ASTBURY CENTRE

UNIVERSITY OF LEEDS

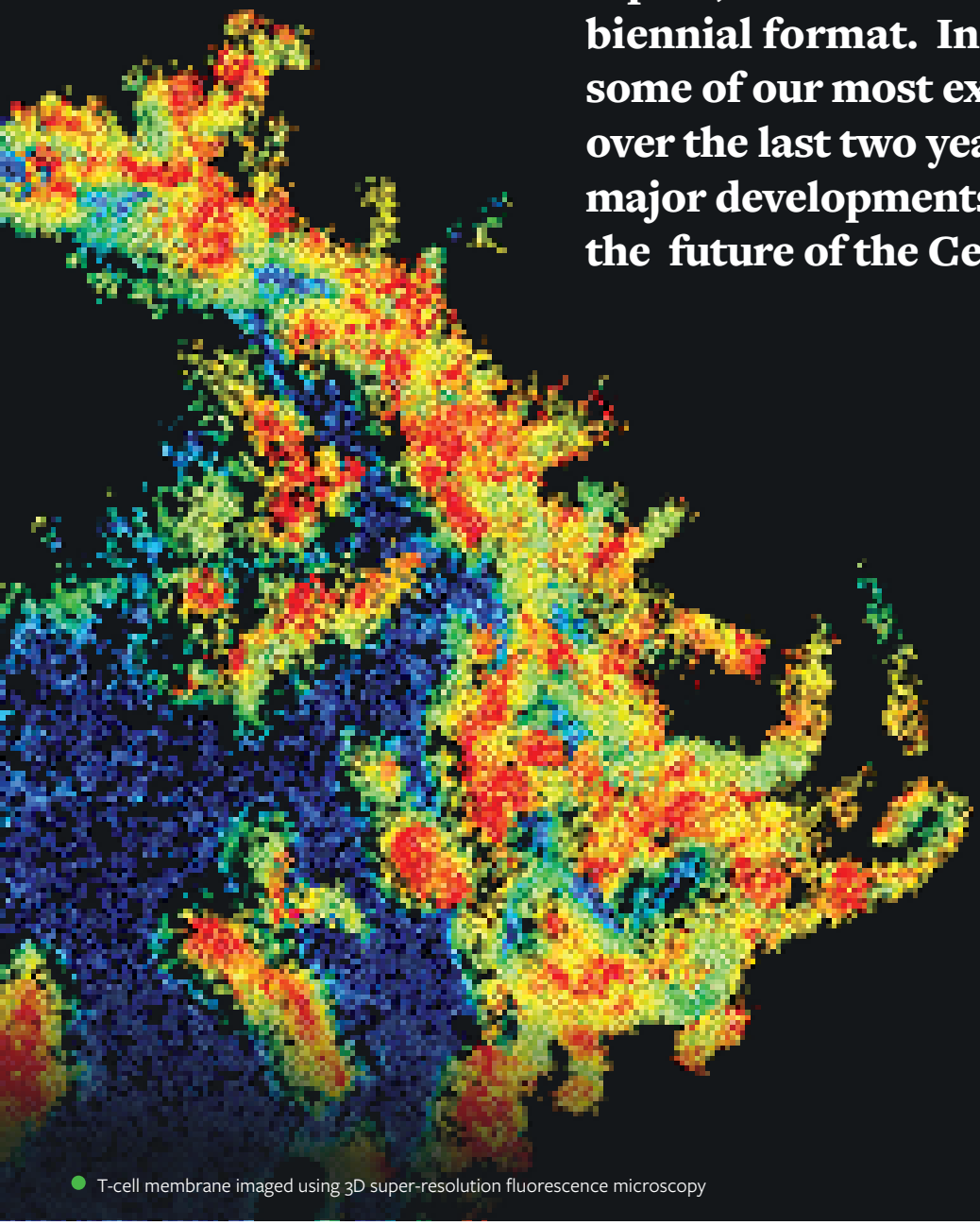
The Astbury Centre

June 2024

Welcome from the Director

Professor Neil Ranson

Welcome to the Astbury Centre's report, the first edition in our new biennial format. In it, we'll describe some of our most exciting science over the last two years, alongside major developments that will shape the future of the Centre.



T-cell membrane imaged using 3D super-resolution fluorescence microscopy

From left to right: Adele Parry (Astbury Research and Development Officer), Adam Nelson (Deputy Director), Neil Ranson (Director), Lucy Gray (Astbury Administrator) and Ste Muench (Deputy Director).

The Astbury Centre for Structural Molecular Biology is many different things. It is an interdisciplinary Centre that exists to promote research across disciplines, seeking to understand how molecules behave and how this behaviour impacts us in health and disease. The Centre brings together more than 400 researchers, primarily from biology, chemistry, medicine and physics, and we're all joined by a common passion to understand life in molecular detail. The Centre is also a vibrant, inclusive community where all members can tackle the toughest problems using interdisciplinary approaches 'without walls'.

We are an open, outward-facing grouping that collaborates widely both nationally and internationally. Our links with industry are enhanced through our Industry Advisory Board, which comprises scientists from multiple pharmaceutical companies and other organisations across the life sciences sector. We are funded by Wellcome and MRC to lead delivery of national training in cryo-electron microscopy. We also welcome users from around the world – from industry and academia – who access our outstanding infrastructure such as cryo-electron microscopy, NMR spectroscopy and mass spectrometry.

