03751674, incorporated 14/4/1999). The university-based research provided the basis of all subsequent work in Astex, including approximately thirty "campaigns" against many targets, mainly of interest in fighting cancer. In 2001 the University of Cambridge invested £250k and was given equity in the company. The company has signed deals worth in excess of $1.8bn (approximately £1bn) between 1999 and 2011. Investors in Astex have included Abingworth, Apax, Oxford (Boston), Advent, Alta and others with £80 million equity in multiple financing rounds. Astex also has had major collaborations with investments of up to £25 million from each of GSK, Johnson and Johnson, Novartis and AstraZeneca (Ref. 1, Section 5); of these the GSK investment occurred after 1/1/2008, while the Johnson and Johnson, Novartis and AstraZeneca investments have continued after 2008 (Ref. 2, Section 5). In 2011 Astex Therapeutics was purchased by NASDAQ-listed oncology company SuperGen, Inc. for $150 million (ca £100 million). The new company was named Astex Pharmaceuticals, to reflect the strong brand name of Astex. Subsequent to the impact period (ie in Sept 2013) Astex was acquired by Otsuka Pharmaceutical Co., Ltd for $886 Million (ca £565 Million).

Jobs have been created/protected:

Over the past decade, the company has secured constant employment for between 70 and 120 workers in Cambridge (Ref. 1, Section 5), the current number of employees in the UK and US is ~120.

Highly skilled people have taken up specialist roles:

Prof Blundell has been a member of the main Astex Board from 1999 to 2011; he has chaired the

Astex Science Advisory Board from 1999 to the present, and he attends research discussions and visits Astex regularly (Ref. 1, Section 5).

A business or sector has adopted a new technology or process:

Astex changed the way that drug discovery is carried out not only within its own labs but also in other small companies and large pharmaceuticals. The former Head of Worldwide Discovery for Pfizer states: "As a consequence of Astex success, fragment–based approaches are common place throughout Pharma and Biotech, and the power of the technology is also recognised by academia and drug discovery institutes through the UK 3D Fragment consortium, for example. While many companies have in-house capabilities, it is perhaps telling that GSK established a major fragment collaboration with Astex as their internal expertise was apparently not competitive. Importantly, fragments may open the door to blocking protein-protein interactions which would lead to totally new classes of therapeutic agents designed to meet the medical needs of the 21st Century." (Ref. 3, Section 5)

Most pharmaceutical companies now use fragment-based methods in early discovery. They include J&J, GSK and Astra Zeneca, all of whom have first collaborated with Astex; and GSK, UCB, Heptares and Evotec, where Astex employees and/or former members of the Blundell lab have moved to take posts (Ref. 4, Section 5).

Impact on health:

New clinical interventions have been developed:

Astex has developed a strong pipeline (Ref. 5, Section 5), and three drugs that were developed using the fragment-based approach (AT13387, a HSP90 inhibitor, AT7519M, a CDK inhibitor, and AT9283, a JAK/Aurora Inhibitor) are now in Phase II clinical trials for the conditions Gastrointestinal Stromal Tumour (NCT01294202), Mantle Cell Lymphoma (NCT01652144), Chronic Lymphocytic Leukemia (NCT01652144) and Multiple Myeloma (NCT01145989) ;Refs 6-9, Section 5). The same drugs have completed Phase I and are about to enter Phase II for other related clinical conditions (Multiple Myeloma (NCT01183949), Non-Small Cell Lung Cancer (NCT01712217), and Prostate Cancer (NCT01685268)), and in combination with other drugs (Refs 10-12, Section 5).

Early discovery candidates from Astex structure-guided fragment-based drug discovery are now being taken forward in Phase I trials through collaborating companies, include: FGFR Inhibitor JNJ 42756493 (NCT01703481, against Solid Tumours or Lymphoma, taken forward by Janssen Research & Development, LLC), CDK4 Inhibitor LEE011 (e.g. NCT01747876, against MRT and Neuroblastoma, taken forward by Novartis), PKB/Akt Inhibitor AZD 5363 (e.g. NCT01692262, against Prostate Cancer, taken forward by Astra Zeneca) and BACE Inhibitor AZD 3293 (e.g. NCT01795339, against Alzheimers, taken forward by Astra Zeneca).

5. Sources to corroborate the impact (indicative maximum of 10 references)

1. Letter of support from President of Astex
2. Astex corporate partnering information: http://astx.com/partners/corporate-partnering/
3. Letter of support from former Head of Worldwide Discovery at Pfizer
4. Letter of support from Vice President Respiratory Therapy Area at GSK
5. Astex pipeline: http://astx.com/pipeline/products/
6. *Drug*: AT13387 and Imatinib; *Phase:* II; *Study title:* A Study to Investigate the Safety and Efficacy of AT13387, Alone or in Combination With Imatinib, in Patients With GIST.
Sponsor / collaborators: Astex Pharmaceuticals; *Trial dates*: 1/3/2011- 1/8/2013
Trial information link: http://ClinicalTrials.gov/show/NCT01294202
7. *Drug*: AT7519M; *Phase:* II; *Study title:* A Phase II Study of AT7519M, a CDK Inhibitor, in Patients With Relapsed Mantle Cell Lymphoma.
Sponsor / collaborators: NCIC Clinical Trials Group | Novartis Pharmaceuticals | previously: Astex Pharmaceuticals; *Trial dates*: 1/8/2012 - 1/2/2015
Trial information link: http://ClinicalTrials.gov/show/NCT01652144
8. *Drug:* AT7519M; *Phase:* II; *Study title:* A Phase II Study of AT7519M, a CDK Inhibitor, in Patients With Relapsed and/or Refractory Chronic Lymphocytic Leukemia
Sponsor / collaborators: NCIC Clinical Trials Group | Novartis Pharmaceuticals | previously: Astex Pharmaceuticals; *Trial dates*: 1/8/2012 - 1/7/2014
Trial information link: http://ClinicalTrials.gov/show/NCT01627054
9. *Drug*: AT9283; *Phase:* II*; Study title:* A Study of AT9283 in Patients With Relapsed or Refractory

Multiple Myeloma
Sponsor / collaborators: NCIC Clinical Trials Group; *Trial dates*: 1/6/2010 - 1/10/2013
Trial information link: http://ClinicalTrials.gov/ct2/show/
10*. Drug*: AT7519M, Bortezomib; *Phase:* I&II; *Study title*: Effect of AT7519M Alone and AT7519M Plus Bortezomib in Patients With Previously Treated Multiple Myeloma
Sponsor / collaborators: Astex Pharmaceuticals | Multiple Myeloma Research Consortium; *Trial dates*: 1/11/2010 - 1/10/2013
Trial information link: http://ClinicalTrials.gov/show/NCT01183949
11. *Drug*: AT13387, Crizotinib; *Phase:* I&II; *Study title:* A Study of AT13387 in Patients With Non-Small Cell Lung Cancer (NSCLC) Alone and in Combination With Crizotinib
Sponsor / collaborators: Astex Pharmaceuticals; *Trial dates*: 1/10/2012 - 1/11/2014
Trial information link: http://ClinicalTrials.gov/show/NCT01712217
12. *Drug*: AT13387 and abiraterone | AT13387 alone; *Phase:* I&II*; Study title:* A Study of HSP90 Inhibitor AT13387 Alone or in Combination With Abiraterone Acetate
Sponsor / collaborators: Astex Pharmaceuticals; *Trial dates*: 1/9/2012 - 1/1/2015
Trial information link: http://ClinicalTrials.gov/show/NCT01685268