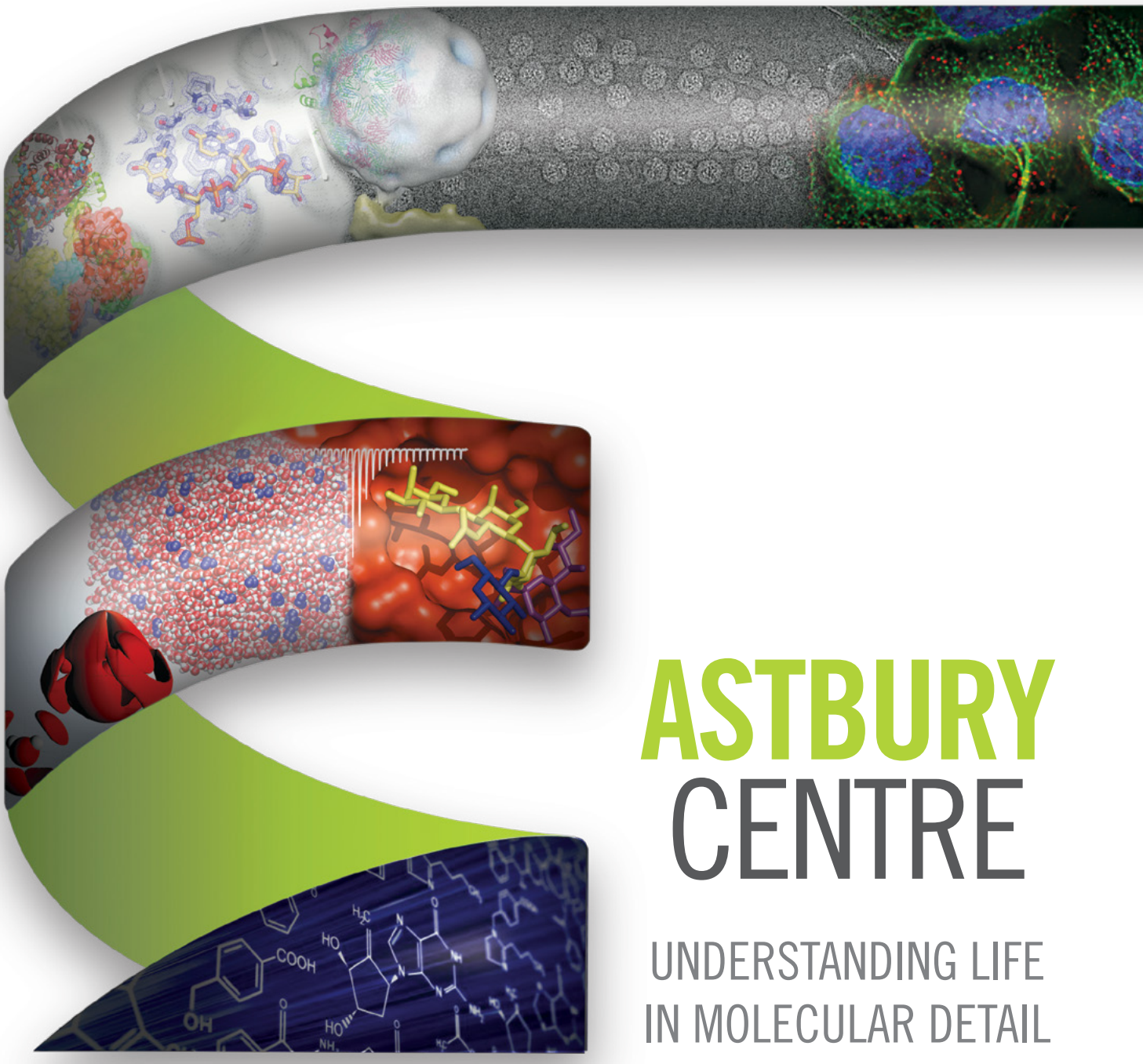
The Astbury Centre for
Structural Molecular Biology

UNIVERSITY OF LEEDS



ASTBURY CENTRE

UNDERSTANDING LIFE IN MOLECULAR DETAIL

CONTENTS

WELCOME TO THE ASTBURY CENTRE

Welcome to the Astbury Centre for Structural Molecular Biology. Our Centre was formally constituted in 1999 and uses the latest tools available to understand life in molecular detail. We hope that you will find much of interest in this brochure that describes the full range of the Centre's activities.

The Astbury Centre brings together around 70 academic staff and 400 researchers (including PhD students, post-doctoral scientists and research fellows) from physics, the biological and medical sciences and chemistry to facilitate interdisciplinary approaches to unravel life's mechanisms.

The Centre has outstanding expertise and research infrastructure with all the major techniques required to carry out world-class structural molecular and cellular biology research. Our members address major questions associated with biological mechanisms in areas as diverse as chemical biology, structural biology, biophysics and molecular interactions in cells.

> "The Astbury Centre's pre-eminence in Structural Molecular Biology could unlock the secrets of mankind's deadliest diseases."

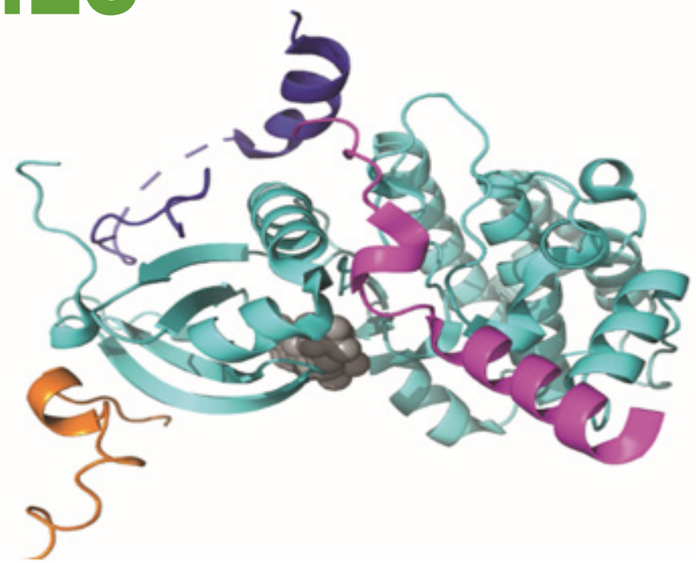
Our centre today is a lively, buoyant and invigorating research arena that allows new research discoveries to be made. The aims of the Centre are to research mechanisms that underpin health and disease and to develop new tools, methods and technologies.

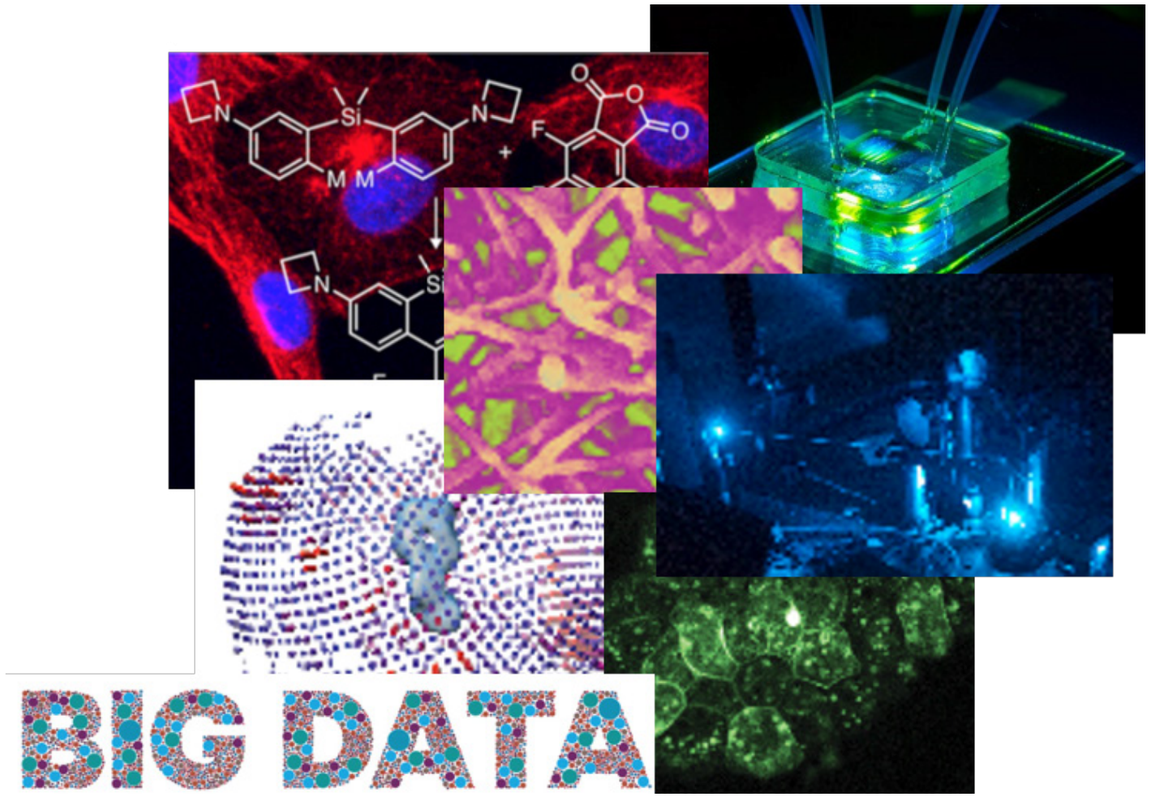
These aims are focussed on distinctive strengths in the Centre: the dynamic interactome; communication at the cell membrane; enabling tools for biological and medical discovery healthcare and host-pathogen interactions.