I would like to personally thank everyone who has contributed to Astbury Centre life over the last couple of years. Kate Langton has moved onto pastures new, after many years of stalwart service. However, it's been a great pleasure to start work with Adele Parry, our Research and Innovation Support Officer, who is supporting us in major funding initiatives going forward. As ever Lucy Gray has been at the heart of almost everything we do, working tirelessly to support everyone in the Centre. Once again, I thank the Deputy Vice Chancellor (for Research and Innovation), members of our Industrial Advisory Board, and the Executive Deans, Pro-Deans and Heads of School who support the Centre's work. Finally, I'd like to thank every Centre member at every career stage. Each one of you makes the Centre what it is: a fantastic place to do our science!

Crossing Biomolecular Scales with Neutron Scattering

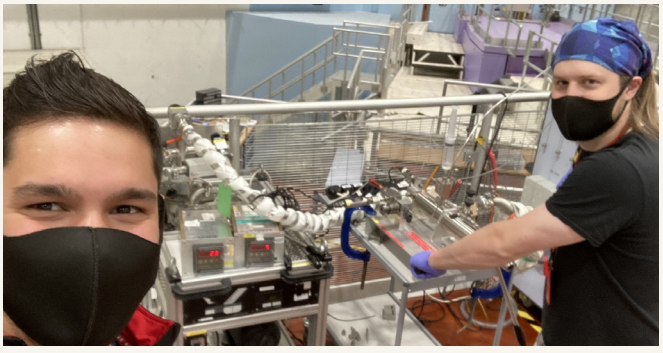
Simultaneously understanding the large scale and the atomistic details of how biomolecule building blocks come together is crucial for predicting how drugs bind and how biomolecules assemble to create useful biomaterials.

Neutron scattering offers a unique opportunity to study biological systems as it is non-destructive, deeply penetrating, and highly sensitive to hydrogen atoms in biomolecules. Researchers at the Astbury Centre combined the differing length scale sensitivities of two instruments (Zoom and NIMROD) at the ISIS facility, Oxfordshire, UK to reveal the assembly of β-hairpin into a hairpin stack and the hydration of the assembled structure with atomic resolution.

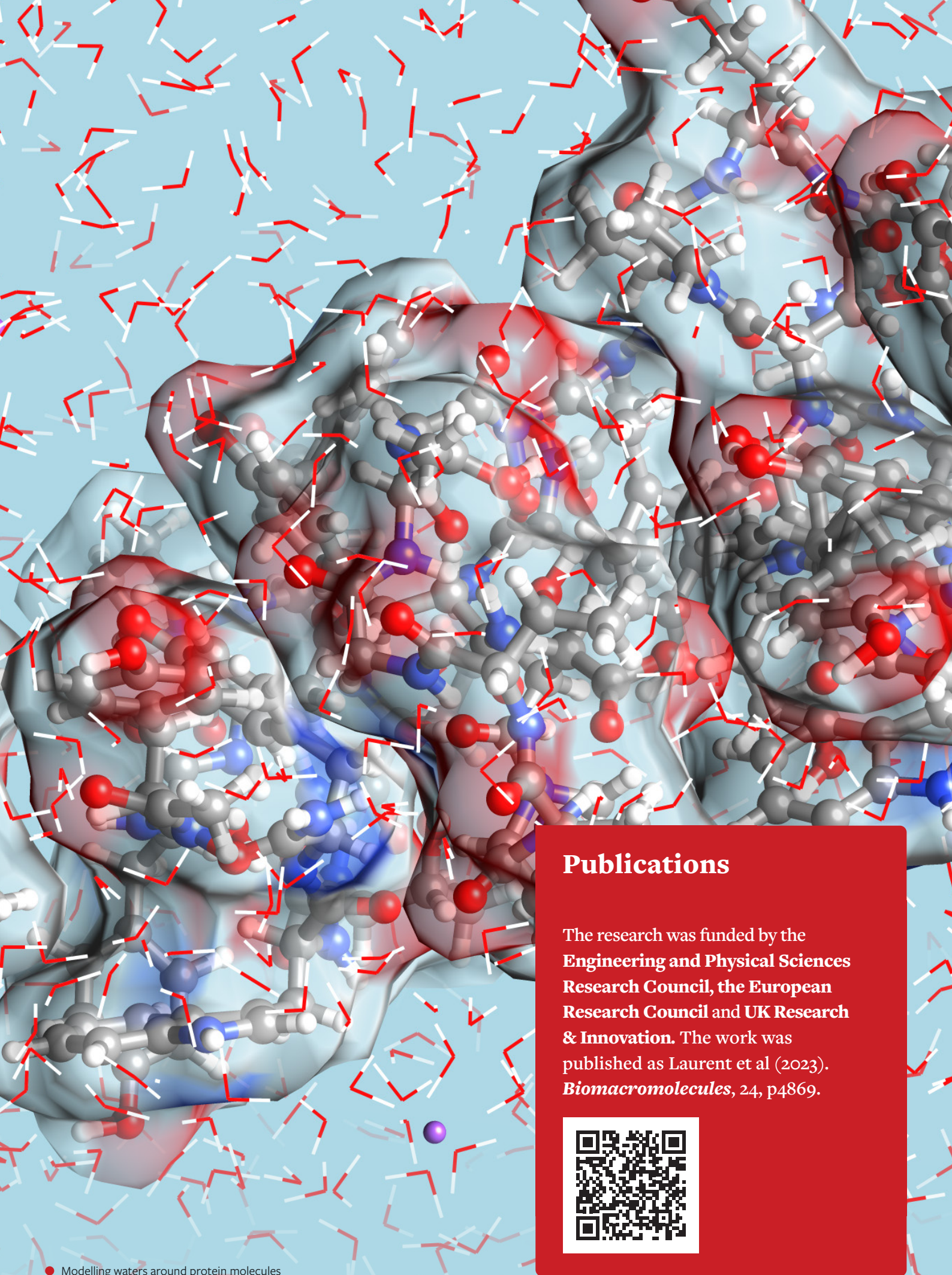
Dr Harrison Laurent, first author of the study and winner of the 2023 Don McKenzie Paul national thesis prize for his neutron scattering PhD research said "This study, requiring expertise from both the Astbury Centre and ISIS facility, lays the groundwork for complex biomolecular interactions in solution to be studied with higher resolution than ever before".

