Equipment Audit and Preliminary Strategy Review of Mass Spectrometry in Biomedical Sciences

Medical Sciences Division

(Updated version May 2013)

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1. Executive Summary

Research progress in modern Biology and Medicine is always intertwined with technical advancements in analytical methodologies. In parallel to efforts unraveling the genome sequences of human individuals and other organisms, recent mass spectrometry (MS) based technological advancement has also allowed comprehensive assessments of proteomes and metabolomes and their dynamic changes in the context of biological and medical problems, leading to key advances in understanding molecular mechanisms in disease and novel entry points for therapeutic approaches.

It is imperative for cutting edge biomedical research to keep up-to-date with the latest developments in mass spectrometry equipment and also to build up and retain expertise at the University wide level in the years to come.

In this report, an overview of mass spectrometry equipment and expertise within the biology and biomedical sciences sector is provided. Based on this, future trends and needs within this area are formulated, most prevalently centered on more rapid and sensitive measurements of peptides, proteins, metabolites, drugs nucleic acids and other molecules in biological and clinical samples. Not only there is a requirement for attracting expertise, but also for keeping existing equipment and infrastructure up-to-date by a regular upgrade of LC&MS instrumentation, but it is also important to expand capacities in the areas of analytical chemistry, proteomics, metabolomics, lipidomics and the detection of nucleic acids in order to remain at the forefront in basic biology research and biomedicine.

The specific recommendations are:

1. To remain up-to-date with MS expertise & equipment for proteomics to survey and quantitate the dynamics of whole proteomes and posttranslational modifications
2. To further develop substantial bioinformatics support for the analysis of MS data, and also to integrate with genomic (other –omic) and clinical (patient health care) information
3. To expand capabilities (key personnel / MS instrumentation) for the analysis of biomolecules such as drugs, metabolites, lipids, nucleic acids, and promote exchange of different expertise and capacities between existing specialized laboratories through the establishment of a coordinator / central laboratory
4. To explore novel MS instrumentation / approaches for Imaging and tracking biomolecules in cells / animal models and humans
2. Mass Spectrometry Equipment and Infrastructure Audit

As part of the prospective strategic planning process that the academic community with an interest in biomedical mass spectrometry wishes to engage in, the Research Committee is invited to provide comments and guidance on where further developments could be initiated to increase the overall impact of the Oxford programmes in biological and biomedical mass spectrometry.

To provide an overview, current research groups, key personnel and facilities with their equipment are listed that are part of the Medical Science Division, Chemistry Research Laboratories, Department of Physiology, Anatomy & Genetics, Biochemistry and Plant Sciences. This inventory does not include mass spectrometry equipment available in the Earth Sciences Department as this is highly specialized and not necessarily accessible to measurements compatible with biomedical research (at least not directly). The information listed in Table 1 is based in part on the new web-based list of available equipment at the University of Oxford (www.research-facilities.ox.ac.uk). For an extensive list of personnel with specific expertise in mass spectrometry and affiliations, see Table 2. The different mass spectrometry based capabilities will be discussed in a subject-specific manner in more detail below with an emphasis on the key personnel with this expertise.

Table 1: List of researchers & laboratories with expertise in biological / biomedical mass spectrometry and instrumentation in Oxford

