Institution: Imperial College London

Unit of Assessment: 5 Biological Sciences

Title of case study: 2 - Pioneering Methods for Biopolymer Analysis and their Impact on Biopharmaceutical Characterisation and Regulation in the Drug Industry

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

The protein research of Imperial's Mass Spectrometry group led to the development of Mass Mapping /Fingerprinting for rapid protein characterisation, and new methods for disulphide bridge and glycosylation assignment. Commercialising these discoveries, the company M-SCAN has developed methods to accelerate industrial research and commercialisation of the next generation of recombinant drug therapies, such as monoclonal antibodies targeting cancers. M-SCAN is the pioneer of Biopharmaceutical Characterisation. It has influenced the regulatory advice and, in the past ten years, has assisted many hundreds of companies worldwide in developing their products for market, leading to the growth of a profitable business. In 2010, SGS S.A., a multinational company that provides inspection, verification, testing and certification services, acquired M-SCAN for an undisclosed sum, satisfying SGS's vision to become one of the top players within the Biologics testing arena.

2. Underpinning research (indicative maximum 500 words)

(i) Background: The advent of soft ionisation methods in our *de novo* protein and glycoprotein sequencing research allowed us to produce mass spectra of peptide mixtures from protein digests showing just quasimolecular ions (giving molecular weight information) rather than detailed sequence, and we realised that those simpler data sets, particularly when derived using specific proteolytic methods, provided a powerful new strategy, which we christened "Mass Mapping"/"Peptide Fingerprinting" for identifying and confirming protein structure. The data were quickly and easily produced and assisted the rapid discovery of other key information such as glycosylation. Recognising the potential of these new methods for rapidly characterising proteins and glycoproteins for the fledgling Biotechnology industry, Professor Howard Morris (HRM), gave a series of lectures in Europe and the USA to present these new Mass Spectrometry (MS) methods to the pioneers of the Biotech industry, including Biogen and GD Searle in Europe and Genentech and Amgen in America, all of whom were then limited to gas-phase Edman sequencing methods to characterise their potential drug products. To assist the industrialisation process, HRM formed M-SCAN (Mass Spectrometry Consultants and Analysts) in 1979, which then pioneered the application of MS to the new generation of recombinant proteins and glycoproteins.

(ii) Underpinning Research: Our Group's academic research, and the methods developed from it in the 1993-2012 impact period, supported the translation by M-SCAN of state-of-the-art research procedures into the industrial environment, including the important areas of nano-electrospray, new strategies for O-linked glycosylation analysis and semi-automated software-based interpretation methods [1] - [6]. This research emphasised the development of post-translational modification (PTM) expertise in the fields of glycosylation and lipid biochemistry of relevance to biotechnology, and in automated data-dependent proteomics and glycoproteomics analysis.

Key personnel:

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

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

[1] * 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", J. Biol. Chem., 273, 18242-18249 (1998). DOI, **52 citations (as at 07/10/13)**

[2] Scragg, I.G.; Kwiatkowski, D.; Vidal, V.; Reason, A.; Paxton, T.;Panico, M.; Dell, A. and Morris, H.R., "*Structural characterization of the inflammatory moiety of a variable major lipoprotein of Borrelia recurrentis*", J. Biol. Chem., 275, 937-941 (2000). DOI, **12 citations (as at 07/10/13)**

[3] ***** 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 07/10/13)**

[4] * Moody, A.M.; North, S.J.; Reinhold, B.; Van Dyken, S.J.; Rogers, M.E.; Panico, M.; Dell, A.; Morris, H.R.; Marth, J.D. and Reinherz, E.L., "*Sialic acid capping of CD8 beta core 1-O-glycans controls thymocyte-MHCI interaction*", J. Biol. Chem., 278, 7240-7246 (2003). DOI, **47 citations (as at 07/10/13)**

[5] Morris, H. R., Chalabi, S., Panico, M., Sutton-Smith, M., Clark, G. F., Goldberg, D. and Dell. A., "*Glycoproteomics: past, present and future*", Int. J. Mass Spectrom., 259, 16-31(2007). DOI, **15 citations (as at 07/10/13)**

[6] Rogers DW, Baldini F, Battaglia F, Panico M, Dell A, Morris HR, Catteruccia F., "*Transglutaminase-mediated semen coagulation controls sperm storage in the malaria mosquito*", PLoS Biol. 7(12):e1000272 (2009). DOI, **26 citations (as at 07/10/13)**

Research grants:

