

<p><b>Institution: University of Exeter</b></p>
<p><b>Unit of Assessment: 5</b></p>
<p><b>Title of case study:</b> Commercialisation of a Novel Diagnostic Test for Invasive Pulmonary Aspergillosis</p>
<p><b>1. Summary of the impact</b> (indicative maximum 100 words)</p> <p>Invasive pulmonary aspergillosis (IPA) is a frequently fatal disease of haematological malignancy patients, caused by fungi from the genus <i>Aspergillus</i>. Dr Christopher Thornton has developed and commercialised a novel point-of-care test for the diagnosis of IPA with an <i>Aspergillus</i>-specific monoclonal antibody (mAb) JF5 generated using hybridoma technology. Using this mAb, he has developed a lateral-flow device (LFD) for the rapid detection of <i>Aspergillus</i> antigen in human serum and bronchoalveolar lavage fluids (BALf) that signifies active infection. Commercial exploitation of the patented technology has been met through the establishment of a University of Exeter spin-out company, Isca Diagnostics Limited.</p>
<p><b>2. Underpinning research</b> (indicative maximum 500 words)</p> <p>Dr Thornton's (appointed to Exeter as Lecturer, 2003-07, Senior Lecturer 2007-present) research focuses on the development of next generation monoclonal antibodies for use in fungal biology, and he has a particular interest in IPA which is a leading cause of morbidity and mortality in haematological malignancy patients and hematopoietic stem cell transplant recipients [1], with an estimated 200,000 cases per year worldwide and a death rate in excess of 50%. Diagnosis of IPA represents a formidable diagnostic challenge and usually relies on a combination of clinical data, microbiology and histopathology, none of which provide a definitive differential diagnosis. There are no nucleic acid based tests and currently available enzyme immunoassays are unreliable. The Thornton lab has addressed this problem and developed a series of next-generation monoclonal antibody (mAb)-based assays that detect markers of active infection.</p> <p>In 2008 Thornton described the generation of an <i>Aspergillus</i>-specific mAb (JF5) using hybridoma technology, and its use to develop an immuno-chromatographic lateral-flow device (LFD), similar to those used in many pregnancy tests, for the rapid (10 min) point-of-care diagnosis of IPA [2]. Funding from the US National Institute of Allergy &amp; Infectious Diseases allowed Dr Thornton to validate the LFD in an animal model of IPA [3, 4]. Subsequent funding from Pfizer Ltd allowed Dr Thornton to collaborate with haemato-oncologists at St. Bartholomew's hospital (London), King's College hospital (London), the Royal Devon and Exeter hospital (Exeter), the Medical University of Graz (Austria) and with medical mycologists at Cardiff University hospital, to undertake clinical trials of the LFD in humans. Results of the LFD trials, demonstrated a 100% negative predictive value for IPA diagnosis using human BALf and 100% positive predictive value when used as an adjunct test with PCR of human serum [4-6]. The specificity, ease-of-use, low cost (~£10 per test), and compatibility of the <i>Aspergillus</i> LFD with routine hospital practices [1, 5, 6] means that the onset of IPA can be quickly and accurately monitored using a simple and cheap blood test for circulating <i>Aspergillus</i> antigen [2, 5, 6] or with BALf collected during bronchoscopy and lung biopsy [3,4]. Importantly the test does not suffer from the false-positivity seen with commercial Beta-glucan and galactomannan assays due to antibiotics, anti-cancer drugs or the presence of other fungi [1, 2, 4-6]. This is vitally important in establishing a differential diagnosis of IPA.</p>
<p><b>3. References to the research</b> (indicative maximum of six references)</p> <p><b>Evidence of the quality of the research:</b> this work has been published in high quality peer reviewed journals, has attracted significant external grant funding, has resulted in the granting of patents and establishment of a spin-out company.</p> <p><b>Research publications:</b></p> <ol style="list-style-type: none"> <li>1. Thornton CR. Detection of Invasive Aspergillosis. (2010). <i>Advances in Applied Microbiology</i> <b>70</b>: 187-216.</li> <li>2. Thornton CR. Development of an immunochromatographic lateral-flow device for rapid serodiagnosis of invasive aspergillosis. (2008). <i>Clinical and Vaccine Immunology</i> <b>15</b>: 1095-1105.</li> <li>3. Wiederhold NP, Najvar LK, Bocanegra R, Kirkpatrick WR, Patterson TF, &amp; Thornton CR. (2013).</li> </ol>

## Impact case study (REF3b)

Inter-Laboratory and Inter-Study Reproducibility of a Novel Lateral-Flow Device and the Influence of Antifungal Therapy on the Detection of Invasive Pulmonary Aspergillosis. *Journal of Clinical Microbiology* **51**: 459-465.

