The Rosalind Franklin Institute

Case Studies and Strategic Report 2021-2022

Contents

The Rosalind Franklin Institute has had a fantastically productive first year in our Hub building; these case studies serve to highlight some of that work. The following case studies were selected as examples of great work in their own right, and also exemplify our company values. These values are Novelty, Adventure, Engagement, and Utility.

Adventure

Our projects, by their nature, carry significant risk, combined with significant pay-off in scientific, economic, and patient benefits if successful. Risk is mitigated by engaging experts from across disciplines and working together to approach large challenges.

Novelty

Our technologies will be novel in their application and design, offering tools to the academic and industrial communities which enable significant new research potential and economic benefit.

Engagement

Our projects are not conceived of or delivered by one organisation alone, they engage multiple partners across academia and industry. There is demonstrable support for their development and the Franklin by these communities and the wider public.

Utility

Our technologies will be sought after by both academic and industrial communities, and access will be opened to as wide as possible, ensuring that the research benefits are maximised.

> “We attract people who want to push beyond what is currently possible, who are prepared to tackle the most challenging and high-risk research”.
>
> Professor James Naismith

Driving technological leaps for healthcare

As Phase 1 of The Rosalind Franklin Institute comes to a close, the Director Professor James Naismith reflects on what has been achieved in the years since its formation and offers a glimpse into plans for the next phase.

‘Since 2018, we’ve built the building, staffed it, installed beyond state-of-the-art instrumentation — which we are helping to develop — and published some of the world’s most cited papers,’ Professor Naismith says.

During Phase 1, the Institute secured over £40 million in funding from industry and peer-reviewed grant funding bodies, and delivered ground-breaking science, including neutralising nanobodies, light-driven protein editing in cells and diagnostic technologies, despite the disruption caused by the Covid-19 pandemic.

Research carried out during the pandemic has made huge contributions to the fight against Covid-19. In July 2020, the discovery that a unique type of antibody produced by llamas could provide an effective treatment against the virus made headlines around the world. Since then, researchers at the Institute have shown that a cocktail of llama-based, SARS-CoV-2 specific nanobodies that can be delivered intranasally has potent prophylactic and therapeutic efficacy in animals. Furthermore, they have developed an ambient mass spectrometry assay that can detect the presence of the virus in seconds, without the need for expensive primers or reagents.

‘In Phase 2 we really want to push forward our molecular pathology goals by driving factor-of-ten breakthroughs and in doing so, accelerate the development of novel diagnostic and therapeutic products,’ Professor Naismith explains.

Rather than pursue incremental research, The Rosalind Franklin Institute was set up harness disruptive technologies that can transform our understanding of disease. In Phase 2, Professor Naismith expects the Institute’s five scientific themes: artificial intelligence and informatics; biological mass spectrometry; correlated imaging; next generation chemistry; and structural biology to bear on a range of urgent healthcare problems such as neurodegenerative disease to antimicrobial resistance.

Turning the clock back on disease

Most complex diseases are treated when signs and symptoms manifest, which for many is quite late. Better diagnostics and new cures will require spotting the earliest stages of disease and its molecular drivers. Researchers at The Rosalind Franklin Institute are advancing and integrating technologies to shift the dial on a major challenge: infection and inflammation.

The growing threat of viruses with pandemic potential, spread of parasitic tropical diseases due to global warming and emergence of drug-resistant microorganisms underscore the need for rapidly deployable and effective technologies to detect and eliminate them. In addition, further understanding the human body’s inflammatory response will not only aid the treatment of infectious diseases but also of many chronic diseases, cancer and ageing-associated conditions that involve inflammation.

‘Genomics gives us a starting point, but it is how proteins interact with one another that is really going to provide useful insights; and by useful, I mean that will influence patient outcomes,’ Professor Naismith says.

Importantly, because the technologies that are being developed are broadly applicable, there is no limit to the scope of biology that can be probed.

Pushing frontiers in life science research technologies

During Phase 2, researchers at The Rosalind Franklin Institute will be working with partners MRC Laboratory of Molecular Biology (MRC LMB) and Diamond Light Source, to deliver the Wellcome-funded project ‘Electrifying life science’. They will develop hardware and software for three new electron imaging technologies that will revolutionise cell biology by allowing a more diverse range of researchers to watch proteins working inside cells at atomic resolution.

Leveraging the Institute’s leadership on in vivo chemical editing of proteins, the Institute plans to build the UK’s first research cyclotron facility for exploring new methods for labelling protein complexes in animal and human tissues that can be used for clinical imaging.

In addition, by developing methods to grow previously unculturable bacteria, researchers at the Institute will be able to tap into what until now was inaccessible microbial ‘dark matter’ to discover new natural products with drug-like properties.

Further plans to extend the Institute’s mass spectrometry capabilities will enable us to resolve the molecular structure of a greater range of molecular species, with greater sensitivity and 30-50 times faster.

The Franklin will also be expanding its research into nanobodies, by developing workflows to rapidly enhance their specificity and potency, with the aim of producing first line therapeutics that neutralise a novel respiratory virus within 12 weeks. To achieve this goal and improve the UK’s future pandemic preparedness, high level containment facilities will be required.

Opportunities for automation and using artificial intelligence and machine learning methods will be seized across the Institute’s entire research portfolio to efficiently speed up data gathering and analyses.

‘Phase 2 will pull everything we are doing to overcome key technological roadblocks together to unpick the biological mechanisms underlying disease and tackle the most pressing health research challenges,’ says Professor Naismith.

A national focal point for transformative change

Staff and colleagues at collaborating organisations in academia and industry are key to the Institute’s success. ‘We attract people who want to push beyond what is currently possible, who are prepared to tackle the most challenging and high-risk research,’ Professor Naismith says.

The Institute currently employs 75 researchers and collaborates with over 46 universities and 20 companies. It also offers placements for industry, training on advanced techniques, and studentships in collaboration with university partners. The Rosalind Franklin PhD student training programme that started in 2021 is enhancing the UK skills base, fostering a generation of interdisciplinary researchers skilled to work at the forefront of physical science applied to biomedicine.