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

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

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

[G4] BBSRC B09326 (1998-2001), PI: H Morris, £192,660

[G5] BBSRC B13433 (2001-2004), PI: H Morris, £206,368

[G6] BBSRC, B19088, PI: A Dell, 14/07/03-13/12/08, £668,100, 'Core support for mass spectrometric studies of glycosylation and other key post-translational events'

[G7] BBSRC, BB/F008309/11, PI: A Dell, 01/01/08-31/12/12, £1,393,842, 'Core support for collaborative glycomic and proteomic research'

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

The research described above has been extensively developed for the commercial environment by M-SCAN (formed in 1979) [A], both by designing advanced Protocols (standard operating procedures, SOPs) for good laboratory practice/good manufacturing practice (GLP/GMP) analysis of Pharmaceuticals and by developing instrumentation methods applicable to the specific problems encountered. The work was guided by the academic Consultancy of Imperial Professors Howard Morris (M-SCAN founder) and Anne Dell. The commercial SOPs and methods are confidential to the clients whose products they were designed for.

Between 1990 and 2010, regulatory bodies such as the FDA started to receive new drug applications supported by mass spectrometric structural characterisation data, and today some of the methods pioneered by the Imperial Group and M-SCAN, including Peptide/Glycopeptide Fingerprinting and Disulphide Bridge Analysis, appear in the ICH guideline recommendations [B] for the provision of analytical data to support a well-characterised new Biopharmaceutical product.

Prior to the Imperial Mass Spectrometry group research (e.g. [1-6]), and to the formation of M-SCAN, the only methods available within Biotech or Pharmaceutical manufacturing companies for the characterisation of genetically engineered protein products were the classical procedures of Gel Electrophoresis, IEF, HPLC and Edman sequencing. With the exception of Edman, the methods were relatively crude and non-definitive (Molecular Weight estimates +/-10%), with no chemical identification of charge state differences in IEF, peptide fingerprinting by HPLC retention-time only, with laborious methods involving collection and Edman for peptide identification. As late as 1993, there was still no efficient classical method for estimation of oxidation or de-amidation, and glycosylation or disulphide bridge analysis involved long and technically difficult procedures. The Regulatory Bodies controlling drug licencing of the new Biopharmaceuticals in the 1990s were

cognisant of the Thalidomide experience, but the Joint Committees of the main US, UK, Japanese regulators could only advise on the use of somewhat inadequate classical technologies for Product characterisation.

HRM recognised that the methodologies developed for academic projects at Imperial should also be used by the manufacturing industry to characterise better their new Biopharmaceuticals. M-SCAN was set up as a professional GLP/GMP accredited contract research organisation to drive these industrial applications. All M-SCAN laboratories operate to GLP/GMP and are regularly inspected [C]. Research on the refinement of methods continues to the present day, and M-SCAN assists Biotech and Pharma clients in producing quality characterisation packages for Regulatory inspection.

Getting exciting new drug products such as monoclonal antibodies to market is a process of discovery, pilot production, safety testing, manufacturing scale-up, clinical trials, marketing approval and continuing batch release screening, which overall can cost a billion dollars. Anything which can both improve the effectiveness of proper product characterisation and shorten the time-to-market will reduce these costs and have impact on the viability of present and future healthcare innovations. Many of the new mass spectrometric biopolymer testing methods pioneered for academic purposes at Imperial and translated into industry by M-SCAN have greatly facilitated the rapid characterisation of numerous new drug products for Biotech companies worldwide, and in this way the academic research has had a profound impact on society in general. These MS methods now feature in the International Committee on Harmonisation (ICH) guidelines for Test Procedures and Acceptance Criteria for Biotechnology Products [A].

The time-lag for industrial acceptance of new technologies and strategies is always surprising, and it is only in this century that MS methods of analysis were recognised as the proper way to do certain characterisations. The first mention of Mass Spectrometry in an FDA document “Points to Consider” was in 1997, in reference to monoclonal antibody analysis [D]. Accordingly, the impact of the M-SCAN research and development programme did not reach fruition until the 2000-2010 decade, generating a turnover of some $13 million p.a. Assistance with this impact has been achieved with M-SCAN educational courses for the Biotech and Pharma industry, in which Professors Morris and Dell have played prominent roles alongside M-SCAN experts [E].

