Institution: Imperial College London

Unit of Assessment: 5 Biological Sciences

Title of case study: 1 - Revolutionising 'omics and forensics research: conception and development of Q-TOF mass spectrometry

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

First commercialised in 1996, Quadrupole Orthogonal Acceleration Time of Flight (Q-TOF) Mass Spectrometry (MS) has become the most important of the enabling technologies for structural characterisation in 'omics research including Proteomics, Metabolomics, Glycomics and Lipidomics. Prior to this revolutionary development, mass spectrometric methods lacked the sensitivity and resolution needed for unambiguous structural characterisation at the femtomole (10^{-15}M) level. Today, research is both enabled and accelerated by the use of many thousands of Q-TOF instruments in medical research, cancer research, pharmaceutical, biotechnology, forensics and chemical industry laboratories worldwide. As a consequence of this innovation, which resulted from the research and consultancy advice of Professor Howard Morris, industry has invested in R&D, and highly skilled (mainly British) jobs have been created as well as protected.

2. Underpinning research (indicative maximum 500 words)

(i) **Background**: Prior to the Q-TOF development, identification of proteins at low femtomole levels usually failed. This was despite improved strategies including wide-angle array detection. The latter development, initiated by Professor Howard Morris, first demonstrated (on the Imperial ZAB2SE2FPD and later on ZAB-T instruments) that low femtomole detection with good resolution and mass accuracy was possible for certain samples, but a universal solution to give the high sensitivity/mass accuracy "holy grail" still eluded the mass spectrometric community. Our group had the necessary experience to solve this conundrum, leading us to reject magnetic sector and triple quad solutions, and to consider novel geometries. In 1988, Professor Howard Morris (HRM) was invited to become the Senior Biopolymer MS Consultant to the Directors of the major UK mass spectrometer manufacturer VG/Fisons (which became Micromass and then part of Waters Corporation) at a time when the sheer range of instrument options regarding ion source, mass analyser and detector choices was bewildering. Manufacturers needed to know what they should invest in to meet the real needs of the biomedical market and HRM was asked to concentrate on new instrumentation development advice for biopolymer analysis.

(ii) **Development and Testing Research on the new Q-TOF geometry**: A number of innovations came from this consultancy collaboration between 1988 and 1995, but the most important was that arising from HRM's vision and advice to build a novel tandem geometry liquid chromatography–mass spectrometry (LC-MS)/MS instrument, the quadrupole orthogonal acceleration time of flight (Q-TOF) mass spectrometer. It took some time and effort from '92-'95 to convince the VG/Fisons board of the potential of such a device for what HRM described at the time as "ultra-high sensitivity low energy CAD unambiguous biopolymer sequencing". Much of the international MS community was, at that time, wedded to the perceived advantages of high energy CAD tandem MS/MS geometries, including magnetic sector analysers favoured by some American groups, and initially by the company itself. Nevertheless, with perseverance, the decision to build a prototype Q-TOF was made and, in 1995, after some excellent engineering by the VG/Fisons team, HRM's initial test data fulfilled all of his predictions and expectations with regard to resolution, mass accuracy and sensitivity, demonstrated to be in the femtomole to attomole sample range, together with speed of

acquisition in the LC-MS mode. Between 1995 and 1996, the Imperial team's pioneering research on the prototype Q-TOF, led by Professor Morris and Professor Anne Dell, laid the groundwork for the instrument specifications, and unequivocally demonstrated the huge potential of the new geometry for advanced biomolecular and 'omics research. Initial research demonstrated the sensitivity, resolution and mass accuracy of the prototype machine [1,2] followed shortly afterwards by structure elucidations of molecules with important biological functions [3,4] and leading edge proteomics and glycoproteomics discoveries [5,6].