4. Thornton C, Johnson G, & Agrawal S. Detection of invasive pulmonary aspergillosis in haematological malignancy patients by using lateral-flow technology. (2012). *Journal of Visualised Experiments* **61**: e3721, DOI: 10.391/3721. URL:
5. Hoenigl M, Koidl C, Duettmann W, Seeber K, Wagner J, Wöfler A, Raggam RB, Thornton C, & Krause, R. Bronchoalveolar lavage lateral-flow device test for invasive pulmonary aspergillosis diagnosis in haematological malignancy and solid organ transplant patients. (2012). *Journal of Infection* **65**: 588-591.
6. White PL, Parr C, Thornton CR, & Barnes RA. (2013). An Evaluation of Real-Time PCR, Galactomannan ELISA and a Novel Lateral-Flow Device for the Diagnosis of Invasive Aspergillosis. *Journal of Clinical Microbiology* **51**: 1510-1516.

**Research grants:**

7. Wiederhold N (University of Texas) and Thornton CR (UoE), Invasive Aspergillosis Diagnosis by Antigen Capture with Lateral-Flow Technology, US National Institutes of Health/National Institute of Allergy and Infectious Diseases 01/06/10 to /05/12, \$230,262.
8. Thornton CR. (UoE), Clinical Evaluation of a Lateral-Flow Device for Rapid Diagnosis of Invasive Aspergillosis, Pfizer Ltd., 01/10/10 to 30/09/11, £59,617.
9. Thornton CR (UoE). Development of a lateral-flow device for rapid serodiagnosis of invasive aspergillosis. Higher Education Innovation Fund 4, 2010, £15,000.
10. Thornton CR (UoE). Creation of Isca Diagnostics Ltd., a University of Exeter Spin-Out Company. Higher Education Innovation Fund 5, 25/05/12 to present, £4,750.
11. Thornton CR (Isca Diagnostics Ltd.). New Molecular-Functional Imaging Technologies and Therapeutic Strategies for Theranostic of Invasive Aspergillosis. European Commission FP7-HEALTH-2013-INNOVATION-1 SME-targeted Collaborative Project, 2013-2018, €1,397,800.

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

The commercial value of Dr Thornton's research in fungal immunodiagnostics has led to protection of his intellectual property through a patent application in 2008 (section 5; source 1), and commercial exploitation of the *Aspergillus* LFD through establishment of a University of Exeter spin-out company, Isca Diagnostics Limited ([www.iscadiagnostics.co.uk](http://www.iscadiagnostics.co.uk), section 5; source 2-4), and a global distribution agreement with OLM Medical ([www.olmmedical.com](http://www.olmmedical.com), section 5; source 5).<sup>14</sup> Dr Thornton, as CEO of Isca, was also awarded €1.4M as an SME participant in a 5 year FP7 HEALTH-INNOVATION-1 consortium grant in 2013. Dr Thornton's role is to generate JF5 antibody fragments (Fabs, scFvs, minibodies) and a humanised JF5 antibody for radio-immunotherapy and Positron-Emission-Tomography/MRI imaging of IPA in animal models and in human clinical trials (<http://www.mathias-imaging.eu>).

**1. Intellectual Property Protection and Patenting of the LFD and mAb JF5**

A patent "New Method of Detecting and Diagnosing Invasive Aspergillosis", with Dr Thornton as the named inventor, was filed by the University of Exeter in the US in Jan 2009 (US61/145,282), and PCT filing (PCT/GB2010/000064) in Jan 2010 (section 5; source 1). Regional and National Phase registration was initiated in July 2011, with protection being sought in the US, EU, Russia, China and India. In line with the Budapest treaty, the variable heavy and light chains ( $V_H$  and  $V_L$ ) and Complementarity Determining Regions (CDRs) of mAb JF5 were sequenced and published, and the hybridoma cell line deposited in the European Collection of Cell Cultures (ECACC). The sequencing and deposition work was funded by a HEIF 4 grant to Dr Thornton.

