

Funded PhD studentships in Structural Mass Spectrometry



Working in the laboratories of...



Prof Frank Sobott



Dr Anton Calabrese

For more information, scan the QR code, or search for us on FindAPhD for details of projects.

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UNIVERSITY OF LEEDS

The Astbury Centre at the University of Leeds brings together researchers from across the University - largely from the biological sciences, chemistry and physics - to allow interdisciplinary approaches to be harnessed to understand the molecular basis of life. The Centre has outstanding expertise and research infrastructure in chemical biology, biophysics and all of the major techniques in structural molecular biology. Together, these approaches are combined with analyses of biological function with the ultimate aim of understanding the molecular basis of biological mechanisms in living cells.

Recent investment of more than £17 million in state-of-the-art laboratories for structural biology has put Leeds at the forefront of this research, with electron microscopy, NMR spectroscopy as well as mass spectrometry equipment matching the best in the world.

1) Insights into the assembly of viral factories from structural mass spectrometry

Viral replication factories in cells (sites of viral replication/assembly) are formed by viral non-structural proteins (NSPs) in a number of important human and animal pathogens, including Reoviruses and Rotaviruses (the major cause of >200,000 child deaths per annum). However, the molecular mechanism of viral factory assembly, and their precise role in virus replication remain unexplained. In this project, mass spectrometry (MS) based methods will be developed to understand the structure, dynamics and interactions of the non-structural proteins that mediate viral factory assembly, using non-structural proteins from Rotavirus as a model system. A suite of MS-based tools, including native ion mobility-mass spectrometry, chemical crosslinking, hydrogen-deuterium exchange and fast photochemical oxidation of proteins, will be used to interrogate the structure, conformational dynamics and interactions of the proteins that are essential for viral factory assembly. The ultimate aim of this work is to determine if targeting viral factory formation is a viable, novel strategy to combat viral infections.

You will work under the supervision of Dr Anton Calabrese (co-supervised by Prof Frank Sobott) in Leeds' world class Biomolecular MS laboratory which houses 7 instruments dedicated to structural mass spectrometry. This is a collaborative project with Dr Alex Borodavka's laboratory at the University of Cambridge. You will receive training in structural mass spectrometry methodologies, molecular biology techniques and other biophysical approaches to characterise protein-protein and protein-small molecule interactions, and push the limits of current structural MS capabilities.

You are highly motivated, can work independently and have good communication skills. You have a degree in Biochemistry, Chemistry or a related subject. Both UK and EU-based students can apply.

2) Structural Ribosomics: towards a proteomics toolbox for comprehensive characterization of the composition and dynamic structure of specialized ribosomes

Ribosomes are known to be key cellular machines which translate RNA into protein sequences. While the exact composition of these 2.5 MDa particles is known to vary somewhat between different organisms, allowing the design of antibiotics which specifically interfere with bacterial ribosomes, it has recently also become apparent that heterogeneity in ribosome composition results from differential expression and post-translational modifications (PTM) of ribosomal proteins, altering their function. During viral infection the ribosome composition and structure may be somewhat altered to bias their translational specificity. Ribosomal RNA diversity and the activity of associated factors may generate 'specialized ribosomes' that have a substantial impact on how the genomic template is translated into functional proteins.

Mass spectrometry methods are central to analyzing this diversity, starting with post-transcriptional (RNA) and post-translational modifications (proteins). Proteomics is routinely used to map PTM sites, but we aim to paint a much more complete picture of the presence and abundance of all these modifications, including on RNA, and their role for subunit interactions, the overall architecture and stability of the particle as well as subtle conformational changes linked with functional states. This project will provide a unique opportunity to push the boundaries of current MS technology, and contribute significantly to our understanding of the diverse functional roles of specialized ribosomes.

You will work under the supervision of Prof Frank Sobott and Dr Anton Calabrese in collaboration with Prof Ade Whitehouse (Leeds, ribosome biology) in Leeds' world class Biomolecular MS laboratory which houses 7 instruments dedicated to structural MS. You will receive training in structural mass spectrometry methodologies, molecular biology techniques and other biophysical approaches to characterise protein-protein and protein-RNA interactions, and push the limits of current structural mass spectrometry capabilities.

