Institution: University of Bath

Unit of Assessment:8: Chemistry

Title of case study:
Atlas Genetics – "Test and Treat" diagnostics for infectious diseases

1. Summary of the impact

This case study outlines the impact in generating investment in a spin-out SME and in developing a technology for clinical diagnosis based on chemistry research carried out in Bath. The research led to a spin-out company, Atlas Genetics, which has raised over £18M funding in the REF period specifically to develop the Atlas io™ platform, novel technology for rapid (<30 minute) and robust detection of infectious diseases suitable for point-of-care. The investment has created new jobs for highly skilled workers at the cutting-edge of medical diagnostics, with Atlas currently employing 36 staff. The io™ platform has been fully developed and has undergone successful clinical tests on multiple infections (based on bespoke Chemistry developed at Bath) prior to clinical trialling and rollout in Europe and the United States.

2. Underpinning research

The group of Professor Chris Frost synthesises organic and biomolecular systems with potential sensing applications, aligned with the Bath Chemistry Sensing & Healthcare theme. Fast and accurate detection of DNA is an important sensing methodology for a wide range of biological targets, especially pathogens. Although existing DNA sensor technology is largely based on fluorescence detection, other sensor transduction paradigms are known including electrochemistry. The detection of specific oligonucleotide sequences using electrochemistry has significant advantages: no need for optical sample transparency; direct signal read-out; ease of miniaturisation and device manufacture.

In the Bath research that underpins this Impact Case Study, an oligonucleotide detection assay was developed based on electrochemical detection, with an assay based on the appearance of a distinct electrochemical signal when an electronic label (based on ferrocene) is cleaved from an oligonucleotide probe. The higher diffusion mobility and enhanced access of the enzymatically cleaved ferrocene label to the electrode surface results in an increase in ferrocene oxidation current. The labelled oligonucleotide probe is designed with a complementary sequence to a unique section of the target DNA and since cleavage of the label from the probe and appearance of a signal occurs only when the target is present, this allows the sensing of any particular oligonucleotide sequence [1, 2]. The ferrocene labels were designed and prepared in Bath and the initial research generated key intellectual property (detailed below) for a relatively simple, potentially widely applicable assay for detecting DNA targets with no surface modification required, followed up by collaborative knowledge transfer funding [3].

This research led to the launch of a University spin out Atlas Genetics Ltd, a diagnostic company developing ultra-rapid point-of-care tests for a range of infectious diseases based on the described ferrocene reagents and electrochemical assay. The technology comprises a low cost instrument (the io™ platform) and a disposable test-specific cartridge to which an unprocessed clinical sample is added and which offers fluidic and temperature control, end-point electronics and software that can be automatically processed without user intervention. All reagents required to perform the test are located on the cartridge in an ambient-stable format. The platform nature of the technology allows detection of multiple pathogens or sequences (multiplexing), offering up to 20 tests per cartridge. To achieve this requires multiple ferrocene labels that produce unique electrochemical signals and the chemical functionality on ferrocene can be modified by synthesis to tune the oxidation potential. The successful ongoing development of novel multiplex ferrocene labels for the Atlas io™ detection system has been led by Frost at Bath and funded by AtlasGenetics [4].

Timeframe: The relevant initial work was carried out in 2001-2005, with initial publication in 2004 and subsequently developed further with Atlas Genetics, forming the subject of patent applications and continued collaborative funding to fund further label development.

Key Researchers

Professor Chris Frost (Lecturer, now Professor, at Bath since 1996; synthesis of sensor molecules; lead academic)

Dr Toby Jenkins (Lecturer, now Reader, 2000-), Prof Laurie Peter (1990-), Prof Frank Marken (Lecturer, now Professor 2004-) (electrochemistry and prototype device implementation)

S C Hillier (2001-05), J Sharp (2009-2012) (PhDs in Frost group); S E Flower (PDRA in Frost research group, 2001-2003)

3. References to the research

[1] S. C. Hillier, S. E. Flower, C. G. Frost, A. T. A. Jenkins, R. Keay, H. Braven & J. Clarkson (2004). *Electrochem. Commun*., **6**, 1227 ; [5-year I.F. = 5.1]. *An electrochemical gene detection assay utilising T7 exonuclease activity on complementary probe-target oligonucleotide sequences.* [DOI: http://dx.doi.org/10.1016/j.elecom.2004.09.019]

[2] S. C. Hillier, S. E. Flower, C. G. Frost, A. T. A. Jenkins, R. Keay, H. Braven & J. Clarkson (2004). *Bioelectrochemistry*, **63**, 307. *An electrochemical study of enzymatic oligonucleotide digestion.* [DOI: http://dx.doi.org/10.1016/j.bioelechem.2003.10.028]

Industrial/Translation Funding

[3] Teaching Company Scheme Programme grant (Frost, with Molecular Sensing plc), 2001-2003 (£94k); Knowledge Transfer Partnership Programme grant (Frost, with Molecular Sensing plc, UK) 2005-2008 (£151k); Great Western Research (Frost, with Atlas Genetics plc, UK) 2008-2011 (£55k)