**2. Establishment of University of Exeter Spin-Out Company Isca Diagnostics Ltd.**

On 29<sup>th</sup> March 2012, Dr Thornton, with financial and legal support from the University of Exeter and funding of £85k from private investors (section 5; source 3), established a spin-out company Isca Diagnostics Ltd. (section 5; source 4), for commercial exploitation of mAb JF5 and the *Aspergillus*-specific LFD. Subsequent funding in 2013 through an EC FP7 consortium grant has enabled Isca

**Impact case study (REF3b)**

to expand its portfolio of diagnostic and therapeutic agents for IPA over the next five years (2013-2018). It has also enabled Isca to employ a full-time R&D scientist and for Dr Thornton to spend 0.33FTE as an Isca employee (2013-2018).

**3. Distribution and Sales of the *Aspergillus* LFD as a CE marked medical IVD.**

MHRA CE marking of the LFD for use as a general medical IVD in the European Union was obtained in 2013 and external US evaluation of the LFD, conducted by the NIH/NIAID-funded *Aspergillus* Technology Consortium ([www.astecdiagnostics.org](http://www.astecdiagnostics.org)), will commence in Nov 2013, providing the data for a 510k FDA approval. An agreement with OLM Medical has been signed for distribution and sales of the LFD worldwide (section 5; source 5). Prior to September 2013, purchase orders of the CE marked device had been received from Australian and Canadian hospitals (section 5; source 6), and internal validation audits of the LFD, prior to order placement, are currently being undertaken in hospitals in the UK, US, France, Germany, Austria, Israel, Turkey, Peru, Iran, and South Africa.

In addition to its commercial activities, Isca is a sponsor of the *Global Action Fund for Fungal Infection* ([www.gaffi.org/our-partners/](http://www.gaffi.org/our-partners/)), a Geneva-based foundation whose vision is to reduce illness and death associated with fungal diseases worldwide. As a GAFFI partner, Isca supplies the *Aspergillus* LFD as a research tool for use by resource-limited countries.

Dr Thornton also entered into an IPR agreement with Pfizer Ltd. in November 2013, allowing Pfizer to promote the LFD alongside its antifungal voriconazole, VFend® (section 5; source 7).

The success of the LFD device, prompted by Dr Thornton's research and the subsequent incorporation of Isca Diagnostics Ltd has stimulated a large amount of interest in the media. A list of web references to these are included as section 5; source 8.

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

1. New Method of Detecting and Diagnosing Invasive Aspergillosis", with Dr Thornton as the named inventor, was filed by the University of Exeter in the US in Jan 2009 (US61/145,282), and PCT filing (PCT/GB2010/000064) in Jan 2010.

Details of the *Aspergillus* LFD and mAb JF5 patent can be found at:

(<http://www.wipo.int/pctdb/en/wo.jsp?WO=2010082034&IA=GB2010000064&DISPLAY=DESC>)

**Supporting documents relating to the establishment of Isca Diagnostics Ltd. and distribution and sales of the *Aspergillus* LFD.**

2. Isca Diagnostics IP License Agreement.
3. Isca Diagnostics Shareholders Agreement and Written Resolutions.
4. Isca Diagnostics Incorporation Certificate.
5. OLM Medical Distribution Agreement.
6. LFD purchase orders from Australian and Canadian hospitals.
7. Isca Licence Agreement with Pfizer Ltd.

**8. Reports in public domain (web links)**

*Media release by the Society for General Microbiology:*

(<http://www.alphagalileo.org/PrintView.aspx?ItemId=56558&CultureCode=en>)

*Other website coverage:*

(<http://aspergillusblog.blogspot.com/2009/04/quick-new-test-for-aspergillus.html>)

(<http://www.sciencecentric.com/news/article.php?q=09040225-a-new-test-deadly-fungal-infection-patients-with-damaged-immune-systems>)

(<http://www.physorg.com/news157869734.html>)

(<http://computescotland.com/2209.php>)

(<http://www.sciencedaily.com/releases/2009/04/090401200437.htm>)