Professor Sheena Radford FMedSci, FRS
Director of the Astbury Centre

RESEARCH THEMES

Our research themes address major impact-oriented challenges by drawing on the full breadth of our interdisciplinary capabilities. In each theme, there is a buoyant portfolio of research involving large numbers of PIs within the Centre that additionally draws on our partnerships with academic, clinical and industrial collaborators. The themes are part of broader remit of Astbury Centre which is to harness interdisciplinary approaches to understand life in molecular detail.





The dynamic interactome

Mission: To understand molecular mechanisms across spatial and temporal scales and to uncover new opportunities for intervention.

This theme focuses on understanding and manipulating biological processes over different time scales, and determining how these molecular mechanisms relate to life. Approaches exploited include: structural biology, disruptive molecular discovery, molecular dynamics, super resolution imaging, chemical tools, single molecule biophysics, biomolecular mass-spectrometry, -omics and cutting edge spectroscopies.

Our goals are to drive a step-change in our understanding of biological molecular mechanisms via:

- application and innovative combination of state-of-the-art tools to study biomacromolecule folding, aggregation and interactions in a systems and cellular context
- development of methods to manipulate and understand dynamic biomolecular mechanisms.

Key areas of focus:

- Intrinsically disordered proteins and intrinsically disordered regions;
- Protein-protein interactions and their regulation by post-translational modification;
- The life cycle of proteins;
- Cell signalling networks and interactomes.

Key discoveries made:

- Integrated chemical tools and microfluidic technology to map dynamic interactions
- Characterization of functional states of the β-barrel assembly machinery
- Understanding of the functional regulation of Aurora A kinase by protein-protein interactions
- Structural mapping of oligomeric intermediates in amyloid assembly pathways
- Characterization of allosteric regulation in mechanosensitive ion channels.

Enabling tools for biological discovery

Mission: To facilitate the development and application of cutting-edge tools, often inspired by the physical sciences, to enable researchers to tackle current challenges in biology and medicine.

This theme encompasses method- and tool-driven science, such as chemical and physical approaches for understanding and manipulating biological processes. Our goals are to develop approaches to drive step-changes in our ability to interrogate biological mechanisms and to facilitate future hypothesis-driven life-science research. This includes both the application and innovative combination of current state-of-the-art tools and the invention and refinement of new tools.

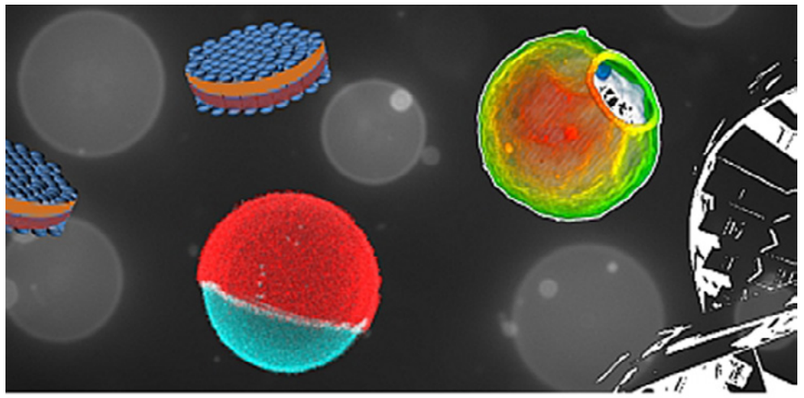
Some approaches currently being developed are: platforms to discover next-generation small molecule tools, surface mimics of biological interfaces, advanced microfluidic devices, soft matter tools for biology, computational methods and the development of analytical tools (such as single-molecule spectroscopy, combined microscopies and structural mass spectrometry).

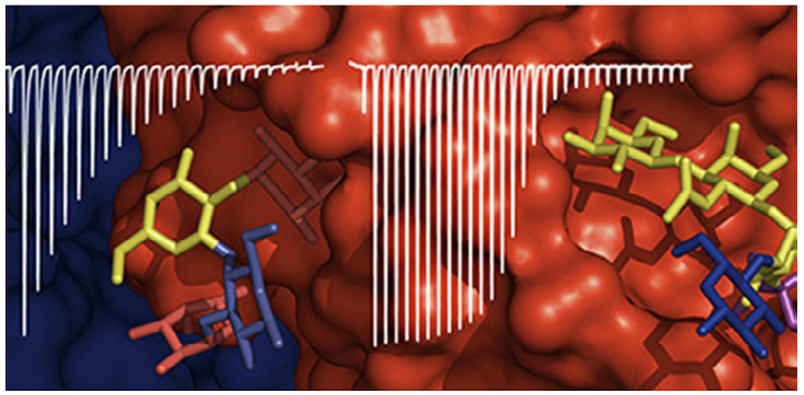
Key areas of focus:

- Integration of machine learning and technologies to enable discovery of manufacturable biopharmaceuticals;
- “Seeing into Cells” using chemical, biophysical and bioanalytical approaches to study the mechanism and function of proteins and other macromolecules in cells.

Key discoveries made:

- Chemical photocrosslinkers for rapid mapping of protein interactions
- Chemical “prosthetics” for restoring protein function
- Affimers as renewable affinity reagents for studying biological mechanisms
- Functionalised quantum dot probes of multivalent protein-ligand interactions
- A platform for the discovery of diverse functional small molecules with novel functions.





Communication at cell membranes

Mission: To understand how interactions at cell membranes result in cellular responses in health and disease.

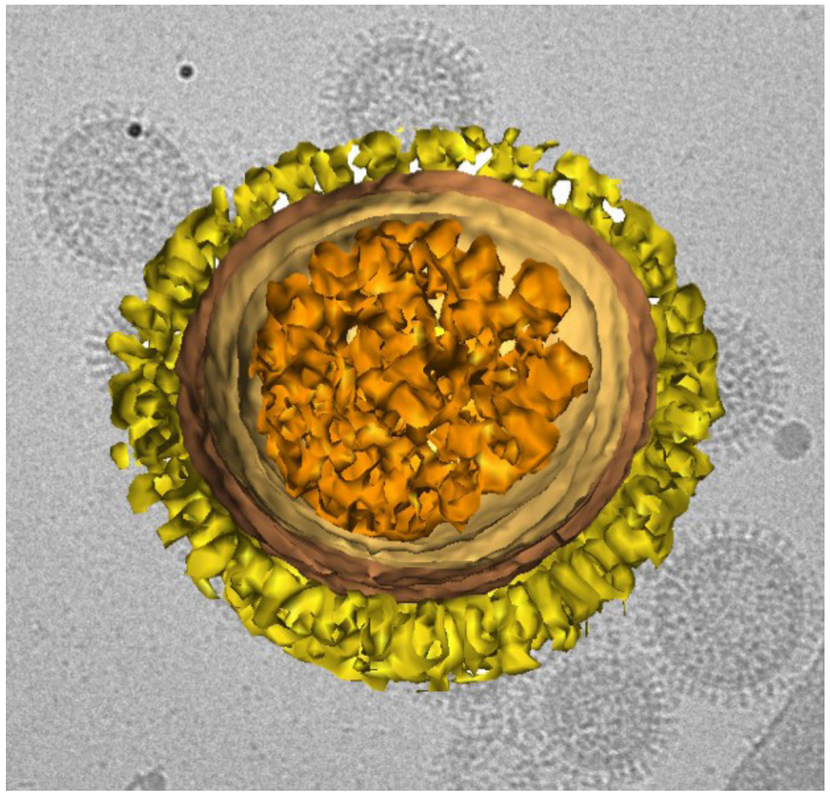
Cell membranes are the centres of communication between the inside and outside cellular worlds. We are working across disciplinary boundaries to understand, at the molecular scale, the mechanisms that regulate the reception of signals, their integration and processing, and the formulation of a response. This is a formidable challenge, but it will provide novel opportunities to enhance our understanding of fundamental biological processes. Moreover, it will aid in the development of bioactive surfaces, scaffolds and delivery vehicles to control and sense cellular fate for applications in regenerative medicine, targeted drug delivery and diagnostics.