[4] Atlas Genetics Industrial Secondment (Frost), 2009-2010 (£24k); Atlas Genetics Industrial Funding (Frost), 2011-2014 (£206k)

4. Details of the impact

"*I am delighted to confirm the essential role of Chemistry research in the formation and growth of Atlas Genetics. Atlas is building a world class diagnostics company based on technology for the electrochemical detection of specific sequences of DNA. The underpinning research was carried out in collaboration with Professor Frost [and team] in the Chemistry Department at Bath*" [A]

Impacts from this work: company, investment, people and a new technology

- A spin-out or new business has generated revenue or profits (**Atlas Genetics; >£18M new investment in REF period**)
- Highly skilled people having taken up specialist roles that draw on their research (**Atlas staff expansion from 12 to 36, largely in technical scientific roles**, including three recruited from Bath at doctoral level)
- A new diagnostic or medical technology has been developed (**the io™ platform – trialled in the USA and EU; successful clinical trialling**)

Economic, Wealth and Opportunity Creation

The research carried out in Bath Chemistry, and the development of the key technology of the electrochemical sensor [B], resulted in the *formation of Atlas Genetics in 2005*, to exploit commercially the technology originating from the University of Bath. Atlas was launched with £500k initial funding, 50% of which came from the Sulis Seedcorn Fund, established by the University of Bath to provide support for new businesses. Prior to the REF period, in 2007 Atlas completed Series A financing of £2 million and the company relocated from the University to a 2,500 sq. ft. site on a business park close to Bath (Trowbridge, Wiltshire). The number of full time staff increased to 12 and a commercial programme to develop the Atlas system io™ was initiated.

Atlas [C] is currently venture capital funded and ***to date has raised ca. £22m***, including a **£16.9M investment in July 2011**, specifically to develop the io™ system and a molecular Chlamydia test. Atlas investors include YFM, South West Ventures Fund, Finance South West Growth Fund, Braveheart Ventures, Sulis Investment Management Fund, GEIF Ventures, Consort Medical plc, Novartis Venture Funds, Life Sciences Partners, BB Biotech Ventures and Johnson & Johnson

Development Corporation and private investors [D]. Atlas has recently expanded its office and laboratory provision to 9,500 sq. ft. and currently **employs a total of 36 permanent staff**, representing an *increase of 24 in the REF period*, the majority of whom have higher education qualifications in science (MSc/PhD), engineering (BEng/MEng) or business (MBA).

The company has continued to invest in the research and development of new reagents and electrochemistry technology with the establishment of a new post for a senior chemist, who spends 3 days/week at Bath and 2 days/week at Atlas. Professors Frost and Marken are both engaged as consultants by Atlas Genetics.

The Route to Clinical Implementation

Atlas' proprietary io™ system enables the sensitivity and accuracy of laboratory testing to be achieved in a point-of-care environment. The io™ system will initially be launched for the testing of Chlamydia [E], allowing clinicians to test and treat patients in a single appointment. Around 40 million tests are carried out for this and related diseases in Europe and the US every year. According to the European Centre for Disease Prevention and Control and the World Health Organisation [F], Chlamydia is the most frequently reported bacterial sexually transmitted infection (STI), causing an estimated 92 million new cases of genital Chlamydia infection annually and prevalence rates in young people between 5-10% [F]. Rapid diagnosis is key to preventing disease spread. The electrochemical technology at the core of the Atlas io™ tests offer a time-to-result turnaround of less than 30 minutes, which is within the acceptable waiting period for a point-of-care diagnostic test result. The "test and treat" approach offers significant benefits to the wider population and could include a decrease of onward transmission and new infections. To establish the validity of the prototype assays, Atlas have collaborated with Professor Charlotte Gaydos of the Johns Hopkins University Medical School (Baltimore, USA; [G]) to evaluate the io™ system technology for Chlamydia detection on **306 patient samples**, showing a sensitivity of 98.1% and specificity of 98.0% using the prototype io™ *Chlamydia trachomatis* assay. This is comparable with that of existing commercial nucleic acid amplification tests (the slower, lab-based and non-point of care, tests Gen-Probe Aptima Combo 2™ and the Roche Cobas Amplicor™ were used as comparator tests). [H, I]. **These impressive clinical test results support the adoption of the Atlas io™ tests in clinical environments**.

Clinical trials with Public Health England (PHE) for the Atlas io™ platform and Chlamydia detection product commence in late 2013 with final formal clinical evaluation in March 2014. The platform launches in Europe with CE certification in 2014, followed by roll-out in the US.

