

<p><b>Institution: Manchester Metropolitan University</b></p>
<p><b>Unit of Assessment: A3 Allied Health Professions, Dentistry, Nursing and Pharmacy</b></p>
<p><b>Title of case study: Pioneering Research at MMU which transformed microbial identification using MALDI-TOF-MS.</b></p>
<p><b>1. Summary of the impact</b></p> <p>MMU Researchers were the first to develop a novel method of microbial identification using intact bacterial cells and MALDI-TOF-MS (matrix assisted laser desorption ionisation, time of flight mass spectrometry). The research laid the foundations for the development of a new commercial microbial identification system that is now being purchased in diagnostic, pharmaceutical and other applied microbiological laboratories. The system allows real time identification of isolated organisms, reducing the diagnosis time by at least 24hours.</p> <p>The huge patient benefit and clear potential to save many lives comes with economic gains already evidenced by sales of 800 units at circa £100k per unit in 2011 and 2012, delivered globally to microbiology laboratories by one of two companies selling the system. The ultimate potential of the market of laboratories seeking empowerment is estimated at £10bn.</p>
<p><b>2. Underpinning research</b></p> <p>Traditional microbial identification uses a variety of biochemical, immunological, and microscopic methods. It is vital that any identification method is accurate and achieved rapidly, especially where there is a possibility of serious infectious disease. A number of new technologies have emerged including a method known as the polymerase chain reaction (PCR), but this carries a risk of contamination with extraneous DNA. In the early 1980's mass spectrometry was applied to microbial identification and a Nobel Prize winning ionisation technique known as matrix assisted laser desorption ionisation (MALDI) was introduced into analytical chemistry, enabling accurate identification of molecules based on their mass to charge ratio.</p> <p><b>The Research Programme</b></p> <p>MALDI-TOF-MS was applied to the intact bacterial cell in 1994 by a group of biology researchers at Manchester Metropolitan University led by Professor Derek Gordon. The group observed that highly reproducible mass spectra were rapidly produced from a bacterial colony with very little preparation of the intact bacterial cells. The technique produced reproducible mass spectra for the same species and there were distinct spectral differences.</p> <p>The preliminary data was first presented in a poster presentation at the Staphylococcal conference in Aix les Bain in France and the seminal journal article published in Nature Biotechnology in 1996 [1]. MMU patented the concept of generation of spectral libraries and embarked on the production of a standard spectral library.</p> <p>From 1996 Professor Derek Gordon, Dr Martin Claydon, Professor Valerie Edwards-Jones, Dr Simon Davey developed a large number of partnerships at international laboratories. A collaborative agreement was created with the Identification Unit, Health Protection Agency, Colindale, under the direction of Professor Haroun Shah whereby all standard NCTC cultures would be supplied to create a standardised database and an instruments were placed in three locations – MMU, the Health Protection Agency and Waters Corporation (then Micromass Ltd) for research purposes.</p> <p>Identification of organisms in real time illustrated the potential to reduce diagnosis times by 24 to 48 hours.</p> <p>Following the deaths of Professor Gordon and Dr Claydon, the University continued to lead on efforts to exploit the commercial impacts of the technology in an initiative based at the Heath Business and Technology Park involving Dr. Diane Dare (from 2000) and Helen Sutton (from 2001) (see 4 below).</p>

**Impact case study (REF3b)**

Professor Edwards Jones continued her own research and from 2002 she investigated the application of intact cell MALDI-TOF-MS as a typing method and identification of key biomarkers, of the superbug methicillin resistant *Staphylococcus aureus* (MRSA) [2-5].

*Staphylococcus aureus* is a bacterium that is frequently found in the human respiratory tract and on the skin. It is a common cause of skin infection and respiratory disease. MRSA is the most important cause of antibiotic-resistant healthcare-associated infections worldwide. Infections with MRSA may result in prolonged hospital stay and increased mortality rates, and so vital research continues.