Key areas of focus:

- Understanding how signalling at the cell membrane can result in disease states
- Understanding the role of the glycocalyx in transport and signalling across membranes
- Development of new scaffolds to generate more native-like environments for membrane proteins

Key discoveries made:

- Detergent-free isolation of membrane proteins in their lipid environment
- Understanding how extracellular matrix can discriminate cells by their receptor density, and how this ‘superselectivity’ can improve targeting of cells in biomedical applications.
- Re-engineering of peroxisome import pathways to deliver cargo to different cellular compartments.
- Understanding multivalent lectin-carbohydrate recognition using functionalised quantum dots.



Host-Pathogen interactions

Mission: To understand the molecular biology of viruses and bacteria that cause disease in humans, animals and plants, and to translate these findings into new tools for prevention, detection and eradication of these pathogens.

Viruses and bacteria are the cause of significant disease in humans, animals and plants. For example, bacteria are developing resistance to current antibiotics, threatening our ability to treat common infectious diseases, resulting in prolonged illness, disability, and death. Viral infections are also a cause of global mortality and morbidity, with pandemic virus being the most significant human disease risk in the UK, according to the National Risk Register of Civil Emergencies (e.g. COVID-19). To reduce the risks of these and other infections, our research uses molecular and cellular techniques, combined with structural and chemical approaches, to understand in molecular detail how these pathogens grow, cause disease and evade treatment. We harness our knowledge of these fundamental processes to devise new approaches to prevent and treat infectious disease.

Key areas of focus:

- Understanding virus lifecycles from infection to release using high-resolution structural and imaging approaches.
- Leveraging expertise in chemical biology to interrogate infection and develop novel strategies for anti-infectives.

Key discoveries made:

- The single-stranded RNA genomes of many viral pathogens are a “self-instruction manual” for the production of the infectious virions
- Bunyaviruses require cellular potassium to infect cells, a finding that we are harnessing to repurpose clinically-approved drugs to treat these viral infections
- Activation of an IL-6 signalling axis drives autocrine STAT3 activation, providing an opportunity to use clinically approved drugs to treat HPV-mediated cervical cancer
- Oncogenic herpesvirus Kaposi’s sarcoma-associated herpesvirus (KSHV) sequesters a host cell complex, hTREX, to enhance viral mRNA processing and replication, a finding that has allowed us to inhibit KSHV replication
- Computational drug design has yielded β-lactamase inhibitors which circumvent evolved resistance to many current antibiotics.

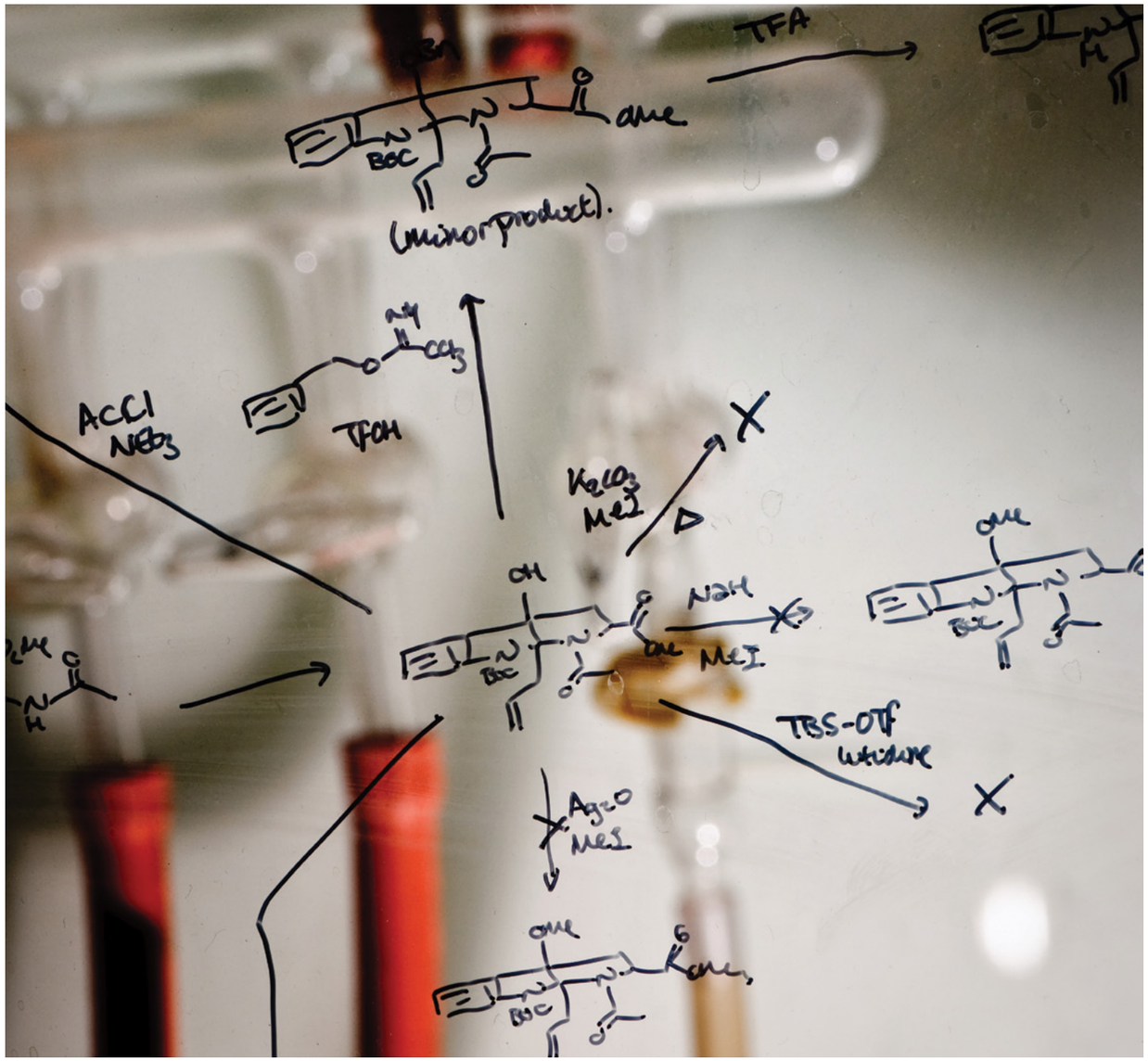
CHEMICAL BIOLOGY

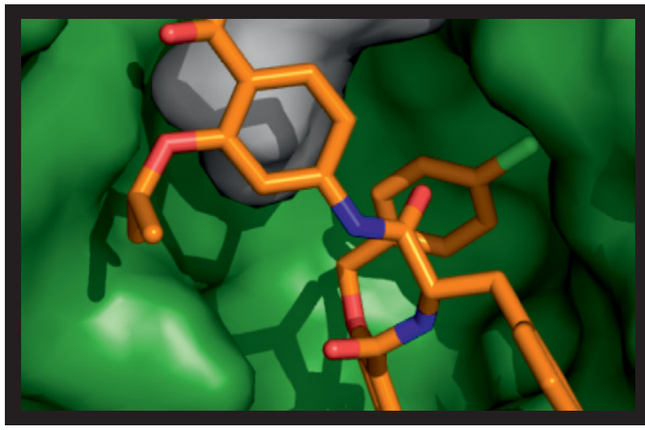
Chemical Biology is the application of chemical tools and approaches to address biological problems. Within the Astbury Centre, chemists are engaged in highly interdisciplinary and collaborative research programmes to address a wide range of biological, chemical and medical problems.

These include the design and synthesis of new drugs, the development and exploitation of small molecule tools to interrogate biological mechanisms, pioneering new approaches in synthetic biology and engineering new enzymes for use in synthetic chemistry.

We have superb facilities for Chemical Biology including integrated synthetic and biological laboratories, a computer cluster dedicated to ligand design, a facility for screening compound libraries for biological function and a suite dedicated to the high-throughput synthesis of small molecules.

We exploit these facilities, in conjunction with biophysical, structural and cellular approaches, to address a wide range of problems of direct relevance to society.