By establishing mass spectrometry laboratories in the UK, USA, Switzerland and Germany, M-SCAN has served and assisted hundreds of beneficiaries (pharmaceutical, biotechnology and chemical clients) per annum across the world from small innovative biotech companies to the industry giants [A]. M-SCAN was the first company in the world to carry out structural characterisation of recombinant proteins by Mass Spectrometry and also the first to offer a commercial service for analysis of genetically engineered proteins and glycoproteins. Thousands of samples have been analysed for hundreds of clients annually during the past decade, in confidential work which has helped in drug filings, batch release testing and discovery research [F]. The consequent impact on health and welfare in the past decade is enormous. The number of clients with different drug molecules means that its breadth of impact, potentially affecting public health and disease prevention, is greater even than an individual large Pharma, with its restricted product offerings. Impacts on the economy and on commerce are considerable since M-SCAN is assisting companies in producing and gaining approval for new drugs in a much more timely, cost-effective and efficient manner. From 1993 to 2013, M-SCAN itself created new jobs for advanced scientists, moving from 12 full-time staff in 1990 operating in two countries to over 65 specialist staff in 2010 (approximately half of them PhDs) operating in four countries worldwide. In 2009, M-SCAN generated revenue in excess of £6.9M [G]. By 2010, M-SCAN was recognised as the top brand for Biopharmaceutical Characterisation amongst worldwide Contract Research Organisations (CROs) as attested to by approaches for merger or acquisition from several of the world’s major CROs during the period 2007-2010.

In 2010, M-SCAN was approached with an offer of merger by the world’s biggest scientific testing organisation (SGS) and the Directors decided that M-SCAN could expand even faster within that organisation. The deal price for the merger between M-SCAN and SGS was confidential.

Commenting on the merger, the CEO of SGS stated: "*This acquisition clearly complements our vision to become one of the top players within the Biologics testing arena (large molecules)…M-Scan's global recognition, and expertise together with its geographic footprint combined with the existing advanced analytical services in SGS Life Science provides an excellent platform for further growth and development.*" [G].

The resulting SGS M-SCAN companies are continuing to expand rapidly, employing even more skilled staff. Impacts on practitioners and services are readily apparent in M-SCAN, which has pioneered the business model where none existed before, and where many of its protocols have influenced accepted practice worldwide, including at the international regulatory level.

The potential future impact of SGS M-SCAN is also great, given the rapidly expanding Biotech/Pharmaceutical industrial sector, which is matched only by IT/Electronics in growth statistics.

The CEO of SGS is able to confirm the acquisition of the M-SCAN, "*the global brand leader in biopharmaceutical analysis*" [F], in 2010 and corroborate the impact from the company:

> "*M-Scan, when it joined the SGS Group, was already present in four countries with a staff complement of 65 globally recognised specialists. Their client base was well diversified in both biopharma and biotech which provided significant leverage for the provision of additional SGS services.*
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> *M-Scan brought, through its management and staff, a step-change in the level of analytical specialization we were able to offer. It provided SGS with an entry into biopharmaceutical testing which would have taken many years to build organically and it provided the world leading analytical specialization needed to be market leader in a new and growing industry.*
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> *M-Scan has been an excellent acquisition for us. It has put our Life Science business at the forefront of biopharma testing technology with a strongly commercial focus. It has provided both world leaders in technology and excellent leadership which we will develop throughout our Group of 76000 staff. We have already expanded the business geographically in India and China and fully expect this to continue as our vision to be the clear leader in biopharmaceutical testing is realised.*
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> *Without a doubt the M-Scan acquisition has had a significant impact on our Life Science business and we fully expect that to continue as we expand the geographical footprint and further enhance the technology offering."*

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

[A] SGS M-SCAN, 'Past – present - future' webpage, http://www.m-scan.com/about-us/past-present-future/ (archived at https://www.imperial.ac.uk/ref/webarchive/n2f on 3/11/13)
[B] European Medicines Agency ICH Topic Q6B, 'Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products' (archived here)
[C] 'Quality Assurance at SGS M-Scan', GLP / cGMP compliant and FDA inspected, http://www.m-scan.co.uk/quality/quality-assurance/ (archived here on 4/11/13)
[D] 'Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use', U. S. Department of Health and Human Services FDA Center for Biologics Evaluation and Research, 28/2/97 (archived here)
[E] SGS M-SCAN, 'Training Events and Courses' webpage, http://www.m-scan.com/training/training-events-and-courses/ (archived here on 4/11/13)
[F] Letter from Chief Executive Officer, SGS S.A., 8/1/13 (letter available from Imperial on request)
[G] SGS News, 'SGS is Pleased to Announce the Acquisition of the M-Scan Group', 1/11/10, http://www.sgs.com/en/Our-Company/News-and-Media-Center/News-and-Press-Releases/2010/11/SGS-is-Pleased-to-Announce-the-Acquisition-of-the-MScan-Group.aspx (archived at https://www.imperial.ac.uk/ref/webarchive/q2f on 4/11/13)