Professor Lorna Dougan, principal investigator of the study said "We have integrated neutron scattering and modelling to develop a structural refinement data analysis workflow that will have a major impact on the study of biomolecules for biosciences and healthcare and support the Astbury Centre's strength in structural molecular biology".

Dr Thomas Headen, instrument scientist at the ISIS facility, said "By combining multiple experimental and simulation techniques, this study has really pushed the boundaries of the length scales we can access, and importantly, reliably interpret, for an improved understanding of biomolecules".



Harrison Laurent (left) and Matt Hughes at the ISIS neutron source



Publications

The research was funded by the **Engineering and Physical Sciences Research Council, the European Research Council** and **UK Research & Innovation.** The work was published as Laurent et al (2023). ***Biomacromolecules***, 24, p4869.

Modelling waters around protein molecules

ASTBURY CENTRE

How do bacteria digest complex glycans?

Dietary fibre contains complex carbohydrates that humans cannot digest, but our gut bacteria use a molecular machine called the Utilisome to do so.

Artistic impression of the utililsome structure, embedded within the bacterial outer membrane

Josh White and Neil Ranson in the ABSL CryoEM Facility

The human gut is home to a diverse microbial community. This includes bacteria that process complex sugars in our diet, which are associated with systemic health benefits.

Scientists already knew that these micro-organisms digest and use glycans that our own digestive systems cannot deal with, generating short chain fatty acids that are important for human health and wellbeing. In 2023, research from the Astbury Centre and the University of Newcastle identified the molecular machine that helps perform this task, which they named the 'Utilisome'.

Professor Neil Ranson, who led the research in the Astbury Centre said "*Long sugar chains need to be chopped up before they can be absorbed, and we were able to describe the structure of the 'protein machine' that binds them, chops them into smaller chunks and then completes the first step in transporting those chunks into the bacterial cell*".

Dr Josh White, was first author of the study, and winner of the 2023 Jordan Radford Prize for the best PhD in the Astbury Centre. Josh said ***"We were lucky to have access to amazing cryoEM facilities that allowed us to show how adding a glycan to purified utilisomes changed their structure – a key step in helping us understand how the machine could work".***

Neil said ***"The research was only possible because of a fantastic collaboration with Professor Bert van den Berg and his team in Newcastle, and because Josh was such a talented PhD student!"***

Funding & Publications

The research was funded by **Wellcome**, and published as **White et al** (2023). **Outer membrane utilisomes mediate glycan uptake in gut Bacteriodetes.** ***Nature***, 618, p583.

In-tissue structural biology of the brain

Dementia, including Alzheimer's Disease, tops the UK's causes of death. Dementia is linked to the accumulation of substances called β-amyloid or tau amyloid in the brain. While new treatments slow Alzheimer's Disease progression, they don't cure it. Understanding these amyloid structures in their natural context is vital.

At the Astbury Centre, Dr René Frank and his team developed methods using cryogenic correlated light and electron microscopy together with cryo-electron tomography to study amyloids within brain tissues. They began by developing methods using mouse models of Alzheimer's Disease, preparing tissues to study protein deposits in their natural state and pinpoint microscopic areas of damage within larger tissue samples.

Dr Conny Leistner was the first author of the study . She said ***"I remember initially thinking this project seemed impossible! We made it thanks to the state-of-the-art facilities and the support of the extraordinary community at Astbury".***

Conny Leistner, former Astbury Centre PhD student and currently staff scientist at Harvard Medical School