Protein-protein interactions

Protein–protein interactions (PPIs) are vital to all biological processes, and have huge potential as targets for drug discovery. PPIs typically occur over large topographically shallow protein surfaces, and can exhibit a broad range of affinities. However, understanding the key determinants of the thermodynamic stability of specific PPIs remains a key challenge.

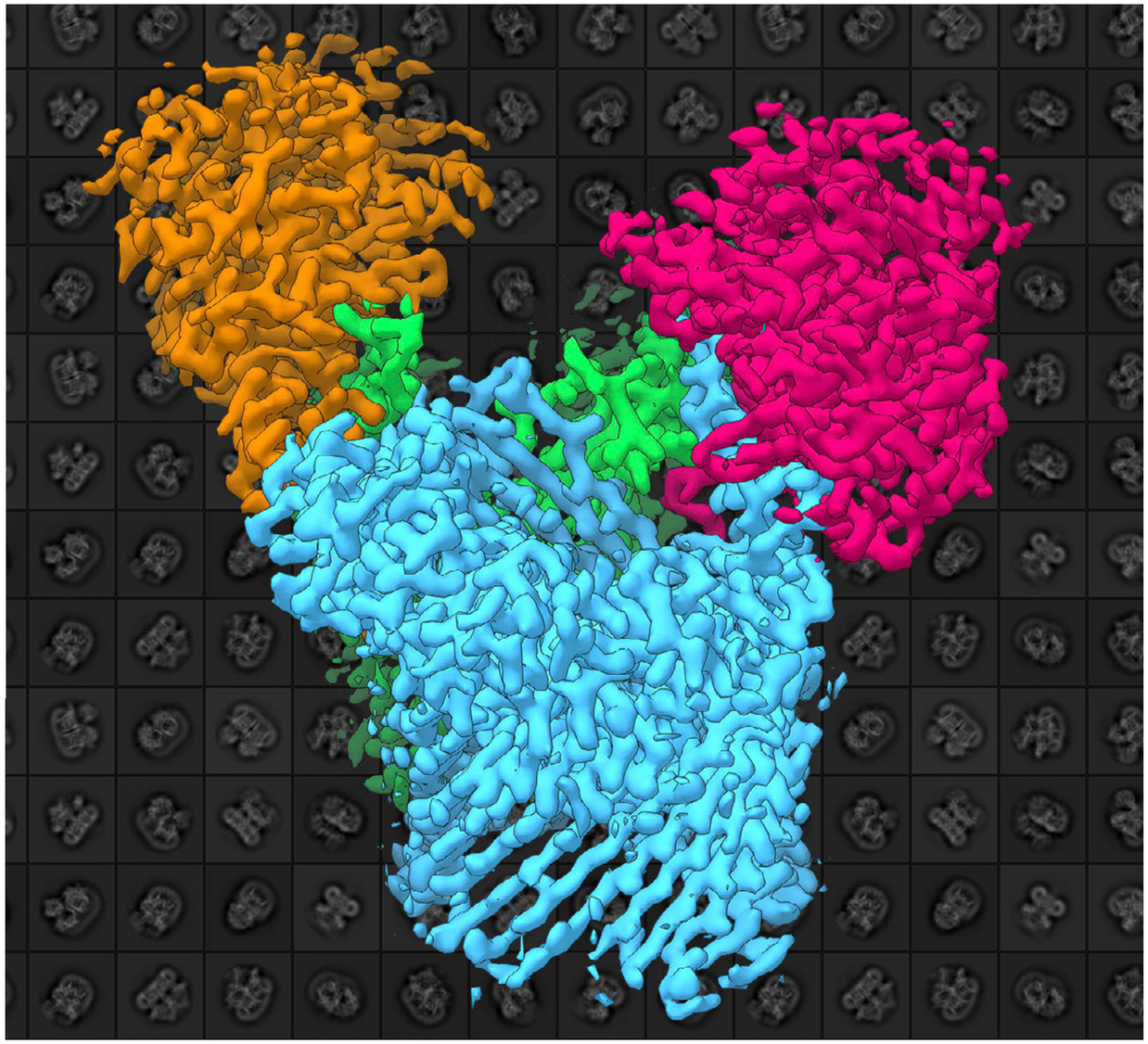
Professor Andrew Wilson is leading an EPSRC programme grant in which new tools to drive the discovery of inhibitors of PPIs are being developed. The programme involves collaboration with researchers from the University of Bristol, and has three project partners: AstraZeneca, Domainex and Northern Institute for Cancer Research.

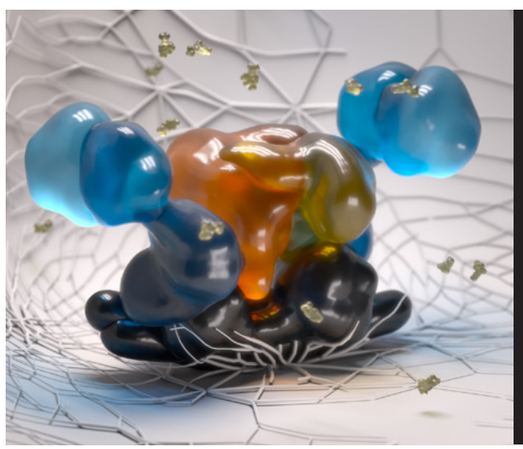
The team has undertaken a comparative analysis of multiple methods for the prediction of hot-spot residues on the basis of PPI structures *(ACS Chemical Biology 2019)*. Here, a new method, BUDE Alanine Scanning, was introduced which can be applied to both single structures (from crystallography) and structural ensembles (from NMR or molecular dynamics data). The approach enabled the accurate prediction of hot-spot residues at a wide range of topographically distinct protein–protein interfaces. Knowledge of the hot-spot residues has enabled the discovery of several different classes of PPI modulators: for example, coiled coils *(Chemical Science 2018)*, oligoamide foldamers *(Chemical Science 2019)* and stapled peptides *(ChemBioChem 2019)*.

STRUCTURAL BIOLOGY

The Astbury Centre has a strong history in structural studies from small molecules to large protein complexes. Bill Astbury's definition of the alpha-helix and beta-sheet structures within proteins laid the foundations for the high resolution structural studies of bio-molecules that are carried out in the Centre today.

Understanding the structure of a protein or protein complex is fundamental to underpinning drug design and understanding the relationship between structure and function. The Astbury Centre has a wealth of expertise in X-ray crystallography, nuclear magnetic resonance spectroscopy (NMR), atomic force microscopy (AFM) and electron microscopy (EM) and this structural information is complemented by biophysical techniques such as analytical ultracentrifugation, isothermal titration calorimetry, circular dichroism spectroscopy (CD), surface plasmon resonance (SPR), and fluorescence. We take advantage of our excellent modern facilities, along with the many cross-disciplinary collaborations within the Centre, to investigate the structural biology of aspects of life sciences such as enzyme mechanisms, membrane proteins, molecular motors, virus biology, molecular dynamics, protein folding and more.





Metabolic control of immune signaling revealed by cryo-EM

The overproduction of cytokines results in hyper-inflammation that can cause tissue damage and lead to autoimmunity. In many autoimmune diseases such as Lupus, systemic sclerosis and rheumatoid arthritis, immune cells produce too much interferon, a natural stimulant that signals to the immune system in ways that can exacerbate inflammation.

Structural biologists in the Astbury Centre led by Dr Elton Zeqiraj, have figured out the structure of a macromolecular complex by using cryo-electron microscopy (cryo-EM). Their findings *(Nature, 2019)* revealed a fascinating molecular mechanism that connected the ubiquitin-processing enzyme BRISC to an enzyme involved in metabolism called serine hydroxymethyltransferase 2 (SHMT2). SHMT2 guides reactions essential for basic body functions, such as building blocks for proteins and DNA, after being activated by a form of vitamin B6.