‘As a high-risk technologically-focussed institute for biomedical sciences, the Rosalind Franklin Institute has a unique role in the UK’s research ecosystem,’ says Naismith. ‘Our Phase 2 plans will enable the UK to become a global leader in imaging life at molecular detail,’ he adds.

ADVENTURE

Launch of the Franklin PhD programme provides ‘unique’ training and development opportunities for early-career scientists

> “This PhD programme is genuinely ground-breaking and unique”.
> Professor Julien Michel, University of Edinburgh

Twenty PhD students are benefiting from access to the Franklin’s world-leading technologies and researchers as part of our innovative doctoral training programme.

The first cohort of ten students joined the Franklin in October 2021, embarking on research projects spanning topics as diverse as stem cell models of neurodegenerative disease, antiviral defence in bacteria, improving the resolution of cryo-EM ptychography, and chromatin reprogramming.

Funded initially for three cohorts by UKRI-EPSRC, the rolling four-year programme combines exciting research with high-quality scientific training and operates in partnership with universities around the UK.

‘This PhD programme is genuinely ground-breaking and unique,’ says Professor Julien Michel from the School of Chemistry at the University of Edinburgh, the Franklin’s primary university partner for the programme.

‘The idea behind it is that you’ve got this fantastic building, cutting-edge equipment, leading scientists – it would be a great environment for training doctoral students. And it made sense to partner with a university because you need that not only to provide the academic accreditation but also for the prior experience and skills of running successful PhD programmes. That required a lot of careful planning and discussion though as it’s such an unusual model.’

For the first three months of the Franklin’s PhD programme, students receive training in key areas including intellectual property, statistics, research ethics, EDI awareness, and critical analysis of scientific literature. That’s alongside rotational immersion in each of the Franklin’s five scientific themes: artificial intelligence and informatics; biological mass spectrometry; correlated imaging; next generation chemistry; and structural biology. During this initial period, participants are affiliated with the University of Edinburgh.

Students then carry out a short research project aimed at shaping their full PhD proposals for the three years ahead. At that point, students’ academic affiliation transfers to the home institution of their external supervisor. They also have at least one supervisor at the Franklin, where they will be based for the vast majority of their PhD.

‘The portfolio of projects available to students to choose from is very rich,’ says Professor Michel, ‘as is the range of experts they can work with. That would be hard to find anywhere else in the UK, and we hope this depth of training and opportunity will help our graduates go on to achieve great things. The Franklin’s ambition is to break barriers between disciplines – that’s certainly something that students on the PhD programme can benefit from.’

Lindsey Spriggs, the Franklin’s Early Careers Lead, says: ‘Our students have the opportunity to be part of exciting, impactful research. And the nature of the programme means we’re hopefully developing students who have a real dynamism and the agility to work across different disciplines, which will stand them in good stead for their future careers. The cohort system is also really valuable, giving the students a community around them and a sense of solidarity.’

It’s this combination of features – the immersion in different scientific themes, the cohort system, the crossdisciplinarity, the network of university partners – that makes the Franklin’s PhD offering unique.

Professor Michel says: ‘The programme is aiming to do something really ambitious: to accelerate the development of scientists through training and by enabling them to plan their own research projects, so that they will be more advanced in their thinking and approach than you would expect from people so early in their careers.’

Lindsey adds: ‘At end of the initial training and rotation period the idea is that participants will have an understanding of the different project options, how they could be developed, and who they might be able to develop them with at the Franklin. They can take that kernel of a project idea and put their own stamp on it. That’s quite unusual for science PhDs.’

By the time the third cohort starts in October 2023, there are expected to be around 30 PhD students based at the Franklin, at various stages of development. Early feedback from participants in the first cohort suggests they value, in particular, the variety of the themed rotation and the sense of community brought about by being part of a group.

Lindsey says: ‘We’re continuously trying to improve the experience for future cohorts based on feedback from our current students, who have been fantastic to work with. For example, in the coming year we’ll reduce the individual rotation periods from two weeks to one week, freeing up time for other aspects of the training. It’s really important to me to make sure the programme functions like a well-oiled machine, that expectations match the delivery, and that students feel a connection both to the Franklin and to their university.’

Professor Michel adds: ‘It’s important to acknowledge that introducing a new, innovative way of doing things does bring its challenges. But I think this model, which is reinventing the way universities and independent research institutions work together on doctoral training, is going to prove very successful.’

Discovery of new Covid infection mechanism offers clue to SARS-CoV-2 leap to humans

One of the best-known aspects of the Covid-19 pandemic is that the virus 'jumped' into people from animals – perhaps bats or pangolins – in a process known as zoonotic transfer.

What hasn't been clear to scientists is exactly how, from a mechanistic point of view, the virus moved between animal and human cells as part of that initial leap – and what tricks it might have used in its journey.

An international team led by scientists at the Rosalind Franklin Institute demonstrated that, despite prior uncertainty, SARS-CoV-2's spike protein can latch on to sugars known as sialic acids found on the surface of human host cells. That's in addition to the ACE2 protein that has long been known to attach to the receptor-binding domains (RBDs) that sit atop SARS-CoV-2's crown-like spikes.

Professor Ben Davis of the Rosalind Franklin Institute, one of the study's senior authors, says: 'Two of the ongoing mysteries of the coronavirus pandemic are the full mechanisms behind viral transmission and the origins of the zoonotic leap. While it's well known that the combination of RBD in the spike and ACE2 protein on the human host cell surface gives the virus one of its footholds, that always seemed unlikely to be enough to give it the flexibility it needs to control fully how it enters and then exits our cells to carry on infecting.

'In influenza, it's been known for a long time that the virus grabs hold of a sugar on the surface of human host cells called sialic acid, and then uses that as a way of getting into the cell. Flu treatments such as Relenza stop the virus from getting back out of the cell by inhibiting a particular enzyme and ensuring it gets stuck at the surface. Coronaviruses don't have an equivalent enzyme, but nevertheless it's been suggested that they might still use sugars as an early attachment point to grab hold of and get into human host cells. This therefore means that as viruses they may have to tread a much finer line when it comes to the balance of getting in and out of the cell.'