Sheena Radford and René Frank

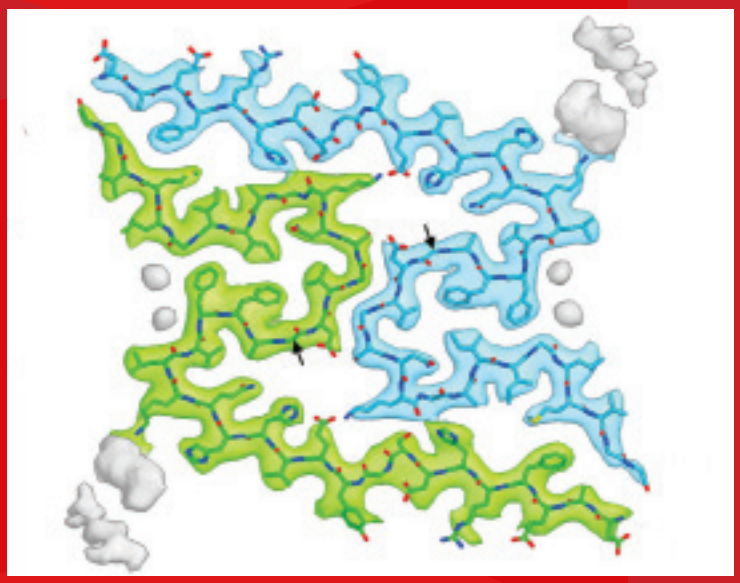
Their technique revealed intricate details of how β-amyloid structures interact with cells and other parts of tissues. They identified various forms of β-amyloid bundles and structures, which could explain why plaques form in specific areas rather than spread throughout the brain. Moreover, they found additional components within these plaques, like droplets and vesicles, absent in healthy tissues. These elements might contribute to the harmful effects or cellular responses related to amyloid accumulation.

This breakthrough is now allowing them to apply these techniques to human brain tissues of deceased Alzheimer's Disease patients.

The goal is to bring in-situ structural biology insights to a broader context, potentially influencing basic biology, disease research, and even patient care decisions.

ASTBURY CENTRE

In-tissue structural biology of the brain



High resolution cryoEM structure of ex vivo purified β-amyloid fibrils

Dr René Frank, a UKRI Future Leader Fellow, was the lead author of this research in the Astbury Centre. René said ***"We are working with international partners, pathologists, and clinicians toward a future in which fundamental, disease research, and perhaps even patient care decisions could be informed by these new methods."***

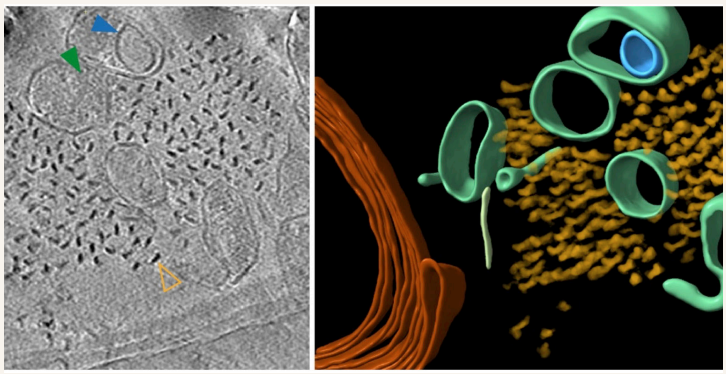
Funding and Publications

The research was supported by the **Academy of Medical Sciences, UK Research & Innovation and the Medical Research Council, Wellcome, The Royal Society and the University of Leeds.**

The work was published as **Leistner et al (2023). The in-tissue molecular architechture of β-amyloid in the mammalian brain. *Nature Communications*, 14, 2833.**

The Cheney Accelerator and PhD scholarships

The largest philanthropic gift in University of Leeds' history will empower Astbury researchers to understand the structure and behaviour of biological macromolecules inside healthy and diseased cells and tissues.



Cryo-tomography of amyloid fibrils in post-mortem human brain

Peter and Susan Cheney

Until very recently, structural molecular biology has been dominated by studies on purified proteins and the complexes they make. However, recent advances mean that we are now able to study structure and function inside cells and tissues. **This new discovery science is called 'in situ structural biology'**, and is driven by state-of-the-art imaging, focused ion beam thinning of specimens, and cryo-electron microscopy/tomography.

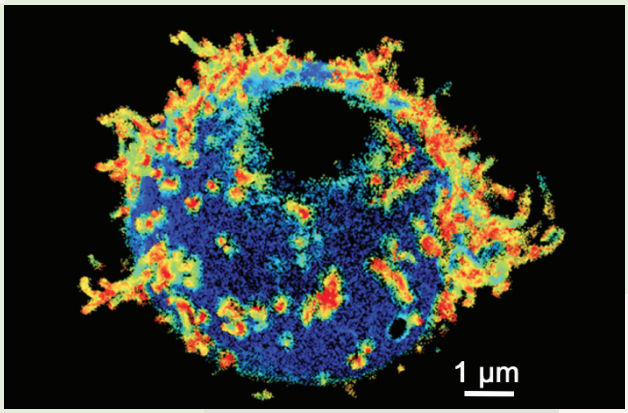
The Cheneys' gift, together with support from BBSRC and the University of Leeds, has brought the latest plasma focused ion beam microscope to Astbury in 2024. This will be supported by fantastic facilities across campus, including mass spectrometry, biomolecular NMR, light microscopy, atomic force microscopy and much more.

> ***"The ultimate prize is to better understand biology, and discover more effective, targeted medicines with fewer side effects that can transform human health and well-being."***
>
> **Professor Francesco Del Galdo**
> Consultant Rheumatologist and Professor of Experimental Medicine

As well as outstanding infrastructure, the Cheney's gift will establish the Cheney Biomedical Accelerator, which will create a state-of-the-art hub for biomedical discovery science. The Accelerator will bring together researchers from the Astbury Centre and the Leeds Biomedical Research Centre to understand how changes in protein structure *in situ* lead to dysregulation and disease, and to discover ways to treat such diseases to the benefit of patients.

Finally, we are thrilled to be founding a new Cheney 4-year PhD Scholarship programme, that will train up to 25 PhD students over the next 5 years to exploit these new developments, across a broad range of research areas.