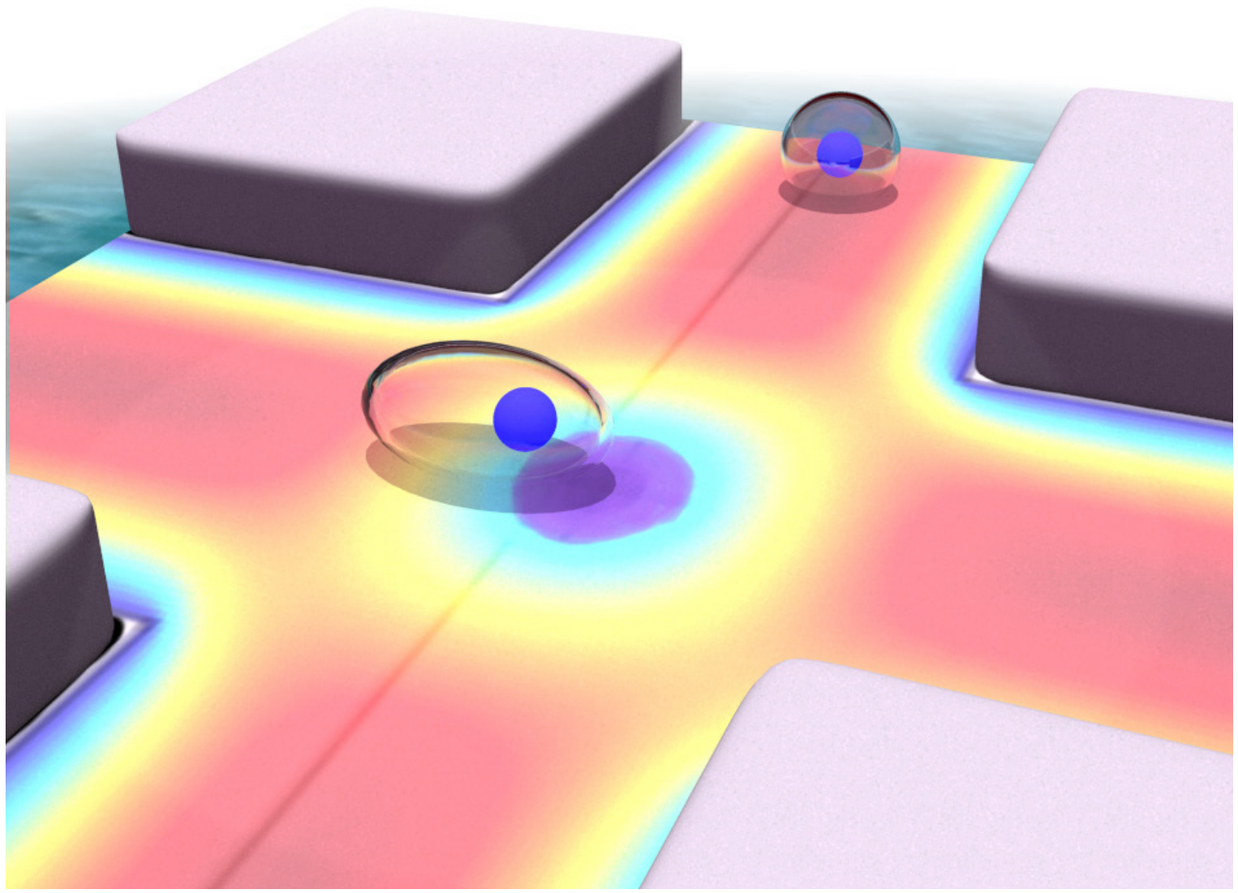
The team solved the cryo-EM structure of the human BRISC-SHMT2 molecular complex. They found that it is composed of eight BRISC-enzyme protein subunits forming in a U-shape structure, with different enzyme components protruding from each side. SHMT2 bridges the gap between the two arms, blocking the active-site pocket, and inhibiting enzyme activity. This block is thought to prevent abnormal BRISC activity and restrict it to inflammatory sites to keep immune signaling in line.

By probing the detailed structure of the complex and in collaboration with cell and clinical biologists from the University of Pennsylvania and University of Leeds, the team found that SHMT2 is also required for immune cells to send out cytokine signals through its interaction with the BRISC complex. Mutations that disrupt the interaction surface of BRISC-SHMT2 complex interfere with this onslaught of inflammation. This interaction was also regulated by vitamin B6 levels in cells, providing clues to the impact of metabolism on immune response regulation.

BIOPHYSICS

The understanding of life requires a detailed knowledge of the structure of biological macromolecules and how they interact with each other and with other molecules in the living cell. Our researchers exploit the widest possible array of biophysical methods to determine the specificity, rates, and equilibrium free energies of interactions between proteins, nucleic acids, lipids, carbohydrates and small molecule ligands. Techniques such as microfluidics, surface plasmon resonance (SPR), isothermal titration calorimetry (ITC), quartz crystal microbalance (QCM-D) and fluorescence based assays (intensity and anisotropy) are used to elucidate binding constants, whilst structural methods including circular dichroism (CD), ion mobility mass spectrometry, and nuclear magnetic resonance (NMR) reveal information about conformational changes during binding.

Single molecule methods, including fluorescence resonance energy transfer (FRET) and force spectroscopy are also being used to reveal new information about protein stability and force-induced conformational changes. Combined with insights from molecular dynamics simulations and mathematical modelling, our aim is to use state-of-the art biophysical methods to develop new approaches able to elucidate how macromolecular assembly and recognition is controlled within cells and tissues to the exquisite sensitivity required for healthy life.

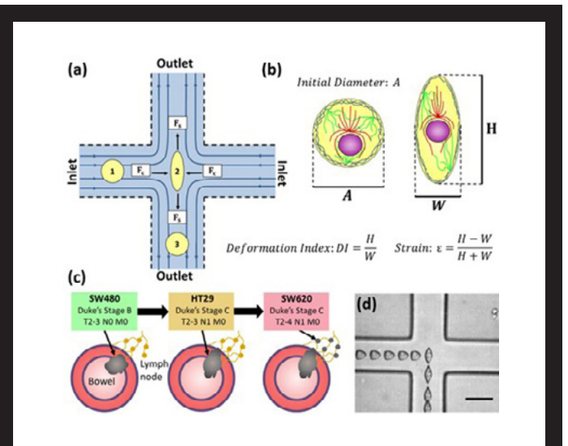


High throughput mechanical phenotyping of single cells

The mechanics of a single cell can be an indicator of diseased state, thus mechanophenotyping offers many potential diagnostic applications. A high-throughput method is required for single cell mechanical measurements to account for cell heterogeneity which arises due to cell-cycle stage and biological noise. Microfluidics can be used to hydrodynamically deform cells in a high-throughput manner, allowing automated single cell analysis.

Professor Stephen Evans along with PhD student Fern Armistead used a microfluidic technique called deformation cytometry for various studies on the sensitivity of cells to subcellular alterations, and mechanical changes with colorectal cancer progression. Here, cells were deformed at the stagnation point of an extensional flow across a wide range of flow conditions. One study *(Biophysical Journal, 2019)* showed that different flow conditions probe different aspects of the cell structure. For example, changes in actin structure, due to drug induced destabilisation, led to cells becoming more deformable and was best observed in a shear-force dominant regime. In contrast changes to the nuclear structure are best observed in an inertial force dominant regime. Further work, looked at the mechanical properties of three colorectal cancer cell lines as a model for metastatic progression *(Scientific Reports, 2020)*. Results showed that cells become softer with cancer progression. They also showed that multiparameter analysis is required to accurately characterise the different cell types, including both deformation and relaxation properties.

Overall, the technique provides a range of mechanical parameters for understanding cell behaviour and gives new insights into heterogeneity, disease progression and drug response.