Technology for Widening Diagnostic Reach: The *in vitro* diagnostics (IVD) market is $42 billion and growing at 6% annum, the most rapidly growing areas are molecular diagnostics (valued at $3b and growing at 15% pa) and the point-of-care market (valued at $2.5b and growing at 12% pa); the WHO estimates that 499 milliion new STI infections occur each year [J]. Due to the *platform* nature of the io™ system, Atlas have developed the technology (by commissioning of new bespoke Chemistry from Bath [A]) for a panel of other tests in development to expand their STI test portfolio, including, a duplex test for Chlamydia/Gonorrhoea (anticipated clinical trials in 2014) and Trichomonas (the most prevalent curable STI in the world, causing an estimated 248 million new cases annually of genital *T. vaginalis* infection). The Atlas io™ *Trichomonas vaginalis* prototype test has been evaluated at the Johns Hopkins University Medical School. In this published study [G], clinical sample testing demonstrated a sensitivity of 95.5% and specificity of 95.7%; these are comparable with that of existing central laboratory nucleic acid amplification tests used for screening patients for *T. vaginalis*. In 2010 Atlas started work on an immunoassay programme to expand the capabilities of the electrochemical detection platform with a Regional Development Agency grant for the development of a Syphilis assay. The development of redox-active substrates for electrochemical immunoassays and a novel method for signal amplification are being carried out by a directly-funded PhD student in the Frost group at Bath. Atlas is also developing a rapid test cartridge for Methicillin Resistant *Staphylococcus Aureus* (MRSA) for near-patient testing in high dependency and intensive care units, and other targeted clinical settings. This test further expands the scope for the Atlas electrochemical detection method by employing the technology in a quantitative PCR (qPCR) based system.

Key Impacts Summary

2008 – Establishment of io™ platform , capability for implementation of a range of tests
2011 – Additional £18.4M (£1.5M in March; £16.9 M in July) series B venture capital and strategic investment for Atlas; growth to 25 full-time positions
2011 – Successful clinical sample testing of *Chlamydia trachomatis* test on io™ System in collaboration with Johns Hopkins, University Hospital, USA.
2013 – New office and laboratory provision for Atlas and strategic expansion to 36 permanent staff
2013 – Successful clinical sample testing of *Trichomonas vaginalis* test on io™ System in collaboration with Johns Hopkins, University Hospital, USA.

5. Sources to corroborate the impact

[A] Letter of evidence of impact, CEO, Atlas Genetics

[B] *IP/patents*
O H Braven, R Keay (Molecular Sensing), S E Flower (Bath), *Protease detection assay*, 2005, WO 2005/005657; Patent (Molecular Sensing, now held by Atlas Genetics) http://worldwide.espacenet.com/publicationDetails/biblio?DB=EPODOC&II=3&ND=3&adjacent=true&locale=en_EP&FT=D&date=20101223&CC=US&NR=2010320093A1&KC=A1 ; B Marsh, J Sharp (Atlas Genetics), S E Flower, C G Frost (Bath), *Novel ferrocene labels for electrochemical assay and their use in analytical methods*, 2012, PCT Patent 2012/085591 (Atlas Genetics) http://worldwide.espacenet.com/publicationDetails/biblio?DB=EPODOC&II=8&ND=3&adjacent=true&locale=en_EP&FT=D&date=20120628&CC=CA&NR=2822477A1&KC=A1

[C] *Atlas Genetics:* http://www.atlasgenetics.com/

[D] *Capitalisation*
http://www.atlasgenetics.com/announcements/atlas-ltd-completes-16-9-million-series-b-financing-led-by-novartis-venture-funds
"Atlas Genetics Ltd completes £16.9M series B financing led by Novartis Venture Funds"

[E] *Broader publicity for Atlas Genetics STD testing*
http://www.telegraph.co.uk/women/sex/9740518/20-minute-sex-disease-test-could-curb-infections.html

[F] *ECDC and WHO Statistics on occurrence of STI*
ECDC Guidance, Chlamydia control in Europe, Stockholm, June 2009, ISBN 978-92-9193-165-1 [DOI: 10.2900/11364]; World Health Organisation Global prevalence and incidence of selected curable sexually transmitted infections. Geneva: WHO, WHO/HIV_AIDS/2001,02

[G-I] *Clinical references*
[G] Successful clinical testing of the device for Chlamydia testing has been carried out at Johns Hopkins University Hospital, Baltimore, USA
http://www.hopkinsmedicine.org/Medicine/std/awards/

[H] Pearce D M, Shenton D P, Holden J, Gaydos C A (2011) *Evaluation of a novel electrochemical detection method for Chlamydia trachomatis: Application for point-of-care diagnostics*. IEEE Trans. Biomed. Engin. 58: 755-758; Pearce DM, Styles DN, Hardick JP & Gaydos CA (2013) [DOI: 10.1109/TBME.2010.2095851]. *A new rapid molecular point-of-care assay for Trichomonas vaginalis: preliminary performance data*. Sex. Transm. Infect.; Published Online First: April 20, 2013. [DOI:10.1136/sextrans-2012-051000]

[I] Successful prototype test for the sexually transmitted infection (STI / STD), *Trichomonas vaginalis* (*T. vaginalis*), on Atlas rapid POC io™ molecular diagnostic platform. http://www.atlasgenetics.com/announcements/successful-evaluation-of-trichomonas-vaginalis-poc-test-on-atlas-io-system-in-collaboration-with-joh

[J] WHO Fact Sheet on Sexually Transmitted Infections
http://www.who.int/mediacentre/factsheets/fs110/en/index.html