<table>
<thead>
<tr>
<th>PI / Location</th>
<th>Specialty / Expertise</th>
<th>Equipment</th>
</tr>
</thead>
<tbody>
<tr>
<td>David Staunton, Biophysics facility, Biochemistry</td>
<td>Intact molecular mass</td>
<td>ESI-TOF-MS</td>
</tr>
<tr>
<td>Carol Robinson group Justin Benesch group Shabaz Mohammed / CRL</td>
<td>Intact protein/complexes Proteomics / PTMs</td>
<td>Synapt G2 QTOF, Orbitrap-XL MS, Thermo Q Exactive, Orbitrap Elite</td>
</tr>
<tr>
<td>James McCullagh / CRL</td>
<td>Small molecules / protein-ligands Proteomics / Metabolomics</td>
<td>16 MS instruments including: QTOFmicro, Synapt, FT-ICR, LCT TOF MS, LC-Isotope Ratio MS Orbitrap XL, GC-TOF-MS</td>
</tr>
<tr>
<td>Central Proteomics Facilities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oreste Acuto, Ben Thomas / Dunn School</td>
<td>proteomics, PTM studies, quantitation</td>
<td>Orbitrap XL, MALDI-TOF/TOF 2 x Q Exactives UHPLC-MS/MS</td>
</tr>
<tr>
<td>Benedikt Kessler group / NDM</td>
<td>proteomics, PTM studies, MRM quantitation, target discovery metabolite analysis</td>
<td>UPLC-Orbitrap Velos ETD, 2 QTOFs, iontrap, triple quadrupole, MALDI-TOF/TOF Q Exactive, TripleTOF, GCxGC-MS</td>
</tr>
<tr>
<td>Paul Brennan / TDI</td>
<td>Small molecule synthesis</td>
<td>LC single quad MS</td>
</tr>
<tr>
<td>Eric O’Neil / Gray Institute</td>
<td>protein and PTM analysis</td>
<td>Ion Trap (Bruker, HCT Ultra II)</td>
</tr>
<tr>
<td>Holger Kramer / DPAG</td>
<td>Proteomics</td>
<td>MALDI-TOF/TOF, iontrap Bruker amaZon X</td>
</tr>
<tr>
<td>Pharmacology</td>
<td>Pharmacology</td>
<td>2x Quadrupole LC-MS/MS (QTrap 5500, AbSciex)</td>
</tr>
<tr>
<td>Barbara Fielding Leanne Hodson / OCDEM</td>
<td>Lipid analysis</td>
<td>GC-C-IRMS, GC-MS</td>
</tr>
<tr>
<td>Georgina Berridge, Rod Chalk SGC / TDI</td>
<td>Intact protein analysis Small molecule – protein</td>
<td>LC-TOF-MS, Iontrap Rapid-Fire – TOF MS (flow injection.)</td>
</tr>
<tr>
<td>Plant Sciences</td>
<td>Analysis of metabolites</td>
<td>Agilent GC-MS</td>
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</tr>
<tr>
<td>Inorganic Chemistry Lab</td>
<td>Inorganic chemistry</td>
<td>Shimadzu GC-MS</td>
</tr>
<tr>
<td>Joanna Nettleship OPPF / Strubi (Harwell)</td>
<td>Intact protein analysis</td>
<td>Waters QTOF micro LC-MS</td>
</tr>
<tr>
<td>Glycobiology David Harvey / Nicole Zitzmann</td>
<td>Glycomics, proteomics</td>
<td>QTOF2 (Waters), MALDI-TOF</td>
</tr>
<tr>
<td>Udo Oppermann Botnar/Kennedy Institute</td>
<td>Single cell tracking of molecules</td>
<td>CyTOF (DVS Sciences)</td>
</tr>
<tr>
<td>WTCHG / Ioannis Ragoussis Stephen Chapman, David Buck</td>
<td>SNP QTL analysis</td>
<td>MALDI-TOF (Autoflex, Bruker)</td>
</tr>
</tbody>
</table>

(Please note: This table does not include MS laboratories and expertise in Earth Sciences as well as outside expertise affiliated with Oxford Departments, e.g. Nick White/Nick Day, NDM Thailand and others. Also, David Fell’s group located at Oxford Brookes University is a world expert in metabolomics/genomics bioinformatics).

### 2.1 Proteomics

The Biomedical Sciences Division and other Departments involved in biomedical research possess >40 mass spectrometers, from which >15 are dedicated to proteomics (analysis of proteins and peptides) related service and research. The groups of Prof. Carol V. Robinson (CRL), Dr. Mohammed Shabaz, Prof. Oreste Acuto (Benjamin Thomas, Central Proteomics Facility Dunn School) and Dr. Benedikt Kessler (Central Proteomics Facility, WTCHG/NDM/TDI) represent the laboratories with the most expertise, but also the CRL (Dr. James McCullagh), DPAG (Dr. Holger Kramer), The Gray Institute (Dr. Eric O’Neill), the SGC (Georgina Berridge & Rod Chalk) and the OPPF (Dr. Joanne Nettleship) have setups for this type of analysis. A laboratory with particular expertise in the analysis of protein glycosylation is located at the Glycobiology Institute and is led by Dr. Terry Butters (previously Dr. David Harvey / Prof. Nicole Zitzmann).