The team set out to investigate this by using nuclear magnetic resonance (NMR) spectroscopy and magnetization transfer techniques available at the Franklin. When it became clear that quantifying the complex sugar-pathogen interactions would not be possible with traditional versions of these techniques, the researchers developed a new, more sophisticated method, which they have called universal saturation transfer analysis (uSTA).

Study team member Ben Gaunt, a researcher in the Franklin's PhD programme, explains: 'Using traditional saturation transfer difference, which is an NMR spectroscopy technique, we were able to see that the sialic acid ligand was interacting with the SARS-CoV-2 spike protein, but not *how* it was interacting. We teamed up with our colleagues Professor Andrew Baldwin and Charles Buchanan in Oxford, who have been developing an algorithm for analysing the signal 'peaks' in mass spectrometry readouts of binding interactions, and combined this with complex mathematics – a modified version of what are called the Bloch-McConnell equations – to revamp the saturation transfer method.

'We've called the technique uSTA because it provides a potentially universal way of using saturation transfer analysis to quantify with much greater accuracy the binding interactions between protein and ligand, including structural and kinetic features. It's the first time this has been done in such complex systems, which is hugely exciting.'

Professor James Naismith, Director of the Rosalind Franklin Institute, adds: 'This new technique can now be used by scientists to shed light on other viral structures and answer extremely detailed questions. The work is an example of the unique technologies the Rosalind Franklin Institute was set up to develop.'

Using uSTA and extremely precise high-resolution imaging, the research team showed that the SARS-CoV-2 spike binds to sialic acid in key representative sugars and, unexpectedly, that the binding takes place in a part of the spike protein called the N-terminal domain. The results were confirmed using cryo-electron microscopy.

Professor Davis says: 'What's really interesting is that the N-terminal domain is the location for lots of the mutations that take place in the spike protein as the virus evolves rapidly. Sugar binding may help explain why this is happening.

'And, strangely, it's only the original strain of the virus that exhibits sialic acid binding. The subsequent variants of concern we've seen, such as alpha, beta, delta and omicron, get rid of this mechanism.'

Professor Davis suggests that sugar binding may have been necessary for the initial zoonotic leap into humans from animals, but could then be discarded – particularly if the feature is detrimental to the virus's mission of replication and infection within humans. This so-called 'crypticity' may also be of evolutionary benefit in other ways.

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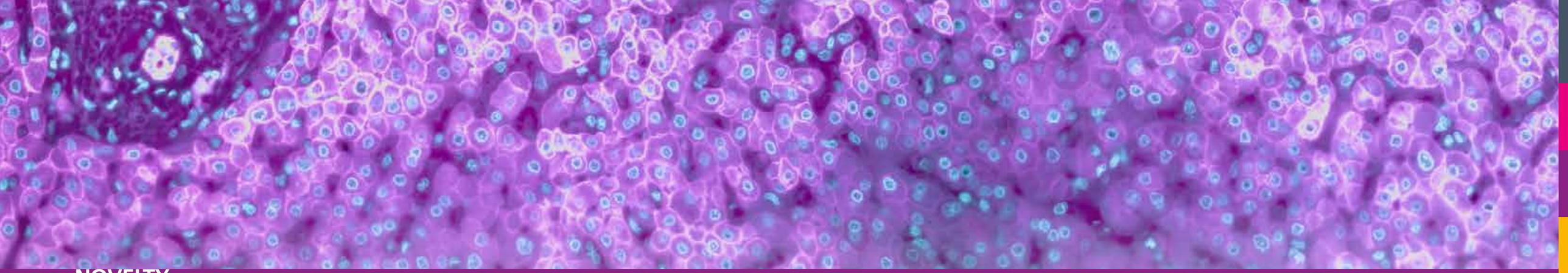

The BioCOP: ‘pushing the boundaries’ of biological imaging across space and time

A first of its kind piece of bespoke imaging technology arrived at the Franklin in April 2022, with the promise of revolutionising the way scientists observe living human cells.

The Biophotonic Correlative Optical Platform (BioCOP) allows researchers to study biological systems across multiple spatial and time scales simultaneously – at unprecedented resolution and sensitivity.

Once fully operational, The BioCOP will generate vital, detailed insights into human health and disease that were previously unattainable. The platform will tackle pressing research questions in human biology ranging from the structure of brain cells to the way our immune systems respond to threats from viruses or cancers.

The BioCOP is a partnership between the Franklin and the Kennedy Institute of Rheumatology at the University of Oxford, where the technology was housed during its design and assembly phases. The project sits within the Franklin’s Correlated Imaging theme, which aims to deepen our understanding of biological systems and processes by enabling information from multiple imaging techniques to be collected simultaneously. While the ‘correlation’ of data from different instruments is well established in fields such as astronomy, the concept has huge untapped potential in the life sciences.

According to project lead Professor Marco Fritzsche, an associate professor at the Kennedy and research fellow at the Franklin, the BioCOP will ‘push the boundaries’ of biological imaging.

‘To fully understand the biological processes happening in the human body during times of good health and illness,’ says Professor Fritzsche, ‘we need to be able to observe those processes across multiple space and time scales, in realistic and relevant tissue microenvironments.

‘The BioCOP allows us to do this by bringing together two cutting-edge imaging modalities at the same time. It’s a platform that pushes the boundaries of what we can currently do in biological imaging, and which fits in very neatly with the Franklin’s focus on making big technological leaps forward. The BioCOP will be up to 100 times faster, 100 times more sensitive, and allow ten times higher spatial resolution than previous technology.’

Replacing traditional imaging technologies

Specifically, the BioCOP system allows high-performance co-incidence and correlation imaging over multiple length and time scales, featuring a combination of fast high-throughput three-dimensional Lattice Light Sheet Microscopy (LLSM), super-resolution 3D Structural Illumination Microscopy (SIM), and minimally invasive long-term imaging within microfluidics at extended spatiotemporal resolution.