MOLECULAR INTERACTIONS IN CELLS

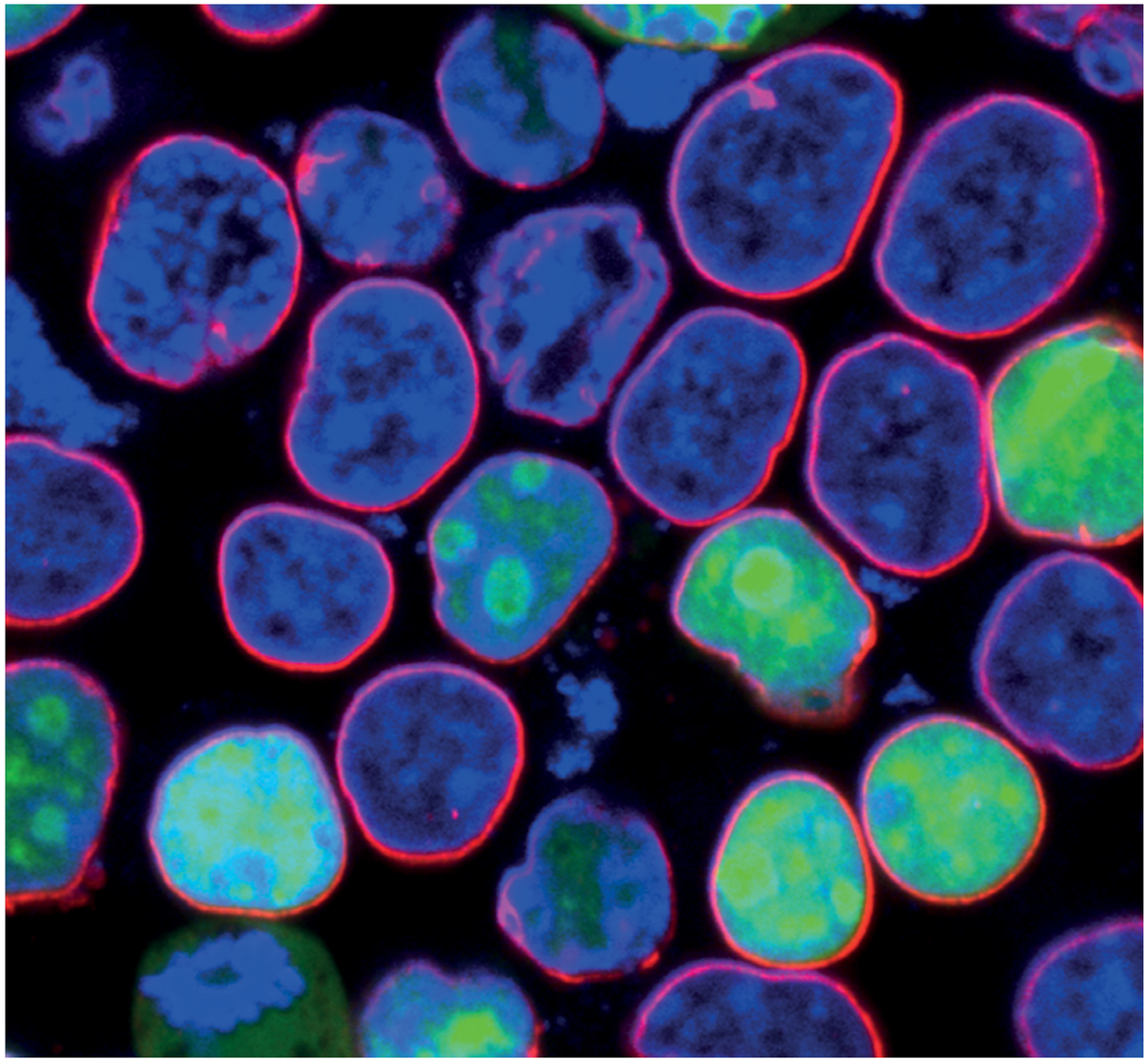
To complement analyses using biophysical approaches *in vitro*, researchers in the Astbury Centre also study molecular interactions in the context of the whole cell.

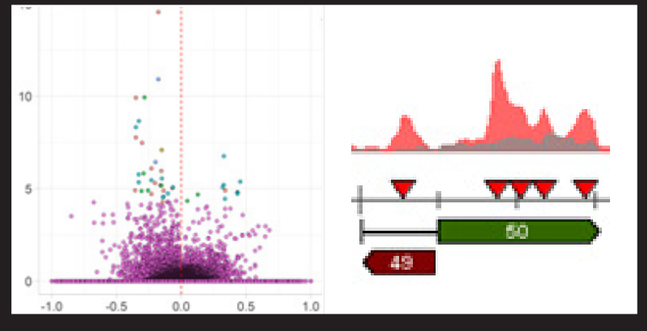
Protein-nucleic acid, protein-protein and protein-lipid interactions within cells are investigated using biochemical approaches such as immunoprecipitation, purification via protein tags and the application of proteomic technologies.

Within the Astbury Centre these methods are complemented by a range of state-of-the-art bio-imaging equipment to investigate the biology of cells at different resolutions. Populations of cells are interrogated by flow cytometry and cell sorting.

At an individual cell level, conventional light microscopy (e.g. confocal and deconvolution) studies can be complemented by super-resolution approaches (PALM/STORM and iSIM). In addition, correlative light-electron microscopy (CLEM) allows the integration of datasets derived from different imaging modalities to provide unique insights into the localisation of biological molecules within cells.

Finally, a confocal microscope situated in the Category III containment facility provides the opportunity to study cells infected with pathogens.





The virus with royal protection

Viruses are the masters of manipulation. Key to their success is the ability to subvert host cell pathways and machinery to enhance viral replication and proliferation. Professor Ade Whitehouse's group have recently identified a novel cellular pathway that the human tumour virus, Kaposi's sarcoma-associated herpesvirus (KSHV), manipulates to enhance its own replication. This host cell pathway, known as the m6A methylation pathway, chemically adds a methyl group to adenosines in messenger RNA (mRNA). Once modified these mRNAs are then recognised by so-called 'm6A reader' proteins which bind the m6A chemically modified mRNA and then determine what happens to that modified mRNA.

The study firstly identified that KSHV manipulates the m6A methylate pathway to chemically modify its own viral mRNAs *(eLife, 2019)*. The study then addressed why this enhances virus replication. Experiments revealed that a new family of proteins, the 'Royal family', could recognise and bind viral mRNAs that contains the m6A chemical modification. Further experiments showed that Royal family members, such as SND1, specifically stabilise viral mRNAs once bound to them. Notably, upon depletion of SND1 from virus infected cells showed that SND1 is essential for KSHV replication. These findings open up new therapeutic strategies to inhibit the replication of this important human pathogen.

INDUSTRY PARTNERSHIPS

The discovery and manufacture of novel, safe, and effective therapeutics remains a difficult and arduous task. For example, it has been estimated that bringing each new drug to market costs over £1bn. Partnerships between academia and industry are an increasingly important mechanism to facilitate early-stage drug discovery through the development of new methods and fundamental science.

Engagement and collaboration with industry is central to the Astbury Centre. The Centre works with a wide range of industrial partners to drive innovation in the pharmaceutical and biotechnology industries, and also supports researchers to commercialise their research. Reflecting areas of research strength within the Astbury Centre which align with industrial needs, we focus on:

- predicting and preventing protein aggregation;
- modulating protein-protein interactions;
- targeted molecular delivery;
- ion channel research;
- translational drug discovery;

Alongside these themes, platform technologies to facilitate therapeutics discovery are also supported.

The Astbury Centre facilitates translational research through a range of activities including linkage to national initiatives, industry-focussed workshops and networking events, implementation of impact activities, funding of proof-of-concept projects, and assisting academics to identify the best route to exploit intellectual property.

To remain focussed on sector needs, the Astbury Centre is guided by an Industrial Advisory Board comprising representatives from large and small pharmaceutical/ biotechnology companies and allied industries. The Centre's Research and Innovation Development Manager also works closely with related innovation professionals across the university (including health and life sciences, and physical sciences) to deliver coordinated support for pharmaceutical research at Leeds.

The Astbury Centre and the University of Leeds are also formal partners of the Rosalind Franklin Institute, further strengthening our industrial engagement and partnership.

More information can be found at:
http://pharmahub.leeds.ac.uk

> "The Astbury Centre has a strong track record of industry engagement and their expertise has delivered value to our R&D."

Principal Scientist, Medicinal Chemistry, AstraZeneca

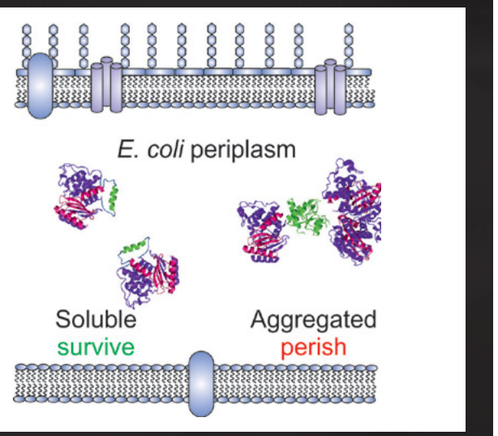
Case study:

Biological (protein) drugs have emerged as effective and high-value therapeutics, capable of treating a wide range of medical conditions not possible with small-molecule drugs. Their large-scale expression, purification and formulation is problematic however, because changes in their environment during processing can lead to their partial unfolding and aggregation which is difficult to predict. Aggregation can lead to a number of problems including loss of (expensive) drug product, a potential immunological response which is damaging to the patient, and ultimately the loss of a drug programme which a company has invested significant resources and where there is medical need.

To address this problem, Dr David Brockwell and Professor Sheena Radford from the Astbury Centre, along with Professor Nik Kapur (Mechanical Engineering), worked with AstraZeneca and others to develop novel methods to predict and prevent protein aggregation *in vitro* using hydrodynamic flow *(Proceedings of the National Academy of Sciences of the USA, 2017)* and in vivo. In the latter method, aggregation is linked to the antibiotic resistance of *E. coli*, allowing high through-put screening and re-engineering of problematic sequences by directed evolution (*Nature Communications, 2020*).