Key personnel:

- Howard Morris, Emeritus Professor, Department of Life Sciences, Imperial College London, 1975-present
- Anne Dell, Professor, Department of Life Sciences, Imperial College London, 1975-present
- Maria Panico, Laboratory Manager, Department of Life Sciences, Imperial College London, 1980-present

3. References to the research (* References that best indicate quality of underpinning research)

[1] * Morris,H.R., Paxton,T., Dell,A., Langhorne,J., Berg,M., Bordoli,R.S., Hoyes,J. & Bateman,R.H., "*High Sensitivity Collisionally-activated Decomposition Tandem Mass Spectrometry on a Novel Quadrupole/Orthogonal-acceleration Time-of-flight Mass Spectrometer*", Rapid Communications in Mass Spectrometry, 10, 889-896 (1996). DOI, **301 citations (as at 7/10/13)**

[2] Morris,H.R., Paxton,T., Panico,M., McDowell,R. & Dell,A., "*A novel geometry mass* spectrometer, the Q-TOF, for low- femtomole/attomole-range biopolymer sequencing", Journal of Protein Chemistry, 16, 469-479 (1997). DOI, **72 citations (as at 7/10/13)**

[3] * Billker,O., Lindo,V., Panico,M., Etienne,A.E., Paxton,T., Dell,A., Rogers,M., Sinden,R.E. & Morris,H.R., "*Identification of xanthurenic acid as the putative inducer of malaria development in the mosquito*", Nature, 392, 289-292 (1998). DOI, **190 citations (as at 7/10/13)**

[4] Teng-umnuay,P., Morris,H.R., Dell,A., Panico,M., Paxton,T. & West,C.M., "*The cytoplasmic F-box binding protein SKP1 contains a novel pentasaccharide linked to hydroxyproline in Dictyostelium*", Journal of Biological Chemistry, 273, 18242-18249 (1998). DOI, **52 citations (as at 7/10/13)**

[5] van der Wel,H., Morris,H.R., Panico,M., Paxton,T., North,S.J., Dell,A., Thomson,J.M. & West,C.M., "*A non-golgi alpha 1,2-fucosyltransferase that modifies Skp1 in the cytoplasm of Dictyostelium",* Journal of Biological Chemistry, 276, 33952-33963 (2001). DOI, **27 citations (as at 7/10/13)**

[6] * Wacker, M., Linton, D., Hitchen, P.G., Nita-Lazar, M., Haslam, S.M., North S.J., Panico, M., Morris, H.R., Dell, A, Wren, B. and Aebi, M., "*N-Linked Glycosylation in Campylobacter jejuni and Its Functional Transfer into E. coli",* Science, 298, (5599) 1790-3 (2002). DOI, **295 citations (as at 7/10/13)**

Grants:

Funding which helped formulate the vision of a Q-TOF and demonstrated the performance in Q-TOF Research Applications:

[G1] MRC Programme Grant G8003129 (1990-1996): £1,534,879

[G2] Wellcome Trust Instrumentation Grant #030826 (1989-1996) £509,030

[G3] BBSRC AO1244 (1993-1997): £147,492

Note: Key outputs of HRM's research were initially made in the form of confidential commercial advice to VG/Fisons under a Consultancy Agreement which ran for eight years from 1988 to 1995,

and as such these outputs are not on the public record. However, evidence of the importance of those outputs, specifically relating to the Q-TOF development, is provided in a May 2000 letter from the Managing Director of VG/Fisons/Micromass (the manufacturer) [A].

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

The impact of the Q-TOF development has been growing steadily since the late 1990s, and continues to accelerate today.

Our early 1995/6 research on the proto-type factory instrument, where having originally proposed the project we had privileged research access for publication purposes, demonstrated a complete step change in performance characteristics compared with other advanced instruments. Our research sample data demonstrated stunning low femtomole and even attomole (10^{-18} M) sensitivity with good resolving power (5,000) and therefore good mass accuracy. This led, as predicted, to the crucial ability to make unambiguous interpretations of fragmentation data, something which had not been possible previously on other geometries at that level of sensitivity. Together with the later research achievements enabled by the Q-TOF, exemplified in the fields of structure elucidation and glycoproteomics [3-6], this body of research has been the key game-changing evidence which has led researchers to switch to Q-TOF mass spectrometry and given rise to the huge impact of this new geometry instrument.