Quantitative correlative imaging of biological processes has become mission critical in the biomedical sciences. In recent years, state-of-the-art research has repeatedly demonstrated that the understanding of living systems demands technology with the capability of monitoring dynamic processes across a range of space and time scales, dissecting the function of living cells within their tissue microenvironments.

Novel developments such as super-resolution SIM and LLSM are transforming how living single cells and tissues can be studied, creating the expectation that these techniques will replace current imaging technologies such as confocal and widefield microscopy.

The therapeutics of the future

A key aspect of the BioCOP setup involves the creation of ‘organ-on-a-chip’ devices that mimic the environment inside the human body and enable the study of biological material – even down to individual cells – within tiny amounts of fluid. This will allow researchers to uncover the biophysical mechanisms taking place when, for example, immune cells interact with the antigens that provoke an inflammatory response to threats such as external pathogens. This has the potential to inform the diagnostic tools and therapeutics of the future.

Professor Fritzsche, whose Biophysical Immunology Laboratory probes at the interface between biology and physics in the context of the human immune system, highlights the ‘light touch’ nature of the BioCOP system as one of its chief benefits. He says: ‘In conventional imaging – particularly in fluorescence microscopy – the process of illuminating cells with lasers causes a phenomenon called phototoxicity. This can degrade the sample and influence the biology that’s taking place. The BioCOP’s superior speed and sensitivity allows us to carry out experiments much less invasively and destructively than before: we can observe cells over longer periods of time without producing those negative effects on the sample.’

A one-metre-cubed ‘black box’ featuring a complex system of lasers and mirrors, the BioCOP is far removed from the traditional optical microscope design that many of us are familiar with. It will take, Professor Fritzsche estimates, up to two years of optimisation before BioCOP is ready to be used in experimental research.

He adds: ‘We have been very lucky in being able to recruit two excellent postdoctoral researchers, Dr Narain Karedla and Dr Anna Schepers, who will establish the BioCOP at the Franklin.

‘There has been a lot of excitement here about the arrival of the BioCOP and what it can do scientifically. The Franklin is the perfect place for this technology – it will benefit from on-site technical expertise in a range of areas, and there will be lots of opportunities for collaboration with researchers from other disciplines.’

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Dorothy and Franklin: ushering in a new era of cellular tomography

In the second half of 2021, the Rosalind Franklin Institute took delivery of its first Titan Krios cryo-electron microscope, named Dorothy, and the second generation of its plasma focused ion beam (pFIB), named Franklin.

Secured as part of the transformative £25m Electrifying Life Science grant from the Wellcome Trust, these cutting-edge technologies use new sample geometries to enable high-resolution, large-volume cellular tomography for the first time. The technology is being co-developed by scientists and engineers at the Rosalind Franklin Institute, Diamond Light Source, and manufacturers Thermo Fisher Scientific.

Large-volume cellular cryo-tomography – a method of obtaining 3D structures via cryogenic electron microscopy (cryo-EM) – has the potential to revolutionise our understanding of life, enabling us to characterise the structure of proteins at atomic resolution within the cell. Utilising the unique capabilities of these technologies will allow researchers to address more complex biological questions, including deepening our understanding of intracellular bacterial pathogen life cycles. Intracellular bacterial pathogens are becoming increasingly resistant to existing antibiotics, so the ability to observe the bacterial life cycle inside the human cell could be a critical first step in developing new drugs to combat this global threat.

Critical innovations are required for this project to be successful – not only in the design of the instrument, but in the data collection and processing software used. Powerful data processing is needed to manage the volume and type of data produced, so close collaboration with the Franklin's Artificial Intelligence and Informatics theme has proved essential.

Dr Maud Dumoux, the Franklin's technology lead for cryo-imaging, says: 'This project is both challenging and exciting to be a part of – it has the potential to revolutionise how we see the cell. Improving our understanding of this basic building blocks of life could have a profound impact on how we create new drugs and understand how they work.'

Focused ion beam milling, as the name suggests, uses a stream of charged particles to prepare ultra-thin biological samples known as lamellae – a technique imported from materials science. In recent years, instruments using plasma beams of noble gases such as xenon have been developed to enable higher-throughput, higher-volume sample preparation. Used in combination with cryo-EM techniques, pFIB instruments like Franklin can streamline the previously cumbersome process of preparing and imaging small molecules inside the cell.

Dr Dumoux adds: 'Until now, it has been very difficult to study the structure of molecules such as proteins at atomic resolution inside human cells. It involves lots of samples and multiple instruments, and can easily lead to the contamination, damage or loss of samples.

'Our new workflow being developed at the Rosalind Franklin Institute will make this process much quicker and more efficient. By using pFIB to thin down the biological material to the required transparency, we then enable cryo-electron tomography of the internal regions of cells as part of a single pipeline. We have now demonstrated, for the first time, that these techniques can be used in combination for in-situ structural biology within cells – in this case, generating sub-nanometre-resolution data on particles called ribosomes.'

Plans are already in motion for a next-generation Titan Krios microscope – known as Hodgkin – which will be built as a collaboration between Thermo Fisher Scientific and the Rosalind Franklin Institute, and which is scheduled for delivery in 2024. There is already a clear vision for this machine, which will contain a special aberration corrector to allow collection of thicker biological samples. The knowledge gained from first-generation Dorothy will be crucial in informing the design of this beyond-state-of-the-art machine.

Steve Reyntjens, Product Marketing Director for Thermo Fisher Scientific, says: 'Thermo Fisher is a company driven by the needs of scientists. It has been thrilling to work with the Rosalind Franklin Institute because they want to make breakthrough innovations, not just incremental changes – so working to meet their scientific needs has been a real challenge.'

The Electrifying Life Science grant was awarded to the Rosalind Franklin Institute and its partners the MRC Laboratory of Molecular Biology and Diamond Light Source to support the development of electron imaging physical sciences technologies with the capacity to transform how we see life. A globally unique resource for the UK, this suite of technologies will change by a factor of ten the accessibility and capability of cryo-EM in both tomography and single particle sub-fields.

