Institution: University of Cambridge

Unit of Assessment: 8 - Chemistry

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

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

In 1999, Chris Abell (Chemistry), Tom Blundell (Biochemistry), and Harren Jhoti co-founded 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 Astra Zeneca. In 2011 the company was sold to SuperGen, Inc., 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 a collaboration between Professor Chris Abell (Professor in Biological Chemistry since 2002; Department of Chemistry since 1984) and Professor Sir Tom Blundell (Sir William Dunn Professor of Biochemistry, Department of Biochemistry, 1996-2009, and now Research Director), who developed their combined expertise in structural biology and organic chemistry to better understand protein-ligand interactions.

Throughout his research career Professor Abell has maintained a strong interest in the mechanism and inhibition of enzymes. This led to increasing collaborative and consultancy involvement with Industry in the 1990s, where high throughput screening was the prevalent method for discovering new hits for drug development. Abell was frustrated by the randomness of this approach, and this fuelled his interest in structure-based approaches to enzyme inhibition. This was facilitated by a major, BBSRC funded collaboration with Professor Tom Blundell on the mechanism, inhibition and structure of enzymes involved in pantothenate biosynthesis.[1,2,3]

In 1998, Blundell and Abell, together with Dr H Jhoti (at the time working at GSK), suggested a novel approach to drug discovery, which underpinned the formation in May 1999 of the spinout company Astex Technology Ltd. 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 300-1000 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 iteratively elaborate these into potent inhibitors.

Research in the laboratories of Abell and Blundell was funded in the University during 1999-2000 by a research grant from Astex Technology. The research was carried out by a post-doctoral researcher in the Department of Chemistry (Dr Martyn Frederickson) in collaboration with two post-doctoral researchers in the Department of Biochemistry (Dr Emil Parasini and Dr Anne Cleasby). Multiple crystals of target proteins were screened with a small fragment library in 1999. They demonstrated in 1999-2000 that binding of very small molecules (MW<300) could be detected, and their positions, including orientation, could be defined at high resolution by X-ray crystallography. In two papers, Abell, Blundell and Jhoti 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.[4,5] The significance of their results enabled Abell, Blundell, and Jhoti to raise substantial further funding and develop the spinout company Astex Technology Ltd. Due to commercial sensitivity, from 2001 further research and development was carried out at Astex Technology Ltd,

and the early results were not published until 2002.

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

1. Albert, A., Dhanaraj, V., Genschel, U., Khan, G., Ramjee, M. K., Pulido, R., Sibanda, B. L., von Delft, F., Witty, M., Blundell, T. L., 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 & Molecular Biology* 5(4): 289-293. DOI: 10.1038/nsb0498-289. (*****)
2. The crystal structure of *E. coli* pantothenate synthetase: a new member of the aminoacyl-tRNA synthetase superfamily. F von Delft, A Lewendon, V Dhanaraj, T L Blundell, C Abell & A G Smith. *Structure* 2001, **9**, 439-450. (*****)
3. Crystal structure of *E. coli* ketopantoate reductase at 1.7A and insight into the mechanism. D Matak-Vinkovic, M Vinkovic, S A Saldanha, J L Ashurst, F von Delft, T Inoue, R Nunez Miguel, A G Smith, T L Blundell & C Abell. *Biochemistry* 2001, **40**, 14493-14500. (*****)
4. Blundell T.L., Abell C., Cleasby A., Hartshorn M.J., Tickle I.J., Parasini E. and Jhoti, H. (2002) High-throughput X-ray crystallography for drug discovery. *Drug Design*: *Cutting Edge Approaches*. Darren Flower, Ed. Royal Society Chemistry, 53-59. DOI: 10.1039/9781847550705
5. Blundell, T.L., Jhoti, H. and Abell, C. (2002) High-throughput crystallography for lead discovery in drug design. *Nature Reviews Drug Discovery* 1, 45-54. DOI: 10.1038/nrd706

(*****) References that best indicate the quality of the research. Reference 5 is a review that contains important original unpublished work.

Grant Information:

- PIs: Chris Abell, Tom Blundell and Alison Smith; Grant Title: Structural and biochemical studies on pantothenate biosynthesis enzymes; Sponsor: BBSRC; Period of Grant: 01/10/98 – 01/10/01; Value of Grant: £161,086.
- PIs: Chris Abell and Tom Blundell; Grant Title: Sponsored Research Agreement; Sponsor: Astex Technology Ltd; Period of Grant: 01/10/99 - 30/09/00; Value of Grant: £279,370.

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

Impact on Commerce

A spinout company has been created and established its viability by generating revenue or profits:

On the basis of high resolution by X-ray crystallographic structures of fragments that bound to protein targets carried out in the Blundell and Abell laboratories, 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 in excess of $1.8bn (approximately £1bn) between 1999 and 2011. Investments in Astex have included Abingworth, Apax, Oxford (Boston), Advent, Alta and others with £80 million equity in multiple financing rounds. Astex has also had major collaborations, which involved investments of up to a total of £25 million from GSK, Johnson and Johnson, Novartis and Astra Zeneca, of these the GSK investment occurred after 1/1/2008.[1, LC1, LC2] 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.[LC1]

Jobs have been created/protected:

Over the past decade, the company has secured constant employment for between 70 and 120 workers in Cambridge.[LC1] The current number of employees in the UK and US is ~120.

Highly skilled people have taken up specialist roles:
Astex employs predominantly PhD students from industry and academia (including some from the Abell Group). Employees from Astex have gone on to major roles in academia (Paul Wyatt, Director of the Drug Discovery Unit, Dundee), and industry (Miles Congreve, Vice President of Chemistry, Heptares). Professor Abell was a member of the Astex Board from 1999 – 2000 and has been on its Scientific Advisory Board continuously since its foundation.[LC1]

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."* [LC3]

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 UCB, Heptares and Evotec, where Astex employees and/or former members of the Abell and Blundell laboratories have moved to take posts.[LC1 & LC2]

Impact on Health

New clinical interventions have been developed:
Astex has developed a strong pipeline[2] and three drugs that were developed using the fragment-based approach (AT13387, an 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).[3,4,5,6] 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.[7,8,9]

Early discovery candidates from Astex structure-guided fragment-based drug discovery that 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 (eg NCT01747876, against MRT and Neuroblastoma, taken forward by Novartis), PKB/Akt Inhibitor AZD 5363 (eg NCT01692262, against Prostate Cancer, taken forward by Astra Zeneca) and BACE Inhibitor AZD 3293 (eg NCT01795339, against Alzheimers, taken forward by Astra Zeneca).[10]

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

Letters of corroboration available for audit
LC1 President of Astex Pharmaceuticals.
LC2 Vice President Respiratory Therapy Area, GSK.
LC3 Former Head of Worldwide Discovery at Pfizer.

References in the public domain
1. Astex corporate partnering information: http://astx.com/partners/corporate-partnering/
2. Astex pipeline: http://astx.com/pipeline/products/
3. *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
4. *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
5. *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
6. *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/
7. *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
8. *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
9. *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
10. http://astx.com/pipeline/products/preclinical/