Most mass spectrometers, often coupled to a liquid chromatography (HPLC, UHPLC, UPLC) system, have service contracts in place (costing £10-£30k/year per device), and with regular maintenance have lifetimes that can be up to 10 years. The equipment that the division possesses ranges in age from >10 years to less than 6 months. The most significant providers of equipment are Thermo Fisher, Waters, Bruker, Agilent ABI-Sciex and Shimadzu. Much of the complexity is in sample preparation and use of the analytical equipment. This requires specialist knowledge that invariably requires dedicated support staff for an efficient usage of such complex instrumentation, also to minimize down-time. The Dunn School, CRL and DPAG have adopted this approach. In the other facilities such as the CPF (WTCHG), the PI provides the principal technical as well as scientific direction.

### 2.2 Mass spectrometry and intact protein analysis

A particular aspect in proteomics research is the analysis of intact proteins and protein complexes. This has been developed to a point that now the dynamics of native protein complexes can be characterised in gas phase, and Oxford has world-leading scientists in this area (Carol Robinson and Justin Benesch, CRL). Besides this, the intact mass of proteins allowing detection of posttranslational modifications etc. is routinely measured in the OPPF (Joanne Nettleship), SGC (Georgina Berridge, Rod Chalk), CRL (James McCullagh) and also the Central Proteomics facilities (Dunn School and NDM/TDI). More recently available MS technologies such as T3 sequencing, IMS and ETD provides scope of development of this research area in the future (see also Section 3).
2.3 Mass spectrometry and small molecule analysis

Nowadays, MS technology is used for the detection not only for peptides and proteins, but for virtually any type of biomolecules. Within the Departments and Institutes at the University of Oxford Campus that are focused on biomedical research, there are a number of laboratories specialized in specific analytical methodologies that allow the monitoring of distinct compound classes and biomolecules. For instance, the Chemistry Research Laboratories Mass Spectrometry Facility led by Dr. James McCullagh mainly performs intact molecular weight analysis for chemistry, but has also started to perform proteomics, amino acid, drug and metabolite analysis (Table 1). The Biophysics Facility in Biochemistry has the capability to perform molecular weight determination, and the SGC and OPPF both have MS capabilities to determine molecular weights of proteins (Table 1). In addition, the OCDEM has available MS instrumentation for lipid analysis, led by Dr. Barbara Fielding. Also, the Department of Pharmacology and Institute of Plant Sciences have capabilities to perform analysis of metabolites by GC-MS (Table 1). Finally, expertise to analysis single nucleic acid polymorphisms (SNPs) is available at the WTCHG in the Genomics Facility (Table 1).

A current problem is that there is little synergy and exchange between these different labs in terms of exchanging expertise and methods. One aspect to note here is that is also challenging as the detection of a wide range of biomolecules with different physicochemical properties requires substantial individual method development with little overlapping capabilities. Therefore, the expertise and scientific interest of key personnel within these different laboratories has often little overlap. Nevertheless, there is the lack of a centralized laboratory, center of other form of coordination where such information is available as a whole and can be accessed by a wider range of the biomedical research community to promote collaborations.

2.4 Translational mass spectrometry

The discovery of key molecular targets or molecular signatures (biomarkers) that are characteristic of disease pathology & progression has attracted a lot of attention in recent years. Mass spectrometry based approaches have contributed and will also play a more dominant future role in the identification of such molecular signatures, especially as the MS technology is advancing in terms of sensitivity of measurement and throughput capabilities (see also Section 3). Profiling changes in protein levels by MS in biological fluids such as serum/plasma, urine, sputum, saliva, CSF, PBMCs and tissue material as an experimental approach is performed in Dr. Kessler’s laboratory (CPF, Headington). The analysis of lipids in the context of endocrine metabolic diseases is the subject of Dr. Barbara Fielding’s laboratory at the OCDEM (Tables 1 & 2). Many other laboratories on Campus such as DPAG, CRL, Pharmacology and Plant Sciences have experience to measure distinct sets of drugs and metabolites (Table 2) and are therefore involved in translational projects to a limited extent.