> ***"We provide a vibrant, interdisciplinary environment, that extends from the physical sciences to clinical medicine, and an outstanding research culture, where PhD students can develop their skills and flourish."***
>
> **Professor Michelle Peckham**
> Director of the Cheney PhD Scholarship Programme.



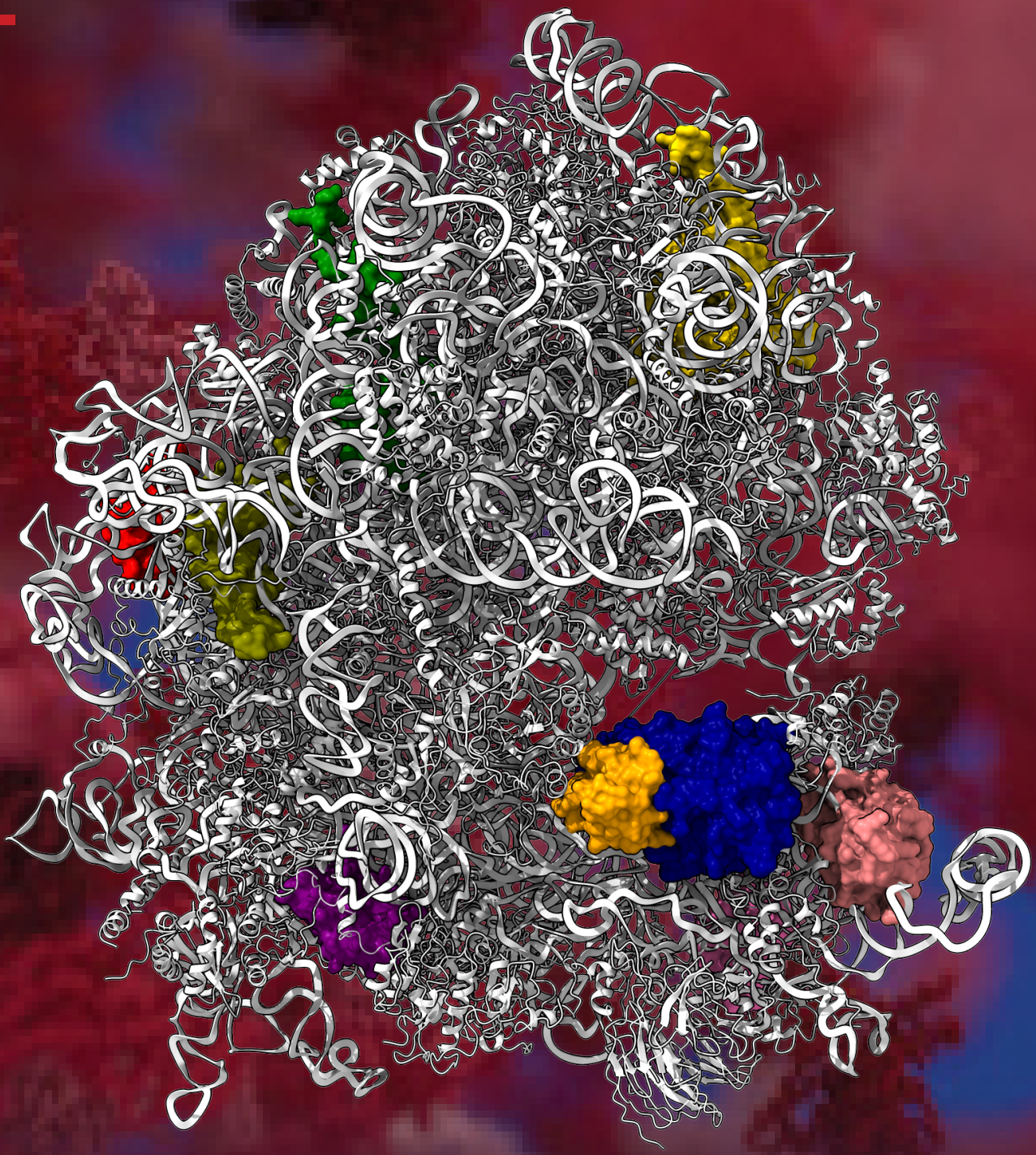
T-cell membrane imaged using 3D super-resolution fluorescence microscopy

Our investment

A generous gift of £11 million by Peter & Susan Cheney has made the Accelerator possible. A FIB microscope arrived in summer 2024, and is being bought with an additional £1 million grant from the BBSRC, and £300k from the University of Leeds.

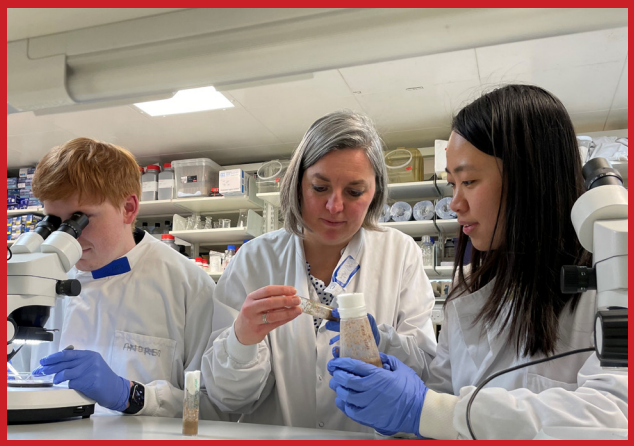
ASTBURY CENTRE

RiboCode: Unlocking the secrets of specialised ribosomes



The 3D structure of a specialised ribosome

Ribosomes are the cellular machines that produce the proteins our body needs to function. Protein synthesis is critical to early development and errors in this process result in a variety of human diseases, including cancer. Ribosomes function by following instructions encoded in our genes. Previously, we believed all ribosomes were the same, but recent discoveries have shown that this is not the case. These 'specialised ribosomes' are able to decode specific genes.