Professor James Naismith, Director of the Rosalind Franklin Institute, adds: 'The delivery of Dorothy in 2021 marked the start of the next stage of this project, and we are all excited to usher in the era of atomic cell biology. This type of high-risk, high-reward multidisciplinary project is what the UK government set up the Rosalind Franklin Institute to do. Electrifying Life Science will be a true factor-of-ten change in our ability to see and understand life, and we are committed to sharing our new advances with the widest community possible.'

> "It has been thrilling to work with the Rosalind Franklin Institute because they want to make breakthrough innovations, not just incremental changes".
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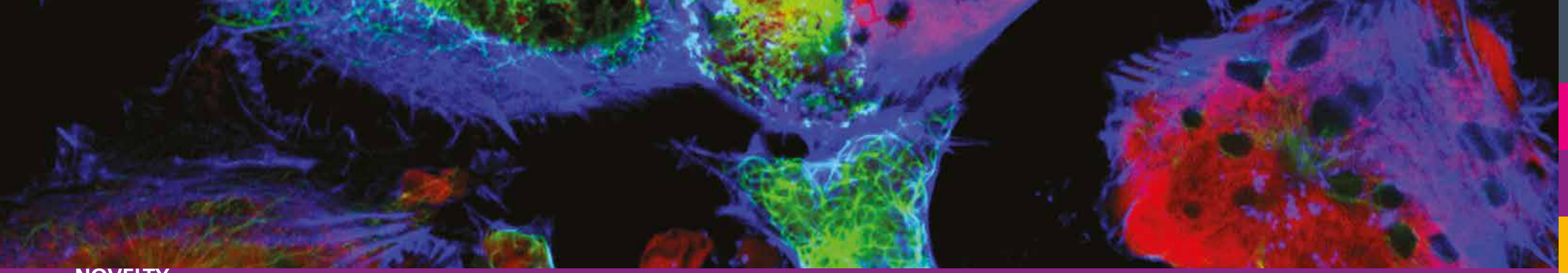


Piecing together a puzzle in protein damage

Working with colleagues in the UK and USA, researchers at the Franklin have helped solve a 20-year-old mystery surrounding an 'orphan' family of proteins called LanCLs.

As we age, and when certain pathogens attack us, marks are left on the proteins in our bodies. The international team found that key enzymes called kinases – vital to many signalling and regulatory functions within mammals – become more active rather than less active when damaged by this process. This suggests that cell signalling could be altered or disrupted by ageing or pathogen attack, adding to our understanding of this area.

The scientists also discovered through this work that LanCLs are capable of 'trapping' and removing such damaged kinases. Thanks to this research, failure to remove these damaged kinases by LanCLs is now thought to threaten the survival of the organism, as knock-out gene experiments suggest there is a high mortality in mice that do not possess these proteins.

LanCLs are found in nearly all living organisms, but their function was previously unknown.

Forming a picture

One of the most curious forms of protein damage is the creation of a carbon-carbon double bond, a process known to chemists as an 'elimination' reaction. Although some of our damaged proteins are eventually remade and replaced, some are not (or may be replaced only slowly) and may function incorrectly when damaged. For many years the consequences of this 'elimination reaction' damage and how cells respond have been unclear.

Enzymes known as LanC proteins were first identified in bacteria. Similar proteins – called LanC-like or LanCL – have since been found in many organisms and are thought to be ubiquitous within animal cells.

Researchers at the Nair lab in the Department of Biochemistry at the University of Illinois had previously solved the structure of one of these LanC-containing proteins in bacteria, noticing that the protein was bound to a kinase.

This discovery led the Illinois team to explore whether LanCL proteins could also bind to kinases, even in mammalian cells. 'We saw that they were able to bind to many kinases, including AKT and mTOR, and all of a sudden the pieces of the puzzle started forming a picture,' says Professor Wilfred van der Donk, a professor of chemistry and investigator at the Howard Hughes Medical Institute, University of Illinois.

Meanwhile, Professor Ben Davis, Next Generation Chemistry lead at the Franklin and a professor of chemistry at Oxford University, worked with Professor Graham Hutchings of the UK Catalysis Hub to show that a specific type of damage in kinases could cause them to become activated. Scientists had previously assumed that such damaged proteins would be inactive.

> "Coming together with our collective findings, and using our shared tools in protein function to help solve this mystery, has been a wonderful – and fun – example of international collaboration".
>
> Professor Ben Davis

Identifying possible targets

The Franklin and Illinois researchers were subsequently able to show that LanCL performs a reaction that traps this damage by adding a small molecule called glutathione. 'We realised that when the LanCL proteins are absent, the cell has a big problem because there are active proteins floating around that need to be turned off,' says Professor van der Donk.

Professor Davis adds: 'We had been working on kinases separately to the US team and saw that when we precisely modified these proteins to explore the effect of this mode of damage, they showed some really unusual activity, becoming more active rather than less. This was also affected by then 'trapping' this damage. The news that the Illinois team had protein with apparently no function but with binding pockets that might do the same thing was one of those beautiful 'bing!' moments in science. Coming together with our collective findings, and using our shared tools in protein function to help solve this mystery, has been a wonderful – and fun – example of international collaboration. Our next steps to explore this chemistry and control this damage 'in vivo' are intriguing.'

The researchers are interested in understanding the role of these proteins and making a complete list of all the possible targets of LanCLs. 'When you have abnormal kinases, it can cause all kinds of problems, including cancer,' says Professor Jie Chen, a professor of cell and developmental biology at the University of Illinois. 'LanCL proteins eliminate these damaged kinases, and it is possible that they also affect other proteins that we are not aware of. We need to connect their cellular functions to the results we saw in the mice.'

The research, published in the journal Cell, was funded by the Howard Hughes Medical Institute, the National Institutes of Health, the Biotechnology and Biological Sciences Research Council with AstraZeneca, the Engineering and Physical Sciences Research Council via both the Franklin and the UK Catalysis Hub and also with Pfizer, the EU Horizon 2020 Programme under the Marie Sklodowska-Curie programme, and the Felix Foundation.