You are highly motivated, can work independently and have good communication skills. You have a degree in Biochemistry, Chemistry or a related subject. Both UK and EU-based students can apply.

3) Conformation-sensitive mass spectrometry: developing HDX and FPOP-MS approaches with high temporal and spatial resolution together with computational modelling

High-resolution structural methods such as x-ray crystallography, NMR and now increasingly also EM are making important contributions to our understanding of biomolecular structure and function. Determining how proteins interact with other molecules is key in understanding most biological process, for the development of novel therapeutics and for biotechnology. Yet many protein structures are highly dynamic and heterogeneous, making it difficult to capture their complete conformational behaviour and assembly pathways using such high-resolution structural snapshots. Structural proteomics methods which take advantage of recent, cutting-edge mass spectrometry approaches are now coming into their own, as they can map out the conformational space of structurally dynamic, even disordered and natively unfolded proteins, as well as characterizing heterogeneous assembly pathways, e.g. in amyloid aggregation. While most “traditional” techniques will highlight either the most dominant (stable) form, or an average of all states, structural MS is uniquely powerful in that it can characterize whole ensembles in an unbiased fashion.

This project involves the development and application of cutting-edge structural MS methods, in particular hydrogen-deuterium exchange (HDX) and hydroxyl radical footprinting (fast photo-chemical oxidation of proteins, FPOP). You will develop novel approaches which aim to increase the temporal and spatial resolution of the labelling and take full advantage of the combination of data from both. You will also work with challenging, high-profile targets such as oligomeric amyloid protein (believed to be the toxic form) as well as membrane proteins. In combination with computational modelling, we can build structural models of complex and dynamic systems.

You will work under the supervision of Prof Frank Sobott and Dr Anton Calabrese, in collaboration with Dr Emanuele Paci (Leeds, computational modelling) in Leeds’ world class Biomolecular MS laboratory which houses 7 instruments dedicated to structural mass spectrometry. You will receive training in structural mass spectrometry methodologies as well as computational data interpretation and modelling, a highly sought after skill for the characterization of protein structure and biotherapeutics, and push the limits of current structural mass spectrometry capabilities.

You are highly motivated, can work independently and have good communication skills. You have a degree in Chemistry, Biochemistry, Physics or a related subject. Both UK and EU-based students can apply.

4) Novel high-throughput approaches for the rapid analysis of target engagement by mass spectrometry (collaboration with Medicines Discovery Catapult)

The ability to provide fast and efficient readouts for drug engagement with targets (proteins and oligonucleotides) is a key driving technology in the biopharma pipeline, e.g. in high-throughput screening. Optical readouts are common but provide a somewhat binary answer, whereas the application of mass spectrometry (MS) to target heterogeneity, stoichiometry of binding and also structural effects (using ion mobility) has so far been hampered by the lack of robustness and the low-throughput of currently used sample inlet methods – mainly electrospray-ionization. This was recognized when a novel acoustic liquid-handling approach (“Echo”) with a capability of injecting 10,000 samples/hour was first adapted to MS analysis. This technology, now hosted at the Medicines Discovery Catapult (MDC, Alderley Edge), enables high-throughput assays for ligand screening (direct binding detection). We propose novel in-line chromatography based separation and purification, as well as further developing droplet-based inlet systems in collaboration with colleagues at Leeds’ Engineering department. This will enable more robust readouts, e.g. from cellular extracts, without need for complex sample preparation, as well as structural/conformational readouts (using ion mobility) and top-down sequencing (ETD/SID).

You will work under the supervision of Prof Frank Sobott and Dr James Ault, in collaboration with Dr Martin Bachman (Medicines Discovery Catapult, Alderley Edge) in Leeds’ world class Biomolecular Mass Spectrometry laboratory which houses 7 instruments dedicated to structural mass spectrometry. You will receive training in structural mass spectrometry methodologies as well as having the chance to further develop a cutting-edge sample inlet system with great interest in the bio/pharma industry, and push the limits of current structural mass spectrometry capabilities.

You are highly motivated, can work independently and have good communication skills. You have a degree in Chemistry, Biochemistry, Physics, Engineering or a related subject. Both UK and EU-based students can apply.