(Left to right): Karl Norris, Julie Aspden and Nan Zhao

Senior research technician Tayah Hopes working on the project said "We have discovered different groups of ribosomes exist in different tissues, but we currently know very little about how these 'specialised ribosomes' target specific genes".

Post-doctoral researcher Dr Karl Norris said "We discovered that different groups of ribosomes in fruit fly gonads are a consequence of incorporating variants of specific ribosomal proteins". The team also found that viruses manipulate ribosomes to facilitate making their own proteins.

Dr Julie Aspden who is leading the team said "We are bringing together a brilliant interdisciplinary team from Leeds (Astbury, LeedsOmics and Bragg Centres), and the Universities of Nottingham and Sheffield to discover how 'specialised ribosomes' seek out their target genes. We hope the research will lead to potential benefits in healthcare, agriculture and biotechnology".

Funding

This work is funded by a 5-year BBSRC Strategic Longer and Larger (sLOLA) award totalling £5.7m to Aspden et al.

Translating Discovery Research into Treatments for Heart Disease

Increasing occurrences of diabetes, high blood pressure, stroke, and heart disease globally mean that there is an urgent need for effective treatments. Researchers at Leeds are working to understand how our body's calcium signals contribute to these conditions.

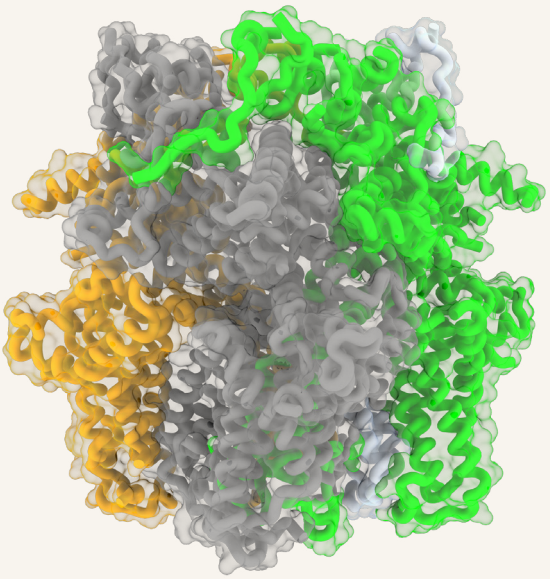
This research, with support from research partners in Germany, the Lead Discovery Center in Dortmund, the Max Planck Society and Prof. Marc Freichel (Heidelberg University), led to the inception of a the pharmaceutical start-up company CalTIC GmbH. CalTIC aims to develop novel medications through targeting less-explored TRPC calcium channels.

Astbury researcher Dr Robin Bon said "CalTIC would not have been possible without a brilliant team of researchers, originating from 9 different countries in Europe and South America, with expertise spanning medicinal chemistry, ion channel pharmacology and physiology, high-throughput assay development, cryo-electron microscopy and drug discovery".

Professor David Beech in the School of Medicine, who led the research at Leeds, said "These channels may contribute to heart failure, high blood pressure, cardiovascular inflammation, cardiovascular complications of diabetes and obesity. We are very pleased to have received substantial initial investment of €3 million from Former Astbury researcher Dr Clara Herrera-Arozamena (now a Life Science Consultant), said "As a postdoc at the Astbury Centre in 2020-2022, I enjoyed working on the CalTIC project

because of the highly collaborative environment. The synergy between disciplines enabled us to swiftly progress towards the development of new compounds. The work also provided me with insights into the foundational aspects of startups and the dynamics involving investors, providing a different point of view from academia".

CalTIC



Cryo-electron microscopy structure of the human TRPC5 channel. The four TRPC5 subunits are displayed in different colours.

The CalTIC Team. From left to right: James Gibbons, Robin Bon, Olekssandr Povstyan, Richard Foster, Klaus Dinkel, Tim Bergbrede, Sebastian Porav, Gregory Parsonage, Clara Herrera Arozamena and David Beech.

The Astbury Community

At the heart of the Astbury Centre is the community, which spans a diverse range of career stages, backgrounds and scientific interests creating a vibrant and inclusive environment. To maximise the potential of our community we run a range of activities to bring people together, discuss science and listen to world leaders invited to speak at our international seminar series. Our annual research retreat attracts ~160 members of the Astbury community where Centre members focus on their science in an informal and fun atmosphere. The event involves talks, posters and plenty of social activities.

Astbury Centre members at the research retreat

A flagship within our scientific programme is the biennial Astbury Conversation, which this year attracted ~300 participants from across the globe, including Japan, Pakistan, Israel, China, USA, Germany and Sweden. This international 2-day research symposium and public engagement event built around the theme of illuminating life and featured talks ranging from molecular biology, microscopy, chemical biology to biophysics. In 2024 this was centred around the plenary speaker Prof Xiaowei Zhuang from Harvard University who gave a scientific talk and a public lecture that was open to all and included students on the University's "Reach for Excellence" scheme. We look forward to seeing the Astbury Conversation grow and develop when it returns in 2026.