**The MMU research team consisted of:**

Professor Val Edwards-Jones (MMU 1995-present)  
Professor Derek Gordon (MMU until 2002 deceased)  
Dr Martin Claydon (MMU until 2002 deceased)  
Dr Diane Dare (MMU from 2000)  
Helen Sutton (MMU from 2001)  
Dr Simon Davey (MMU 1995-1998)

**3. References to the research**

[1] Claydon, M.A., Davey, S.N., Edwards-Jones, V, & Gordon, D.B. (1996). The rapid identification of intact micro-organisms using mass spectrometry. *Nature Biotechnology*; 14; 1584-1586 (cited as the Primary Paper) DOI: 10.1038/nbt1196-1584 (392 citations)

[2] Edwards-Jones, V., Claydon, M.A., Evason, D.J., Walker, J., Fox, A., & Gordon, D.B. (2000) Rapid discrimination between methicillin sensitive and methicillin resistant *Staphylococcus aureus* using Intact Cell Mass Spectrometry *J Med Micro*, 49, 295-300.  
<http://jmm.sgmjournals.org/content/49/3/295.full.pdf> (130 citations)

[3] Walker, J., Fox, AJ, Edwards-Jones, V and Gordon, DB (2002) ICMS used to type MRSA: media effects and inter-laboratory study *J Microbiological Methods* 48, 117-126  
<http://www.ncbi.nlm.nih.gov/pubmed/11777562> (89 citations)

[4] KA Jackson, AJ Fox and V Edwards-Jones (2003). Determination and Structural Examination of Potential Biomarkers for Methicillin-resistant *Staphylococcus aureus*. NATO science series life sciences Vol 352 p: 149-154 edited by Vito Delvecchio and Vladimir Krcmery, 2003 IOS Press, ISBN: 1-58603-343-3

[5] Jackson KA, Edwards-Jones V, Sutton CW, Fox AJ. (2005) Optimisation of intact cell MALDI method for fingerprinting of methicillin-resistant *Staphylococcus aureus*. *J Microbiol Methods*; 62; 273-84. DOI: 10.1016/j.mimet.2005.04.015 (56 citations)

**Indicators of Research Quality**

Oral presentations 2000 – 2004 made to:

International Symposium on the Interface between Analytical Chemistry and Microbiology, Tregastel, France

NATO Advance Research Workshop: Applications of Genomics and Proteomics for Analysis of bacterial Biological Warfare Agents, Bratislava, Slovak Republic.

The Pittsburg Conference, Pittcon, Florida US

50th American Society for Mass Spectrometry and Allied Topics (ASMS) conference Florida, USA

International Symposium on the Interface between Analytical Chemistry and Microbiology, Richmond, USA

Professor Edwards-Jones is Honorary Chair in Microbial Proteomics at Northwick Park Institute of Medical Research.

#### 4. Details of the impact

Following the publication of the primary paper in 1996, the University recognised the huge potential of this technology and invested heavily in a proto-start up business based in The Heath Business and Technical Park in Runcorn employing a Manager (Dr. Dare) and technical support (Helen Sutton). The initial work of this business involved creating a database of spectra of microorganisms. This database was licensed to a number of users worldwide resulting in an income stream to the University. Unfortunately, the intellectual property rights of the technology had not been fully protected and the University has been unable to further exploit its commercial potential. However, MMU's research has underpinned a huge and significant growth in MALDI-TOF-MS technology with myriad applications and potential life-saving developments emerging frequently. This case study is concerned with existing clinical benefits and the economic impact that the research has had on technological solutions since 2008.

##### **Clinical Benefits of MALDI-TOF-MS**

The clinical benefits of MALDI-TOF-MS are considered *revolutionary* as it leads to faster, more accurate diagnosis of microbiological conditions, saving valuable time that can, in turn, lead to the saving of lives. MALDI is also a cost-effective solution as it cuts down on the time and resource needed to take effective decisions. As one Unit Head (Lead Scientist) at Public Health England states [A], *"I have worked with MALDI for many years from the first realisation of its application to medical microbiology by yourself (Edwards-Jones) until the present day. I've seen MALDI become a major technological innovation which has had a major impact in medical and public health microbiology. This is in the rapid and cost effective identification of microorganisms which may allow improved patient management. The true potential of MALDI will impact further in medical and public health microbiology with the application for the rapid identification and confirmation of foodborne pathogens and hygiene indicator organisms and indeed may rewrite some of the accepted dogma around organisms detected in the context of public health microbiology. Furthermore, the contribution of MALDI for the rapid and cost effective identification and confirmation of antibiotic resistance may become a major tool in the armoury to fight emerging antibiotic resistance such as Extended spectrum beta-lactamase producing bacteria and more recently carbapenamase producers. MALDI-TOF MS has been little short of revolutionary in its uptake in medical microbiology and will continue to do so for years to come."*