Since the peptide sequencing problem was the most challenging of its time, it follows that the Q-TOF now makes light work of analytical applications in other fields, including Metabolomics and Forensics. Despite this power, it has taken many years for the instrument to gain wide acclaim. In its first five years of manufacture by Micromass/Waters, instrument numbers were measured in the low hundreds due to the natural conservatism of analytical scientists, together with the long "lead time" before research publications were widely disseminated, and purchase monies approved. Following the original conception of the idea, we have continued to play our part from 1996-2012 in disseminating research outputs in publications and congress presentations showing exciting results from the Q-TOF geometry instruments in our laboratory and elsewhere. The UK manufacturer which in 1995 accepted HRM's strong advice to build the Q-TOF, VG Analytical/Fisons (which became Micromass, and was subsequently acquired by Waters Corporation in 1997), has made an outstanding product, which continues to evolve with faster duty cycles, better resolving power, and other innovations. The new geometry is proving to be remarkably resilient in the face of new technologies including the Thermo Orbitrap. Sales have accelerated during the Impact Period (2008-2012) to the point where, on evidence provided by the VP of Mass Spectrometry Business Operations for Waters, there are now many thousands of Q-TOF geometry instruments worldwide [B]. New manufacturers (Agilent [e.g. C] and Bruker [e.g. D]) have more recently entered the market to copy the success of the Q-TOF geometry demonstrated on the Micromass/Waters instruments. Instrument prices, depending on model (Premier [E] / Xevo G2S [F] / Synapt G2S [G]), accessories and manufacturer, average around £250-300,000 and, although sales are commercially confidential information, Q-TOF has grossed some £1 billion in sales since its inception, most of which have been UK exports. Indeed, Waters won its second Queen's award for Technological Achievement in 2000 for the Q-TOF development.

The beneficiaries of this technology are numerous, as is evident from the statement from the Vice-President of the Waters Corporation [B]:

> *"The Q-Tof family of instruments have become a core platform technology for Waters Corporation and has been an outstanding commercial success all around the globe*

servicing cutting edge analytical research in many applications areas. It now is also importantly used in many routine analytical workflows within the laboratory.

Research, development and manufacturing of the Q-Tof are based in Manchester, UK."

The instrument has helped stabilise and expand skilled jobs in the British mass spectrometry industry (it is manufactured in Manchester [B]), and stimulated the applications of MS to many new areas of scientific research. It is having impacts on health and welfare through its wide use in proteomics and metabolomics, for example in the discovery of disease marker diagnostics. Its impacts on commerce are immense, including the recruitment of new specialists (mass spectroscopists, and biochemists) in thousands of organisations worldwide to carry out research on the instruments, and the consequent industrial investment in new R&D enabled by this technology. In its own small way, the expansion of the contract research company M-SCAN (founded by HRM), which now uses six Q-TOF geometry instruments in its work for the biotechnology industry, attests to the way research is accelerated and made more efficient by better analytical technology. Confirming the use of Q-TOF instruments, M-SCAN states "*the SGS M-Scan laboratories are noted for their early adoption of promising new instruments, for example, the Q-TOF mass spectrometer*" [H]. The Q-TOF's impacts on practitioners and services have been considerable due to the increased quality of data production and unambiguous interpretation, thus helping raise professional standards in testing and discovery research.

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

[A] Letter from Managing Director of VG/Fisons and Micromass (later Waters plc) confirming the importance of HRM's contributions to the Q-TOF concept and subsequent development, 24/5/00 (available from Imperial on request)

[B] Email from VP Mass Spectrometry Business Operations, Waters plc (Jan 2013) (available from Imperial on request)

[C] Agilent Technologies, 6500 Series Accurate-Mass Quadrupole Time-of-Flight (Q-TOF) LC/MS webpage, http://www.chem.agilent.com/en-US/products-services/Instruments-Systems/Mass-Spectrometry/6500-Series-Accurate-Mass-Quadrupole-Time-of-Flight-(Q-TOF)-LC-MS/Pages/default.aspx (archived at https://www.imperial.ac.uk/ref/webarchive/f2f on 1/11/13)

[D] Brucker Q-TOF mass spectrometry products http://www.bruker.com/products/mass-spectrometry-and-separations/lc-ms/o-tof.html (archived at https://www.imperial.ac.uk/ref/webarchive/h2f on 1/11/13)

[E] Waters Micromass® Q-ToF Premier™ mass spectrometer, data sheet (archived here)

[F] Waters Xevo® G2-S QTof mass spectrometer, brochure (archived here)

[G] Waters Synapt® G2-Si mass spectropmeter, brochure (archived here)

[H] M-Scan webpage referring to use of Q-TOF, http://www.m-scan.co.uk/about-us/past-present-future/ (archived at https://www.imperial.ac.uk/ref/webarchive/j2f on 1/11/13)