Beyond research, the Centre maintains a diverse social calendar, led by the Astbury Society, that fosters networking, innovation and participation, whilst giving back to the local community by fundraising for local charities.

Activities include coffee mornings, an Astbury Summer Ball and festive quizzes. Our biennial lecture is followed by a summer BBQ and our traditional sports day, with a range of activities to test the fine motor skills and bean bag carrying ability of the Astbury community!

Astbury Christmas Quiz

Posters at the Astbury Conversation

Our funders

We rely on the generous support of many funders, who underpin every aspect of the Centre's research. Members of the Astbury Centre have £80.5M in live grant funding (with a total value of £125.4M to the University of Leeds).

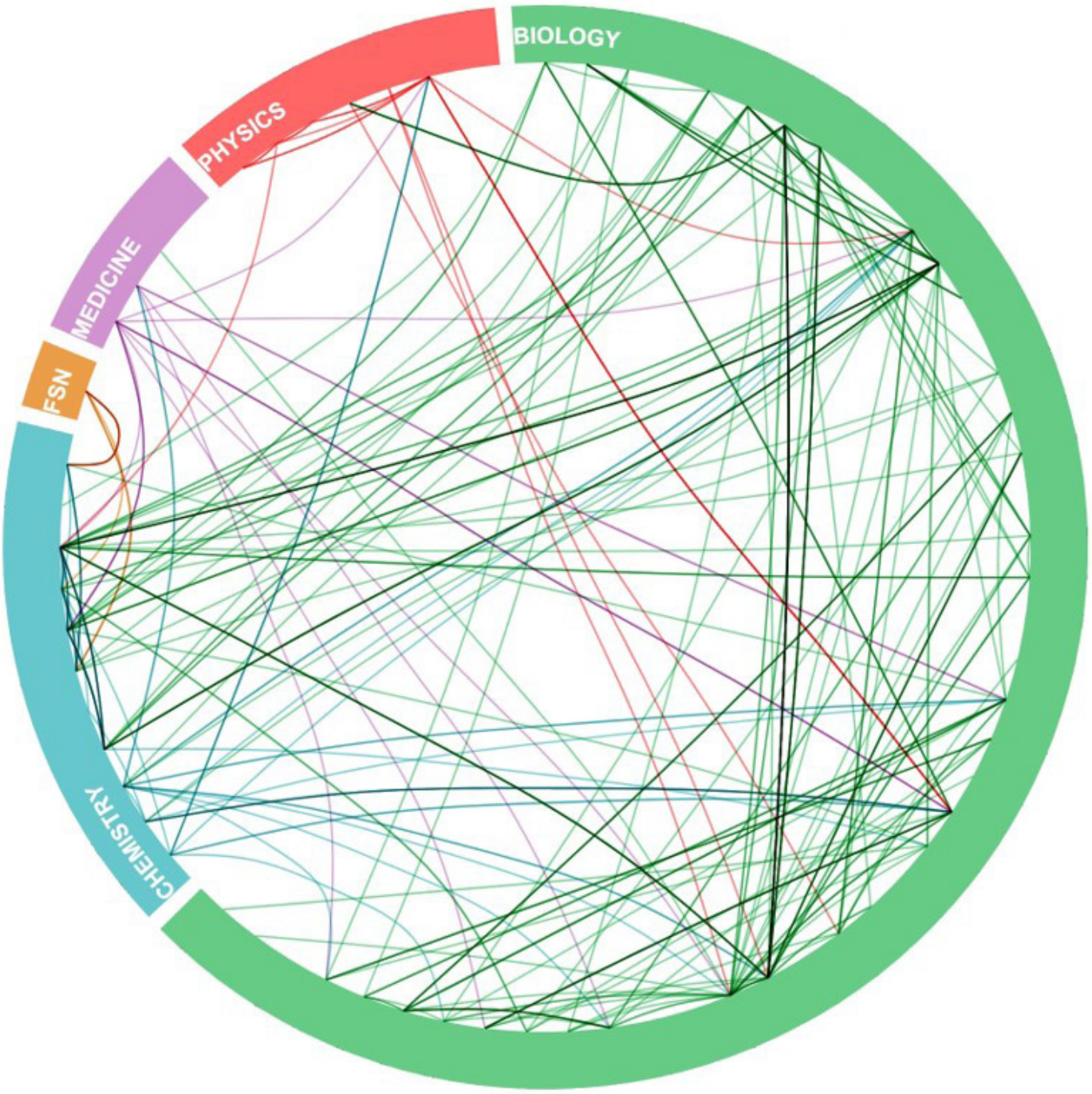


Diagram illustrates just how interdisciplinary our science is, showing how Centre members secure funding together.

Our funding and publications

Grant successes

In 2022 & 2023, Centre members secured around £31m of new awards.

