Institution: Nottingham Trent University

Unit of Assessment: A03: Allied Health Professions, Dentistry, Nursing and Pharmacy

Title of case study: Developing rapid diagnostics for infectious disease agents

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

Research led by Dr A McNally at Nottingham Trent University has driven the development of rapid diagnostic protocols and devices for infectious diseases, principally Influenza, *Salmonella* and *Campylobacter*. This began by working on the validation of a standardised real-time PCR test for H5N1 avian influenza which is now used in European reference laboratories. Follow on funding from European Union and Technology Strategy Board led to the development of fully automated diagnostic devices for companies who have taken their products to market and attracted substantial investment from world-leading pharmaceutical companies.

2. Underpinning research (indicative maximum 500 words)

Diagnostics development research was first undertaken by Dr McNally during his time as a post-doctoral scientist. Working on a Department of Environment, Food and Rural Affairs (Defra) funded project (SE4005) from 2004-2006, his direct role was to validate the newly developed real-time PCR assay planned for use in future European H5N1 outbreaks. The work was presented to an emergency European Union meeting to discuss implementation of molecular detection in reference laboratories. The validation led to the test being approved for use in all avian influenza reference laboratories, and the protocols provided for testing (Ref 1). The work was published when Dr McNally was at NTU (Ref 2), and subsequent work using the assay for research purposes involving Dr McNally was also published (Ref 3).

In 2006 Dr McNally joined Nottingham Trent University (NTU) as a lecturer, and took this work forward in the Spring of 2007 as part of a consortium which secured 3 million Euro funding to develop rapid, point-of-care diagnostics for influenza (PortFastFlu Project, Ref 4). This involved creating new improved assays to detect all influenza subtypes in veterinary and clinical samples by a combination of a PCR amplification and microarray hybridisation. The entire test was to be run in a single self-contained device, providing a simple "inject and forget" diagnostic machine for influenza. Dr McNally was recruited to the consortium as the sole member with experience of designing and validating reference laboratory standard detection tests, and was directly involved in assay design, assay validation, and device validation. As a result there was transfer of knowledge to industrial partners (Genewave, Gaiker, Ikerlan, and GE Whatmann), as well as academic partners at VIB (Flanders Institute of Biotechnology, Prof Xavier Saelens) and Centre for Agricultural Research and Development, France (Dr Emmanuel Albina). The project ended in January 2011 with the lead SME Genewave launching their hardware device to market.

The success of the EU project led to Dr McNally being Principal Investigator on a Technology Strategy Board (TSB) funded project (Ref 5) developing a portable, rapid, automated DNA analysis (PRADA) molecular point-of-care test system for intestinal infectious disease from October 2008 - October 2010. The project involved creating assays for the detection of *Salmonella* and *Campylobacter* in faecal samples, and crucially a sample preparation technique to allow direct fully automated PCR detection of pathogens from faecal sample; thus a wider application for healthcare associated infections. The project was in collaboration with Enigma Diagnostics who developed the hardware and technology. Dr Georgina Manning at NTU was a co-investigator, and Dr Jennifer Ince was employed as a post-doctoral research associate. The University of Nottingham was also involved in the project (Prof Nigel Minton, Professor of Applied Molecular Microbiology, Clostridial Research Group**,** and Prof Richard James, Professor of Microbiology, Director of the Centre for Health Care Associated Infections, both at the Centre for Bimolecular Sciences).

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

1) OIE, FAO approved diagnostic algorithm from molecular testing of H5N1. http://www.defra.gov.uk/ahvla-en/files/pub-protocol-ai-vi492.pdf (first posted 18/09/2007 – present day)

2) Slomka, M.J., Pavlidis, T., Banks, J., Shell, W., **McNally, A.**, Essen, S. C., & Brown, I. H. (2007). Validated H5 Eurasian RealTime PCR and its application in H5N1 outbreaks in 2005-06. Avian Diseases. 51: 373-377. DOI: 10.1637/7664-060906R1.1. Impact Factor 1.734, citations 57 (http://wok.mimas.ac.uk on 18th October 2013).

3) Aldous, E. W, Seekings, J. M., **McNally**, A., Nili, H., Irvine, R. M., Alexander, D. J. and Brown, I. H. (2010). Infection dynamics of highly pathogenic avian influenza and virulent avian paramyxovirus type 1 viruses in chickens, turkeys and ducks. Avian Pathol. 39: 265-273. DOI: 10.1080/03079457.2010.492825. Impact Factor 1.729, citations 10 (http://wok.mimas.ac.uk on 18th October 2013).