“The results are the first step towards developing a new type of treatment against Covid-19, which could prove invaluable amid efforts to combat future waves of disease

NOVELTY

Franklin researchers demonstrate ‘significant potential’ of llama antibodies as potent Covid-19 treatment

Scientists at the Franklin have shown that a unique type of tiny antibody produced by llamas and camels could provide a new frontline treatment against Covid-19.

The research demonstrates that these ‘nanobodies’ can effectively target the SARS-CoV-2 virus that causes Covid-19. Future nanobody-based treatments could be taken by patients as a simple nasal spray.

Short chains of the molecules, which can be produced in large quantities in the laboratory, were found to significantly reduce signs of Covid-19 disease when administered to infected animal models.

The nanobodies, which bind tightly to the SARS-CoV-2 virus, neutralising it in cell culture, could provide a cheaper and easier-to-use alternative to human antibodies taken from patients who have recovered from Covid-19. Human antibodies have been a key treatment for serious cases during the pandemic, but typically need to be administered by infusion through a needle in hospital.

Public Health England described the research as having ‘significant potential for both the prevention and treatment of Covid-19’, adding that llama-derived nanobodies ‘are among the most effective SARS-CoV-2-neutralising agents we have ever tested’. The Engineering and Physical Sciences Research Council, which co-funded the research, said the work was a ‘vivid illustration’ of the impact of long-term discovery research of the kind carried out at the Franklin.

Neutralising variants of concern

‘Nanobodies have a number of advantages over human antibodies,’ says Professor Ray Owens, Head of Protein Production at the Franklin and lead author of the research. ‘They are cheaper to produce and can be delivered directly to the airways through a nebuliser or nasal spray, so can be self-administered at home rather than needing an injection. This could have benefits in terms of ease of use by patients but also gets the treatment directly to the site of infection in the respiratory tract.’

The research team, whose findings are published in the journal *Nature Communication*, generated the nanobodies by injecting a portion of the SARS-CoV-2 spike protein into a llama called Fifi, who is part of the antibody production facility at the University of Reading.

The spike protein is found on the outside of the virus and is responsible for binding to human cells so it can infect them.

Although the injections did not make Fifi sick, they triggered her immune system to fight off the virus protein by generating nanobodies against it. Researchers took a small blood sample from the llama and were able to purify four nanobodies capable of binding to the Covid-19 virus.

The nanobodies were combined into chains of three to increase their ability to bind to the virus. These were then produced in cells in the laboratory.

The team found three nanobody chains that could neutralise both the original variant of the Covid-19 virus and the Alpha variant that was first identified in Kent, UK. A fourth nanobody chain was able to neutralise the Beta variant first identified in South Africa.

When one of the nanobody chains – also known as a trimer – was administered to hamsters infected with SARS-CoV-2, the animals showed a marked reduction in disease, losing far less weight after seven days than those who remained untreated. Hamsters that received the nanobody treatment also had a lower viral load in their lungs and airways after seven days than untreated animals.

A new type of treatment

‘Because we can see every atom of the nanobody bound to the spike, we understand what makes these agents so special,’ says Professor James Naismith, Director of the Rosalind Franklin Institute, who helped lead the research.

The results are the first step towards developing a new type of treatment against Covid-19, which could prove invaluable amid efforts to combat future waves of disease.

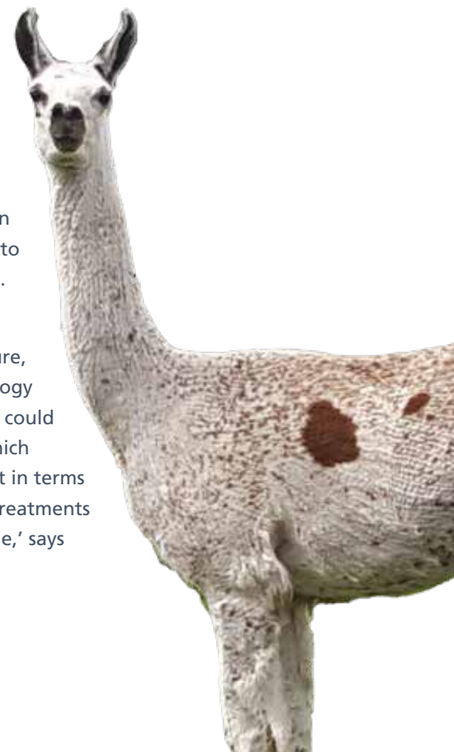
‘While vaccines have proved extraordinarily successful, not everyone responds to vaccination, and immunity can wane in individuals at different times,’ says Professor Naismith. ‘Having medications that can treat the virus is still going to be very important, particularly as not all of the world is being vaccinated at the same speed and there remains a risk of new variants capable of bypassing vaccine immunity emerging.’

If successful and approved, nanobodies could provide an important treatment around the world, as they are easier to produce than human antibodies and don’t need to be kept in cold storage facilities.

The research team, which included scientists at the University of Liverpool, University of Oxford and Public Health England, hopes to obtain funding to conduct further research needed to prepare for clinical studies in humans.

The researchers, who were funded by UK Research and Innovation’s Medical Research Council and Engineering and Physical Sciences Research Council, the EPA Cephalosporin Fund, and Wellcome, also hope to develop their nanobody technique into a so-called ‘platform technology’ that can be rapidly adapted to fight other diseases.

‘When a new virus emerges in the future, the generic technology we have developed could respond to that, which would be important in terms of producing new treatments as quickly as possible,’ says Professor Owens.



The Franklin Hub opening

In September 2021, we were able to officially open the Rosalind Franklin Institute Hub building.

The building was opened by Professor Lynn Gladden, Chief Executive of the Engineering and Physical Sciences Research Council, which funds the Franklin, and delegates from industry and academia, including Nobel Prize winner Richard Henderson.

The £43m building, constructed by UKRI-STFC working with Mace, designed by IBI and project managed by AECOM, now houses both the Franklin team and the cutting-edge technologies in biological imaging being developed by the institute.