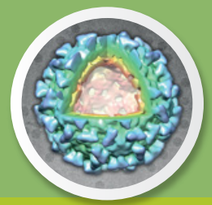
"Working with AstraZeneca has been a brilliant and inspiring experience. This is a true collaboration between academics and industry and is reaping real benefits to all involved."

Professor Sheena Radford,
Astbury Professor of Biophysics, University of Leeds

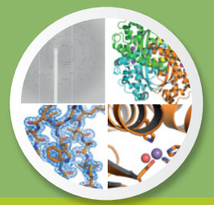


FACILITIES

An abundance of instrumentation that includes both well-established and emerging techniques lies at the heart of the Astbury Centre's research successes. Each is run by dedicated and highly experienced staff scientists and facility managers who offer training to all users. This infrastructure is maintained at the cutting-edge by funding from a diverse range of agencies including charities, private benefactors, the University of Leeds, BBSRC, EPSRC, MRC and the Wellcome Trust. Access to cutting-edge instrumentation is core to the Centre's success and this importance is underlined by the creation of the Astbury Biostructure Laboratory in 2016 – a £17 million investment by the University of Leeds and the Wellcome Trust to provide two Titan Krios cyro-electron microscopes and a 950 MHz NMR and associated staff scientists.

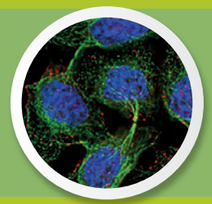


Electron Microscopy
Single Particle Cryo-EM, Tomography, Cellular EM



X-ray crystallography
Automatic dropsetter and imaging, FBDD

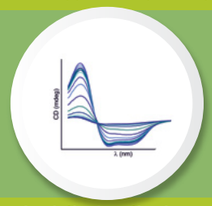
Advanced NMR
Structural dynamics, BRUKER 950 MHz, Cryoprobes



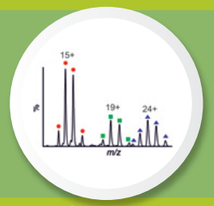
Cell biology
Bioimaging, Super-resolution Microscopy, Flow Cytometry

Molecular interactions
ITC, AUC, DSC, SPR, OPTIM SEC-MALLS, Thermophoresis

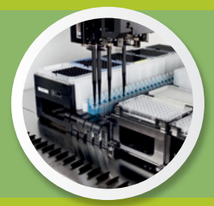
Protein Production
Bacterial, insect and mammalian expression, large scale purification



Analytical methods
HPLC, CD Spectroscopy, Fluorescence Spectroscopy

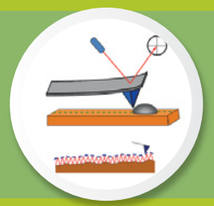


Mass Spectrometry
Non-Covalent Interactions, Chemical Proteomics



Advanced Robotics
High-Throughput Screening, Bioscreening Technology

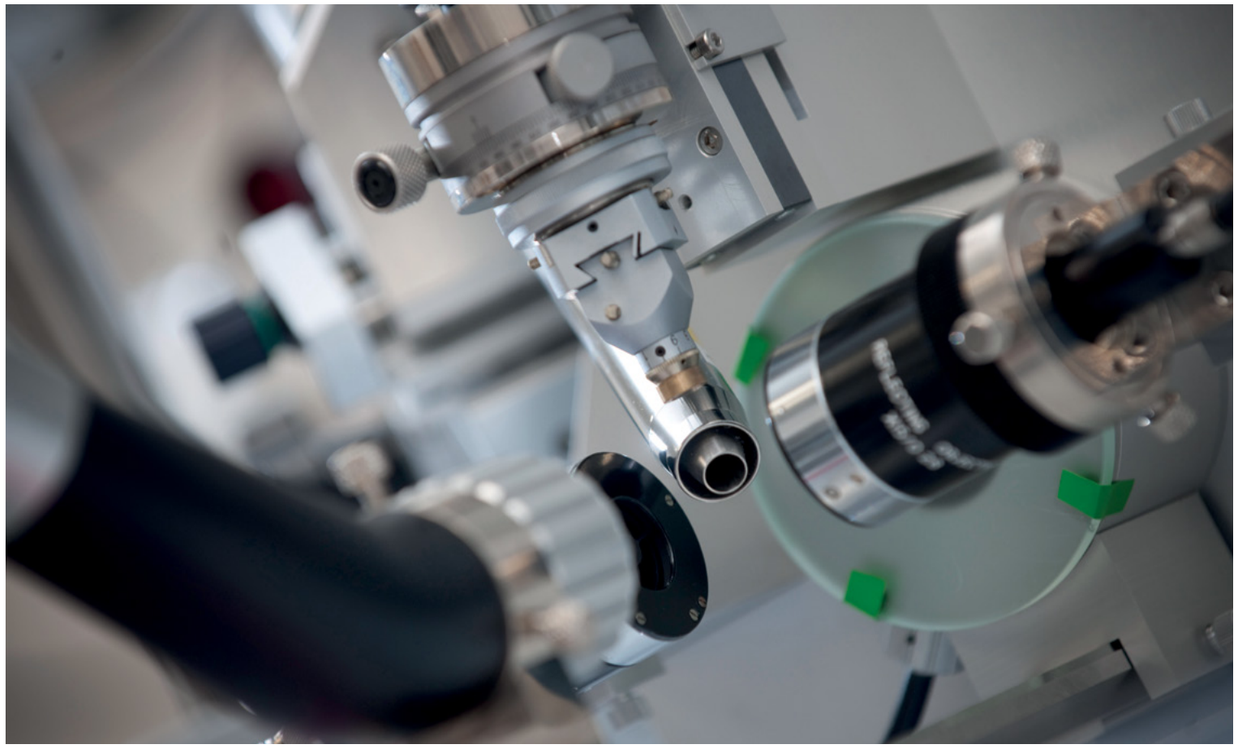
Bioscreening
Affimer technology for specific, high affinity probes



Surface Analysis
AFM, XPS, QCMD

Single Molecule Methods
Single Molecule Fluorescence, Single Molecule Force Methods

For further details please see **www.astbury.leeds.ac.uk/research/facilities.php**

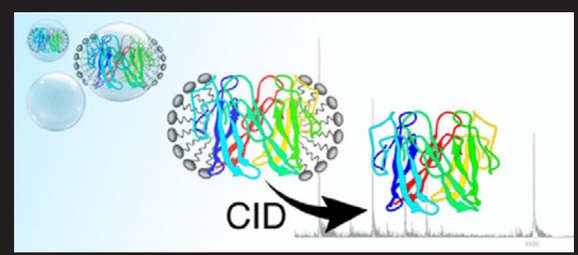


Understanding peptide assembly mechanisms

Understanding the structural mechanism by which proteins and peptides aggregate is crucial, given the role of fibrillar aggregates in debilitating amyloid diseases and bioinspired materials. Yet, this is a major challenge as the assembly involves multiple heterogeneous and transient intermediates. Teams of chemists and structural biologists in the Astbury Centre are engaged in multidisciplinary programmes of research to understand peptide and protein assembly mechanisms and to determine how we can intervene in these assembly processes.

In work performed with Professors Sheena Radford and Andrew Wilson, Sam Bunce, a BBSRC DTP funded PhD student, analysed the co-aggregation of $A\beta_{40}$ and $A\beta_{16-22}$, two widely studied peptide fragments of $A\beta_{42}$ implicated in Alzheimer's disease. Using fluorescence assays, electrospray ionisation MS coupled with ion mobility MS (ESI–IMS–MS), photoinduced cross-linking experiments, and molecular dynamics simulations, they demonstrated that $A\beta_{16-22}$ increases the aggregation rate of $A\beta_{40}$ through a surface-catalysed secondary nucleation mechanism, paving the way to the generation of surfaces able to enhance or suppress aggregation. The work provides the first molecular images of amyloid secondary nucleation that they are now using to inform effective design of ligands that modulate therapeutically important amyloid assembly *(Science Advances, 2019)*.