Evidence of the quality of the research: Key research grants:

4) Alan McNally Co-Investigator on PortFastFlu. European Community's Seventh Framework Programme ([FP7/2007-2013] under grant agreement n° 201914. Grant awarded 3 Million Euro. (01/01/2008 – 31/12/2010)
http://ec.europa.eu/research/health/infectious-diseases/emerging-epidemics/projects/184_en.html

5) Alan McNally Principal Investigator on Portable Rapid Automated Detection and Analysis (PRADA). TSB project– AG182K. Grant awarded £1.8 Million (01/11/2008 – 31/10/2011).
http://www.enigmadiagnostics.com/ufiles/PR%20-%20PRADA.pdf

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

Point-of-care diagnostics for influenza

During the PortFastFlu EU FP7 project, Dr McNally was heavily involved in the transfer of crucial background IP to industry and academia prior to creating and validating reference laboratory quality diagnostic and detection assays. Benefitting organisations included the French SME Genewave, the Spanish SMEs Gaiker and Ikerlan, and Whatman GE Healthcare, all of whom adopted assay design practices based on Dr McNally's scientific input. Additionally the validation of testing procedures and devices during the project was designed by Dr McNally, allowing the final product to be tested to OIE reference laboratory standards. This invaluable input has resulted in a commercial product going to market for the French SME Genewave in early 2011. The product is built upon several concepts developed in the project and for which three joint consortium patents were filed in January 2011 (Source to corroborate 1).

The impact of rapid diagnosis of human cases of H5N1 infection was quantified in a 2008 Lancet study (Source to corroborate 2) which concluded that rapid point-of-care diagnosis of cases in humans would allow more effective infection control measures and quicker delivery of oseltamivir to patients. The work performed also created multiple opportunities for public outreach events educating the public on Influenza and the benefits of rapid diagnostic research. These included editorials in the Lancet, and expert opinion to national and international media such as BBC Radio 5, BBC Radio 4, and Naturenews.com (Sources to corroborate 3,4).

Rapid PCR-based detection system for *Salmonella* and *Campylobacter*

The TSB project PRADA with Enigma saw NTU develop a sample preparation protocol for the ML

Enigma diagnostic device which is incorporated into the marketed product. The sample preparation technique developed at NTU is absolutely integral to the ability of the ML diagnostic device to be used on any sample type, from faecal samples to respiratory samples. This ensures the ML is applicable to detection of any infectious agent from any clinical sample type and is a truly multi-functional platform.

During the lifetime of the project Enigma secured substantial investment from GlaxoSmithKline for development of their device for use in influenza diagnostics (Source to corroborate 5). Since then GSK has further invested in a collaboration with Enigma on the commercialisation of the ML device and assay development (Source to corroborate 6). Currently the device, incorporating NTUs sample preparation method along with an accompanying Influenza rapid test to run on the device, forms the commercial portfolio of Enigma. Up to 30/04/2012 Enigma had a net worth of £2.968 million, total assets of £6.63 million, and cash at bank of £1.805 million.

Now that the Enigma ML device contains a sample preparation method able to be used on any sample type, further collaborative funding is being sought by Enigma and NTU to validate and commercialise the *Campylobacter* assay developed by NTU for use in veterinary diagnostics. *Campylobacter* is the most commonly reported bacterial cause of gastroenteritis in the developed world, thus the impact of the assay is predicted to be large and sustained. There are approximately 1.5M GP consultations for diarrhoea in the UK every year. Defra is now considering a national surveillance programme for *Campylobacter* in poultry. Assuming this covered all broiler birds and pooled sampling was performed (100 birds) that would mean approx. 1.2 million tests per annum. Current tests cost between £14 and £44 so a target of £12 would be very competitive. Scaled up across the EU and USA, this would mean 20 million tests and a total market potential of £240 million.

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

1. European Community's Seventh Framework Programme ([FP7/2007-2013] under grant agreement n° 201914. PortFastFlu – final report. The report contains full details of the role of each partner in this project, and also provides details on the outcomes of the project including consortium patents and stage of product to commercialisation.

2. Kandun et al. 2008. Factors associated with case fatality of human H5N1 virus infections in Indonesia: a case series. Lancet **372:**744-49. DOI 10.1016/S0140-6736(08)61125-3. This article provides a full analysis of the potential benefits of rapid detection of Influenza during an Influenza epidemic.

3. http://blogs.nature.com/news/thegreatbeyond/2008/08/british_scientist_does_good_1.html An example of the positive press surrounding the Influenza diagnostics project.

4. http://www.bbc.co.uk/iplayer/episode/b00jyyl4/Case_Notes_Swine_Flu/ From 4:26 min onwards. BBC coverage of the PortFastFlu project and its potential benefits to the UK.

5. GlaxoSmithKline investment in development of the Enigma ML device http://www.enigmadiagnostics.com/ufiles/21JUL09%20GSK%20Partnership.pdf. Proof of the major investment of GSK into Enigma Diagnostics during the TSB project.

6. GlaxoSmithKline Investment in commercialisation of the Enigma ML device and PPC tests http://www.enigmadiagnostics.com/ufiles/Enigma%20GSK%20press%20release%20Aug%2010th%202011(final).pdf Proof of further investment by GSK into Enigma Diagnostics to commercialise the Enigma ML device.