The building sits within the historic Rutherford Appleton Laboratories, also home to the Diamond Light Source synchrotron, Isis Neutron Spallation source, and the Central Laser Facility.

Professor James Naismith, Director of the Institute, said: 'This was a proud moment for the Franklin. The work we do here will provide major factor-of-ten leaps in our ability to see and understand life. These technologies will be a huge asset for the UK, and this building is the perfect home for them.'

Unique environment

The Franklin was founded by ten leading UK Universities in 2018, with £103 million funding from the UK Government. This funding has created novel imaging technologies in microscopy, chemistry, structural biology and AI. These include world-first time-resolved electron microscopes, technology for imaging cells in 3D at atomic resolution, chemical tools for protein modification and labelling, and mass spectrometry equipment with unrivalled sensitivity for tissue imaging. The institute has already contributed to the fight against Covid-19, with work in member laboratories turning to the pandemic. The new building will continue this work, enabling further research on covid therapeutics and diagnostics, and also working in readiness against the next pandemic.

Dr Judy Kim, Deputy Director of the Correlated Imaging Theme said 'the environments we require for our work are incredibly demanding – there are very few places where you can develop instruments with new technology like this. Having a bespoke building which encourages cross-disciplinary collaboration will make sure we develop new methods to tackle the most crucial problems.'

Sustainability and design

Efficient by design – we calculate that the Hub is the most space efficient public sector research building in the UK. The building is rated BREAAM 'Very Good' – reflecting the commitment to sustainability in the design and delivery of the Franklin Hub.

It is not only the technologies housed inside the building which are ground breaking – the building architects, IBI, won an Award for Excellence in Architectural Technology 2021 for the cutting-edge design of the building itself.

Connecting the physical and life sciences

Professor Dame Lynn Gladden, EPSRC Executive Chair said: 'By connecting physical sciences and engineering to the life sciences, we have the ability to develop new innovations to enhance our understanding of life.

'The opening of the Rosalind Franklin Institute will help us to tackle health research challenges and enable the UK to make leaps in life sciences innovation which would otherwise be inaccessible.'

> "By connecting physical sciences and engineering to the life sciences, we have the ability to develop new innovations to enhance our understanding of life".
>
> Professor Dame Lynn Gladden, EPSRC

Synthetic biology solutions for imaging

Five EPSRC Impact Acceleration Account funded projects strengthen the ties between the Bristol BioDesign Institute and the Rosalind Franklin Institute.

In 2022, the Bristol BioDesign Institute (BBI) at The University of Bristol was awarded EPSRC Impact Acceleration Account (IAA) funding to develop links with The Rosalind Franklin Institute. The aim of these awards is to support knowledge exchange and impact from EPSRC-funded research. One way to achieve this is by fostering collaborations between research organisations

'Our research portfolio has obvious synergies with The Rosalind Franklin Institute and we already had various long-running pairwise collaborations with colleagues there; this award allowed us to explore further opportunities to bring together the expertise and research facilities of the two institutes and deliver impactful research,' explains Kathleen Sedgley, Scientific Manager of the BBI.

The BBI issued a call for research proposals involving scientists from the BBI and The Rosalind Franklin and funded five short-term projects that ran from February until the end of June 2022. The overarching goal of these projects was to develop synthetic biology solutions for imaging molecules in living cells.

Professor James Naismith's team has been working with Professor Dek Woolfson, Dr Mark Dodding and Professor Paul Verkade at the BBI on variations of a *de novo* synthetic peptide system[1] that can enter mammalian cells and label specific proteins for correlated light and electron microscopy.

'The major challenge in transmission electron imaging of human cells is the inherently low contrast, which makes it hard to distinguish proteins from each other,' says Professor Naismith. 'The possibility of delivering peptides that carry fluorescent and electron-dense cargoes to subcellular targets will help locate structures of interest specifically and precisely,' he adds.

So far, they have demonstrated by light microscopy that they can dual-label proteins with both fluorophores and heavy atoms. Their next steps will be to image the cells with an electron microscope and, if they are successfully labelled, apply for a larger grant to continue developing this game-changing technology.

Dr Marco Fritzsche's group has teamed up with Professor Christoph Wülfing at the BBI to explore how mechanical cues within the tumour microenvironment may influence the ability of cytotoxic T lymphocytes (CTLs) to kill tumour cells. They are using bio-synthetic mechanosensors[2,3] to quantify the biomechanical force exerted on specific receptors on CTLs co-cultured with tumour cells in in 2D and 3D systems. This project has the potential to transform cancer immunotherapy by offering new insights into the effects of the microenvironment on tumour immunosuppression.

'Bringing together the BBI's expertise in determining cytotoxic T cell function in 3D tumour cell models and the Rosalind Franklin's microscopy approaches to measure forces on cells in real time is proving to be very fruitful,' Professor Wülfing says.

> "Bringing together the BBI's expertise in determining cytotoxic T cell function in 3D tumour cell models and The Franklin's microscopy is proving to be very fruitful".
>
> Professor Christoph Wülfing, University of Bristol

With the IAA funding they have been able to show that cells in 3D culture systems can be labelled with beads and that bead displacement can be used to measure biomechanical forces.

Another project involves a collaboration between Dr Michael Grange, Professor Mark Dodding and Dr Paul Verkade and aims to integrate two imaging technologies — focussed ion beam (FIB) milling and *in situ* cryo-electron tomography — to examine the inside of microtubules with unprecedented resolution. The presence of filamentous actin in the microtubule lumen[4] suggests that further investigation into this subcellular compartment could offer new insights into microtubule dynamics and functions.

Professor Ray Owens and Professor Imre Berger are examining cryo-EM structures of the G-protein-coupled receptor FFAR1, which has been implicated in long COVID and type 2 diabetes. They are assembling 'megabodies'[5] to stabilise the receptor coupled with water soluble inhibitors. Understanding how such inhibitors modulate the activity of FFAR1 will offer clues for developing new therapeutics for both these conditions.