The mechanisms of Aβ peptide neurotoxicity in Alzheimer's disease are hotly debated. One suggested mechanism is that the peptides assemble in membranes to form β-barrel shaped oligomeric pores that induce cell leakage. Direct detection of such putative assemblies and their exact oligomeric states is however complicated by a high level of heterogeneity. By employing a native mass spectrometry approach Professor Frank Sobott and his collaborators have used native ESI-IM-MS to watch the assembly of $A\beta_{42}$ with membrane mimetic detergent micelles, exploiting the powers of native MS methods to unpick this molecular complexity. The study revealed the formation of hexamers with collision cross sections in agreement with a β-barrel structure *(Journal of the American Chemical Society, 2019)*. The results support the oligomeric pore hypothesis as one important cell toxicity mechanism in Alzheimer's disease and highlight the power of native mass spectrometry as an approach to search for methods to stabilise or destabilise the molecules by molecules of cellular or therapeutic relevance.



PhD TRAINING

Overview

The Astbury Centre plays a major role in training highly motivated researchers to become skilled in interdisciplinary life sciences. Funding for PhD training is provided from a wide variety of sources including the White Rose BBSRC Doctoral Training Programme (with York and Sheffield), BBSRC iCASE studentships in collaboration with industry partners, EPSRC and the MRC Discovery Medicine North (DiMeN) DTP (with Sheffield, Newcastle and Liverpool). PhD students are also funded by bio-medical charities including The Wellcome Trust, the British Heart Foundation, Kidney Research UK, Cancer Research UK and Alzheimer's Research UK.

The diversity of our science and the Centre members is also reflected in the wide range of academic disciplines and nationalities of the students that are studying with us. Our cohort of >200 PhD students includes physicists chemists, biologists and students with a wide range of other undergraduate disciplines, working together from countries spanning the UK, Europe, USA, Canada, Australia, China, Mexico,the Middle East and India.

Our PhD students work in an academically stimulating environment, which is supportive, collegiate and inclusive. All students have a small supervisory team to oversee and facilitate progress and to help promote our ethos of multidisciplinary training. Students form an integrated cohort within the Centre through training days and other activities such as the Annual Research Retreat which all students are invited to attend.

Our programmes investigate the molecular basis of biological mechanisms, and the strategic applications of mechanistic biology. We train students in the wide range of techniques in cell biology, biological chemistry, structural biology and biophysics that are needed to answer key questions in challenge-led including food security, bioenergy and industrial biotechnology and the development of new tools and techniques focussed on key questions and challenges in in bioscience and biomedicine. Our programmes range from 3½ to 4 years duration and may include laboratory rotations to train students in specific techniques or as 'taster' sessions before a main PhD project is chosen.

The PhD training in The Astbury Centre includes bespoke cohort-wide training in core skills such as new technologies allowing students to develop a deep understanding of modern techniques, their principles and applications, mathematics, data-analysis and modelling. These generic skills are supplemented with practical training and skills modules in techniques specifically related to their PhD project. Our programmes encourage interdisciplinarity and provide a wide generic skills base to provide the foundation of a wide range of future careers. Some programmes also include a 3 month 'Professional Internship for PhD Students' (PIPS) gaining experience of work in a professional environment and transferable skills.

LIFE IN THE ASTBURY CENTRE

The Astbury Society

The Astbury Society, comprised of PhD students and postdoctoral members, plays a key role in encouraging cross-departmental collaborations by organising social events including an Annual Sports Day, the May Ball, team working events and seminars with guest speakers. The events of the Astbury Society are enjoyed by postgraduate students, postdoctoral researchers and academic staff alike.

> "Meeting various people from different academic departments in a social environment allows for time to discuss aspects of my PhD and to get a range of ideas that might have not been brought to my attention otherwise."
>
> **Paul Devine, PhD student**

> "Being part of the Astbury Society has certainly had a positive impact on my PhD, predominantly due to the interdisciplinary nature of the Centre. There are always people, from a range of scientific backgrounds, who will happily let you bounce ideas off them to help you along with your PhD."
>
> **Claire Windle, PhD student**

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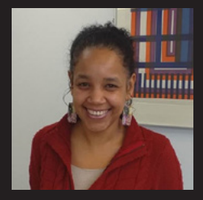

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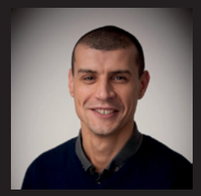

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The staff list is up to date as of day of printing but is subject to change. Please check the Astbury Centre website for up to date information
www.astbury.leeds.ac.uk/people/people.php

HISTORY

The Astbury Centre for Structural Molecular Biology was formally constituted as a University Interdisciplinary Research Centre in 1999. The Centre builds on the visions and achievements of the pioneers of modern biophysics and is named after W.T. (Bill) Astbury FRS, a biophysicist who laid many of the foundations of the field during a long research career at the University of Leeds (1928-1961). Astbury originally identified the two major recurring patterns of protein structure (alpha and beta), took the first X-ray fibre diffraction pictures of DNA (in 1938) and is widely credited with the definition of the field of molecular biology. Astbury's work, in turn, followed on from the pioneering work of Sir William Bragg who was the Cavendish Professor of Physics in Leeds from 1908-1915.

> "We are at the dawn of a new era, the era of 'molecular biology' as I like to call it, and there is an urgency about the need for more intensive application of physics and chemistry, and specially of structure analysis, that is still not sufficiently appreciated."
>
> **Bill Astbury 1947**

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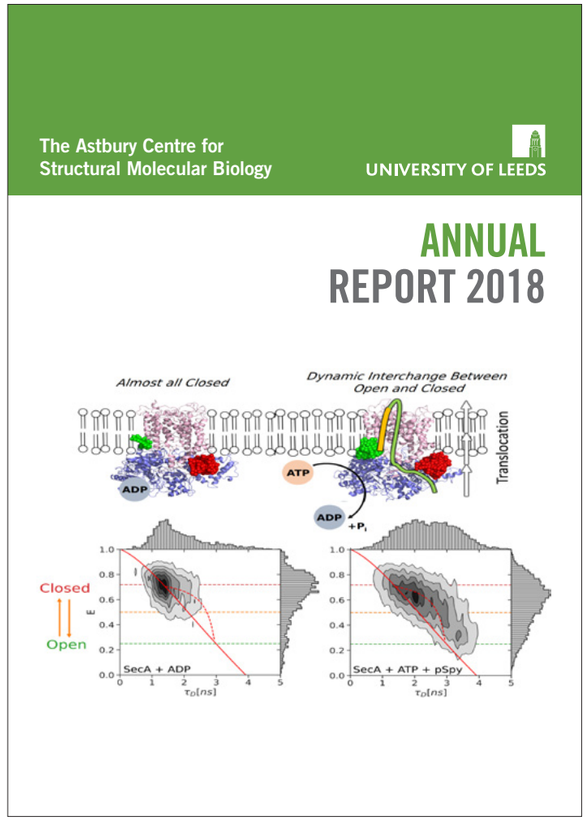
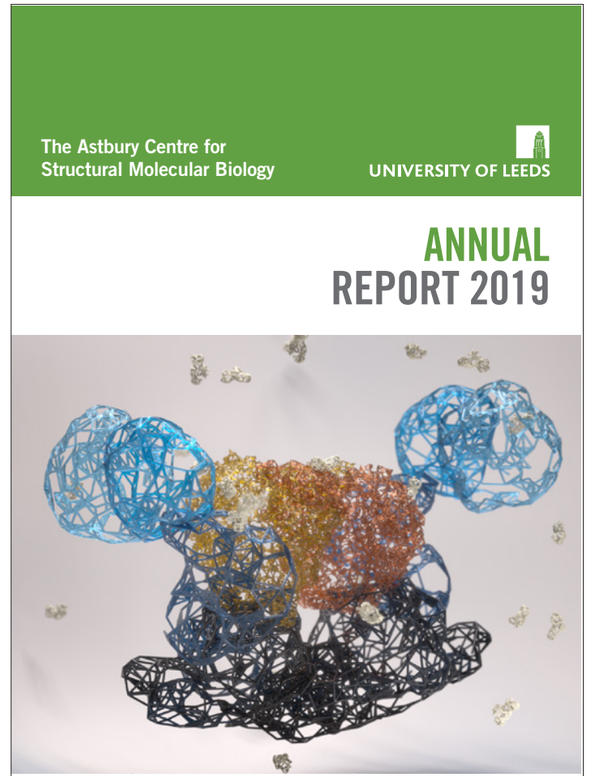
ASTBURY CENTRE

ASTBURY REPORTS

The research undertaken by Astbury Centre investigators is described in greater detail in our annual reports. These accounts, first published in 2000, are available online: **www.astbury.leeds.ac.uk/research/reports.php**





> We need much more cooperation, much more fraternization, much more encouragement of one another, much more sharing of knowledge and much more asking of help.

WILLIAM ASTBURY,
PROFESSOR OF BIOMOLECULAR STRUCTURE, 1948

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