Another senior manager from within the Bacteriology Department at Sheffield Hospitals Trust [B] explains how *"the introduction of MALDI-TOF-MS has proven to be the most important improvement in clinical bacteriology during my 30 year career"* (even surpassing the introduction of molecular techniques). He explains that its introduction has had a direct impact on patient care and that the *"accuracy and usefulness of the technique has become accepted in clinical microbiology"* replacing other traditional techniques that could take a minimum of 24 hours. The cost benefits to the public purse are also significant. At the Sheffield Hospitals Trust the cost of an identification has come down from £3 to 10p [B]. The most profound impact, according to this senior manager is the dramatic improvement in the management of conditions for bacteraemic patients where the preliminary antibiotic choice is critical. *"MALDI-TOF-MS allows identification of a positive blood culture organism within 20 minutes, which in turn leads to a more scientifically based decision on which antibiotic to prescribe."*

##### **Commercial Impacts**

MMU's pioneering research ultimately led to two industrial organisations launching their own database and identification system: Bruker Daltronics with the software Biotyper, and BioMerieux, who partnered with Shimadzu and Saramis to produce the system VITEK MS.

##### *Bruker*

Developed in 2006, there are approximately 800 MALDI Biotypers installed worldwide at an approximate unit cost of £100K each. Bruker's MALDI Biotyper has been designed to be as robust and easy to perform as possible. No experience with mass spectrometry is required. This industrial application is therefore transforming microbial identification in laboratories across the world bringing significant cost savings to the healthcare industry on a global scale.

*Biomerieux*

Biomerieux produced the VITEK MS system in 2011 and there are approximately 400 devices installed worldwide (source: ProteoMonitor website 2013

<http://www.genomeweb.com/proteomics/biomerieuxs-vitek-ms-wins-fda-clearance-firm-battles-bruker-us-clinical-microbio> [D]). In 2013 Biomerieux's VITEK device was cleared for clinical roll-out across the United States following rigorous testing that concluded that "This technology will revolutionise approaches to traditional microbial identification. Combined with rapid antimicrobial susceptibility testing we can now provide diagnosis and treatment options within a time frame that will reduce morbidity and mortality" (source: <http://www.biomerieux.com/en/biomerieux-announces-us-fda-clearance-vitek-ms-revolutionary-technology-which-reduces-microbial>)

Research in this area has exponentially increased since the first two publications in 1996 and as the system is now selling globally, the potential to move into other sectors, any with a biological threat, is clear. There is current research into identification of reproducible biomarkers directly from specimens and production of algorithms that can mine the large volumes of data produced by this technique. The technique is being used to look at molecules and markers on cancer cells.

Professor Edwards-Jones continues to research into new applications of the technique and is conducting research designed experiments on multi drug resistant organisms such as MRSA.

**5. Sources to corroborate the impact**

**[A]** Testimonial on file from Lead Scientist, Unit Head, Public Health England corroborating the impacts of MALDI-TOF-MS on public and medical microbiology

**[B]** Testimonial on file from Manager, Bacteriology Department, Sheffield Hospitals Trust corroborating the impacts of MALDI-TOF-MS on patient care, cost reductions and clinical applications

**[C]** Link to (April 2013) Press release evidencing sales of Bruker biotyper (excerpt from paragraph 4 "The MALDI Biotyper platform is already in widespread clinical use with over 800 systems installed globally" <http://bit.ly/17SsZwC>)

**[D]** Link to Proteomics Monitor website corroborating continued global commercial impacts of MALDI-TOF-MS technology: <http://www.genomeweb.com/proteomics/biomerieuxs-vitek-ms-wins-fda-clearance-firm-battles-bruker-us-clinical-microbio>