As described for section 2.3, there is little synergy and exchange between these different labs in terms of exchanging expertise and methods. As a step towards this direction, the CRL (Prof. Schofield and Dr. McCullagh) together with the WTCHG (Dr. Kessler) and a consortium of >10 predominantly clinical researchers on campus have teamed up to explore possibilities in establishing an MS platform (MS and NMR capabilities) for measuring metabolic profiles, in particular in patient samples. Such a platform will meet the existing demands in this area mainly coming from clinical scientists on Campus (see also section 3).

2.5 Bioinformatics analysis and integration of complex biological & clinical data

A wide spectrum of expertise in mass spectrometry in different research areas is already available within the University, including a large park of high-spec mass spectrometers. One of the major bottlenecks has been the management and interpretation of complex MS data sets generated by
these groups. It would therefore be highly desirable to invest in additional expertise with a focus on bioinformatics able to cover the following subjects in a complementary fashion:

- Intact protein/complex/protein-ligand analysis
- Shotgun proteomics (large scale – in depth)
- PTM identification and characterization
- Quantitative MS approaches (isotope labeling, label-free, isotope ratio)
- Targeted proteomics (MRM/SRM)
- Network analysis and systems biology (integration with other –Oomics technologies)
- Metabolomics / lipidomics
- “Translational proteomics”, biomarker discovery, statistical analysis
- Integration with patient / clinical information / statistics

Existing efforts between the Dunn School (Prof. Oreste Acuto / D. Ben Thomas) and NDM/WTCHG (Prof. Peter Ratcliffe / Dr. Kessler) in collaboration with the Computational Biology Research Group (CBRG) have already provided a competent bioinformatics platform for life science oriented mass spectrometry (e.g. dedicated Bioinformatician Dr. Phil Charles). Integration of other –omic with proteomic data sets has also gained significant interest, and Dr. Kessler’s group is currently collaboration with Agilent Technologies and Prof. Richard Mott (WTCHG) on ways to apply bioinformatics in this fashion.

The statistical analysis clinical patient data is an area covered by Prof. Doug Altman’s group (Centre for Statistics in Medicine, CSM), an expertise that would be very complementary. However, efforts to integrate MS data sets from clinical studies with statisticians from the CSM are only at their infancy and deserve additional support.

Although this effort continues through support from the institutions, facilities and grant applications (e.g. Agilent eMerging Insights in Systems Biology), it will be of vital importance to provide more rigorous long-term support at a higher level in order to maximize and expand values that can be generated from the already existing research groups and infrastructure (maybe through the TDI/BIG?).

Table 2: Personnel with specific expertise in mass spectrometry and affiliations within biomedical research in Oxford