Some major award highlights include:

Julie Aspden, Juan Fontana, Adrian Whitehouse and Anton Calabrese's BBSRC sLoLa: RiboCode - Unlocking the secrets of specialised ribosomes across eukaryotes - £5.7m

Niluka Goonawardane's Wellcome Career Development Award: Revealing the viral and cellular determinants of disease outcome in tick-borne encephalitis virus infection - £1.38m

Neil Ranson and Sheena Radford's MRC grant: Breaking the Barrier: Mapping protein interactions in the bacterial outer membrane as targets for new antimicrobials - £2.19m

Lorna Dougan's European Research Council Consolidator Fellowship: MESONET: Exploiting in situ protein unfolding to understand and control mesoscopic network formation - £1.79m

Peter Stockley's Wellcome Investigator Award in Science: Unmasking the evolutionarily conserved mechanisms within viral pathogens - £1.35m

George Heath's EPSRC Fellowship: High Resolution Imaging Using Transient Binders - £1.22m

Neil Ranson (PI), Sheena Radford, Juan Fontana, Adrian Whitehouse, Yoselin Benitez-Alfonso, Rene Frank, John Barr & Takashi Ochi's BBSRC Alert grant: A plasma focused ion beam microscope for Structural Cell Biology at the Astbury Biostructure Laboratory - £1m

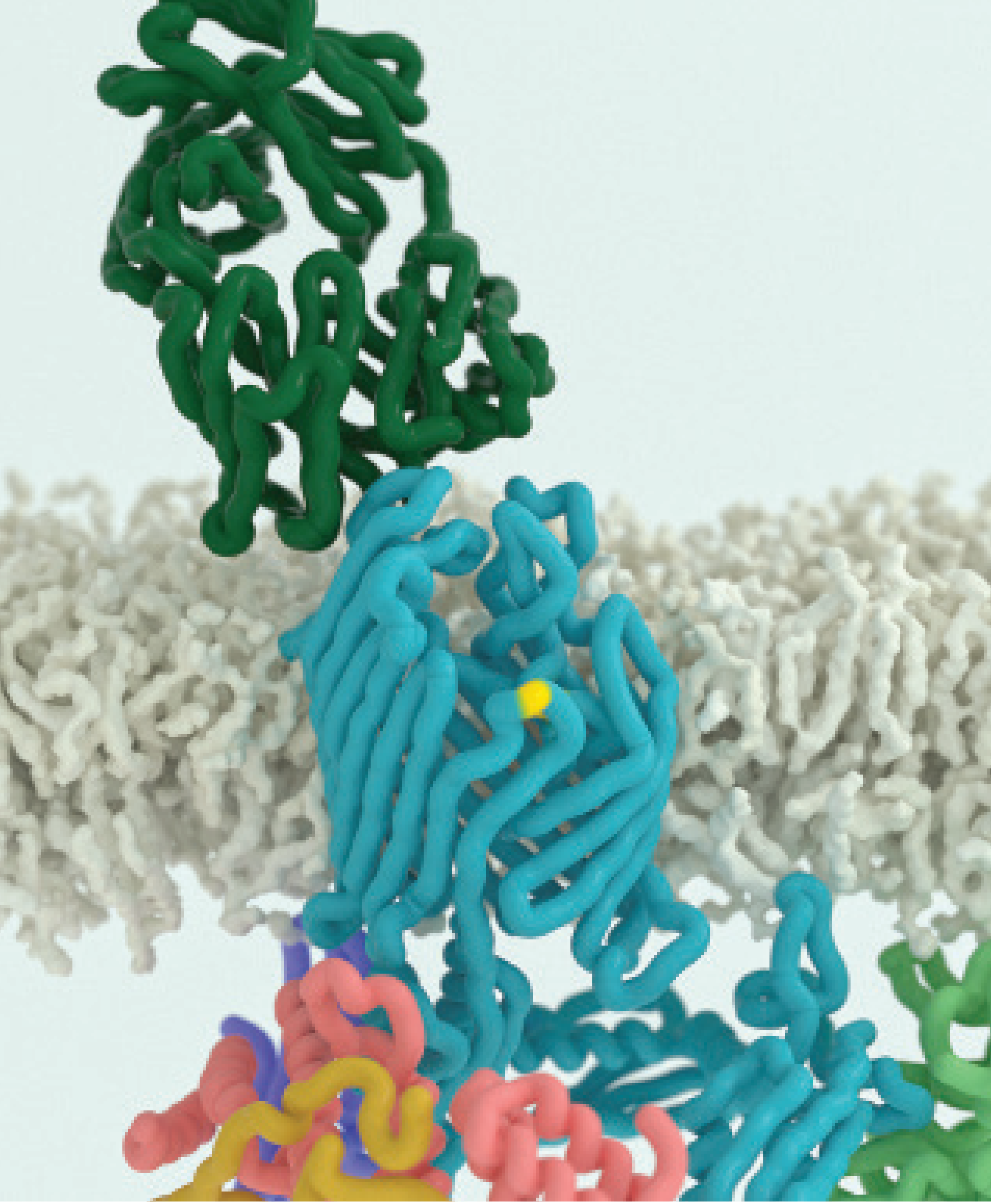
● Funding sources for new grants in 2022 & 2023

Astbury members at a PI Away Day

Publications

The centre published **545** peer-reviewed publications in **2022-2023** – with some popular destinations including:

- ***Nature Communications*** 20
- ***Biophys J.*** 14
- ***Journal of General Virology*** 8
- ***Angewandte Chemie*** 5
- ***ACS Nano*** 3
- ***Science Advances*** 3
- ***Nature Chemistry*** 2
- ***Molecular Cell*** 2
- ***Cell*** 1
- ***Nature*** 1



The Astbury Centre for Structural Molecular Biology

UNIVERSITY OF LEEDS