<table>
<thead>
<tr>
<th>Name</th>
<th>Location</th>
<th>Expertise</th>
</tr>
</thead>
<tbody>
<tr>
<td>David Staunton</td>
<td>Biophysics facility Biochemistry</td>
<td>Intact protein / molecule MW</td>
</tr>
<tr>
<td>Oreste Acuto (group)</td>
<td>Dunn School</td>
<td>Immune signaling assessed by mass spectrometry</td>
</tr>
<tr>
<td>Benjamin Thomas</td>
<td>Central Proteomics Facility Dunn School</td>
<td>Proteomics, PTM analysis, quantitation</td>
</tr>
<tr>
<td>Svenja Hester</td>
<td>Dunn School</td>
<td></td>
</tr>
<tr>
<td>Phil Charles</td>
<td>WTCHG, WIMM, Dunn School</td>
<td>Bioinformatics</td>
</tr>
<tr>
<td>Benedikt Kessler (group)</td>
<td>WTHG / CCMP / TDI</td>
<td>Ubiquitin Protease Biology</td>
</tr>
<tr>
<td>Roman Fischer</td>
<td></td>
<td>Proteomics, PTM analysis, quantitation, metabolomics</td>
</tr>
<tr>
<td>Nicola Ternette</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joanna McGouran</td>
<td></td>
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<tr>
<td>Rebecca Konietzny</td>
<td></td>
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</tr>
<tr>
<td>Climent Casals (Systems biology)</td>
<td>WTHG / CCMP / TDI</td>
<td>Translational mass spectrometry, Systems Biology</td>
</tr>
<tr>
<td>Hong-Lei Huang</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marie-Letitia Thezen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carol Robinson (group)</td>
<td>CRL</td>
<td>Intact protein mass spectrometry</td>
</tr>
</tbody>
</table>
Mohammed Shabaz | CRL/Biochemistry | Proteomics, PTM analysis
----|----|----
Justin Benesch (group) | CRL | Intact protein mass spectrometry
James McCullagh | CRL Mass Spectrometry Facility | MW determination, proteomics
Shweta Chavan | | |
Lingzhi Gong | | |
Colin Sparrow | | |
David Harvey / Nicole Zitzmann / Terry Butters | Glycobiology Institute | Glycomics
Holger Kramer | DPAG | Proteomics
Eric O’Neill | Oncology | Proteomics, PTM analysis
Georgina Berridge / Rod Chalk | SGC | Intact protein analysis
Barbara Fielding | OCDEM | Lipid analysis
Leanne Hodson | | |
Joanne Nettleship | OPPF (Harwell) | Intact protein analysis
David Buck | WTCHG | SNPs analysis, QTL

3. **Strategic Recommendations**

A continuous investment in mass spectrometry-based technology will be a fundamental contribution to the advancement of biomedical sciences. Based on a detailed inventory of the current available technology on campus and future trends in biomedical research, there are five key areas that are recommended for future investments that should be considered at the University level:

### 3.1 Future developments in protein mass spectrometry

The analysis of proteins and peptides will continue to represent a center stage in basic and applied biomedical sciences. This includes the discovery and identification of proteins / protein complexes by peptide-based sequencing (shotgun proteomics) as well as mapping posttranslational modifications. Future demands will require increased throughput and a push towards whole proteome analysis towards the single cell level.

In addition, mass spectrometry based measurements of protein & peptide and levels of posttranslational modifications remain crucial and require more sensitive and accurate instrumentation to perform relative and absolute quantitative studies. It is anticipated that this trend will continue until direct MS measurements of single molecules will be possible. Cutting edge instrumentation specific for this discipline will be within the £300K - £1000K range.

Although shotgun (bottom-up) proteomics is currently still the most powerful approach for protein analysis, alternative methodologies such as “middle-down” and “top-down” approaches are emerging and worth investing in to characterize intact proteins, protein-protein and protein-small molecule complexes. The latter will become increasingly important for drug target discovery. This is of particular note as there is a concentration of strong research groups focused on this area in Oxford, in particular Prof. Carol Robinson’s group who is a recognized world-leading expert in the analysis of protein complexes by native mass spectrometry.

Another area of intense development is the measurement (quantitation) of defined analytes (peptides, metabolites, drugs, nucleic acids, lipids) by targeted proteomics. Increased multiplexing and analytical throughput will allow the measurement and quantitation of hundreds or thousands of biomolecules at the same time, offering the possibility to profile “molecular signatures” associated with molecular processes, disease pathologies or therapeutic treatments. Instrumentation capable of performing these tasks will be within the range of £200K - £500K.
All of these areas will require the support of existing research groups, the attraction or long-term support of key staff members with this expertise, and a periodic renewal of liquid chromatography (LC) and matrix assisted laser desorption ionisation (MALDI) or electrospray ionisation (ESI) tandem mass spectrometry (MS/MS) based instrumentation. Additional information is also provided in section 3.5.

3.2 Global and targeted profiling of drugs, metabolites and nucleic acids
The has been a dramatic increase in the demand of detecting and measuring drugs, metabolites, lipids and nucleic acids in the context of biomedical research in the past few years. Metabolic profiling offers an immediate snapshot of the cell’s physiology that is possible only to a limited extent with the existing infrastructure including proteomics and genomics. Clearly, current MS capacities within the Oxford campus are underdeveloped and do not meet the requirements in this area. The central point here will be to recruit a faculty-level researcher who has a strong track record in the area of Clinical Pharmacology or Metabolomics who can then drive the development of an appropriate MS infrastructure. This includes the integration of liquid chromatography (LC-) gas chromatography (GC-) and capillary electrophoresis (CE-) MS systems. The future of metabolomics rests with its ability to monitor subtle changes in the metabolome that occur prior to the detection of a gross phenotypic change reflecting disease. As an initial step towards this goal, the CRL (Dr. James McCullagh / Prof. Christopher Schofield together with Dr. Benedikt Kessler (WTCHG) and a consortium of <10 researchers with an interest in this area have initiated the establishment of a core laboratory with this expertise. This is currently supported by a Wellcome Trust Instrumentation grant (NMR + orbitrap MS instrumentation), but will need additional support for long-term sustainability.

3.3 Integrative biology by combining multi-Omics information with patient data
An increase in the availability of genomics, proteomics, metabolomics and other 'omics' data has driven the demand for the development of ways to combine this information as well as integrate it with clinical data. This could provide more sensitive ways to detect changes in complex molecular signatures related to disease. To this end, future efforts will require investment on the bioinformatics side (predominantly attracting key personnel with expertise) as discussed in section 2.4 that will allow a comprehensive assessment of very complex data sets.

3.4 MS-based molecular tracking & imaging techniques
Imaging mass spectrometry involves the visualization of the spatial distribution of proteins, peptides, drug candidate compounds and their metabolites, biomarkers or other chemicals within thin slices of samples such as human or animal tissues. It is a promising tool for putative biomarker characterisation and drug development. Initially, scientists take tissue slices mounted on microscope slides and apply a suitable MALDI matrix to the tissue, either manually or now automatically. Next, the microscope slide is inserted into a MALDI mass spectrometer. The mass spectrometer records the spatial distribution of molecular species such as peptides, proteins or small molecules. Suitable image processing software can be used to import data from the mass spectrometer to allow visualisation and comparison with the optical image of the sample. Recent work has also demonstrated the capacity to create three-dimensional molecular images using the MALDI imaging technology and co-registration of these image volumes to other imaging modalities such as magnetic resonance imaging.

In addition, the recently developed CyTOF<sup>®</sup> technology offers the specificity, dynamic range and quantitative capability of atomic mass spectrometry in a format that is familiar to flow cytometry practitioners. Mass cytometry offers a unique opportunity to simultaneously analyze more subtle quantitative changes in intracellular and membrane bound proteins within complex cell populations. It is anticipated that the demand of such techniques will increase dramatically in the future, and currently available expertise within the Oxford campus is very limited.
3.5 *Sustainability of MS laboratories*

In order to sustain laboratories with MS equipment that require significant costs for the establishment and also for being kept operational, there is a need to develop a charging template for equipment access and usage. Different groups have widely differing interpretations of what should and should not be included in a **model for charging their grants and other groups** for use of their equipment (FEC model for MS analysis fees). It might be helpful to develop a University wide guidance charging template that can be used by all MS, but also imaging, genomic or other groups that are responsible for shared equipment used for service & support of external research projects. The challenge will be to create a structure that would be acceptable by the research councils and charities, if challenged. For example, it is not clear whether a FEC charging model should include proportional space charges and/or depreciation of capital. A more widely adopted charging template would also assist shared use of equipment, which at present is patchy and in some cases can be driven principally by the (often arbitrary) fee seen by the end user.

Also, research facilities are now becoming integrated into research laboratories to promote and apply new developments more directly, thereby leading to increased productivity. In such an environment, parts will be covered by research grants (soft money), and often key personnel with high qualifications can do both, provide excellent support but also at the same time conduct their own research. In the current funding streams, it is often challenging to retain people with such capabilities for long-term, which often would be useful to avoid loss of gained essential expertise.

Respectfully submitted by Dr. Benedikt M. Kessler

May 2013

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