'We are aiming to complete the work started under this collaboration through an award from BrisEngBio, the BBI's new Centre for Engineering Biology, with a view to obtaining longer term funding for the project,' Berger explains.

Last but not least, Dr Mark Basham and colleagues are using the IAA seed-funding to speed up the processing of cryo-EM data using novel cluster technology (DisTRaC).

Commenting on the overall experience, Professor Naismith says: 'With IAA funding we've been able to pursue a broad range of high-risk projects that fit with the Institute's vision and strengthen our ties with the BBI,' Naismith says. 'It's been a win-win.'

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New stigmatic imaging prototype shows benefits of academic-industry partnering

> “This rapid SIMS imaging has huge potential for the future and we’re watching closely to see what happens”.
>
> Kate McHardy, Ionoptika

The University of Oxford’s Department of Chemistry is presently home to one of our most exciting prototype technologies, the newly designed stigmatic imaging mass spectrometer.

Scientists including Dr Felicia Green from our Biological Mass Spectrometry team have spent many months on the precise characterization and alignment of the primary ion beam.

Extraction optics and high-speed stigmatic detectors have now been fitted and the instrument is undergoing fine tuning and testing, so that all components can work to their optimum ability.

Whole-surface imaging

This instrument is particularly exciting because it has the potential to achieve a dramatic improvement in mass spectrometry imaging (MSI). Typically, MSI involves slow scanning across a surface, taking a mass spectrum at different points on the surface and gradually building up the image. But the new instrument will be capable of imaging the whole surface simultaneously, using the highest specification cameras that can operate as an array of position- and time-sensitive detectors, to record a mass spectrum for each pixel in the camera image. It will enable the most accurate images at much faster speed - and this would mean that analysing a standard tissue biopsy would take seconds, rather than hours or days, potentially allowing it to become part of routine analysis.

This world-class instrument design is a joint project between researchers at the Franklin, the University of Oxford, and the privately-owned ion beam technology company Ionoptika. Ionoptka’s scientists and engineers are strongly committed to the development of its technology for all scientific analysis applications, such as secondary ion mass spectrometry.

‘Our involvement grew and grew’

From the Franklin’s very earliest days, Ionoptika was closely involved in this particular project, as Kate McHardy, Ionoptika’s Sales Director, remembers.

‘When the Franklin was set up in 2018, we were invited to participate in various working groups that it was organising at the National Physical Laboratory, including those on different types of mass spectrometry imaging. We volunteered to be on the stigmatic imaging system working group, and initially our input was simply to advise on the instrument that was already planned – as well as to recondition an ion beam system that NPL were planning to lend to Oxford. But after lots of discussion and collaboration, our involvement grew – and we ended up designing and building the instrument too.’

In the first phase of the project, the bespoke SIMS instrument was built by Ionoptika at its headquarters near Southampton. It features a vacuum chamber, a stage and a sample handling system.

Separately, but as part of the same project, the team explored whether it might be possible to use a different ion beam technology on the new instrument, namely the use of Ionoptika’s gas cluster ion beam technology with water source, which is able to produce extremely good results from high molecular weight biological samples.

However, a feasibility study showed that this would be extremely challenging. The C60 ion beam gun was ultimately chosen for this prototype instrument. Dr Felicia Green spent time on site in Southampton helping with the build process. She said: ‘It was such a great experience; the team at Ionoptika were brilliant and very efficient. That was a really valuable period of exploration in finding out what was and was not possible.’

Next phase at Harwell

In April 2021 the prototype was moved to the Chemistry department at the University of Oxford, where the final parts of the instrument were fitted and tested in collaboration with their experts in time and position sensitive detectors, led by Professor Mark Brouard. Now the ion beam needs to be fully characterised, with the detector specifications calibrated and fine-tuned by the scientists there, and any additions made.

But this will not be the final iteration. Depending on results, information from this prototype will be used to build the next level instrument, destined for the Franklin’s Biological Mass Spectrometry instrumentation division at its hub in Harwell. Dr Green explained: ‘Our aim at Harwell is to build several instruments that can result in high throughput. This next spectrometer may be built on to a bigger instrument there, or could ultimately become a standalone unit capable of quick scans.’

Although Ionoptika’s commitment to the project is now officially complete, unofficially the collaboration remains in place, with regular virtual meetings with the projects’ in-situ scientists.

Kate McHardy says: ‘We are very much still interested, and hope to be involved when the next phase happens. It’s part of the way we are as a company to be involved from the start on exciting and challenging projects, because we have varied products that in effect can go in any direction. This rapid SIMS imaging has huge potential for the future and we’re watching closely to see what happens’.

Bringing science out of the lab to the public

One of the Franklin's core values is to 'leave a legacy to be proud of', and the communications team has continued to work unstintingly behind the scenes with local Oxfordshire schools to engage directly with pupils in their classrooms.

The Franklin's communications and engagement team work closely with Education Business Partnership's Hi-tech Horizons scheme, which aims to reach 50,000 pupils in five years and interest them in science and technology careers. In regular visits, the Franklin's communications team address school classes, running a core programme of information and activities over several hours.

During the pandemic, the Franklin team worked hard to switch to virtual seminars, which resulted in some additional benefits. Communications and Engagement Manager Dr Caitlin Higgott explains: 'Not only could we reach bigger groups – hosting entire year groups on one call – but being online enabled our scientists to take part in sessions more easily, rather than needing to block a day out to travel.'

The business of science

However, as the pandemic has eased, schools are now keen to engage face-to-face as much as possible. The Franklin typically targets Years 8-10 – the group that is either making decisions about their GCSE options, or already studying those subjects. And a key focus of the sessions is to show that working in science doesn't only mean being a scientist, but can also involve supporting the exciting business of science research.

Starting with an introduction to the Franklin and its work, and an outline of cell biology, the Franklin's sessions then move on to activities that get students thinking about funding and industry, and the decisions that need to be made about what type of science should be done. One central activity is a 'funding review' game, in which students are told about different, real life projects that can be done, and need to choose which one they think is most important.

Dr Higgott explains: 'Pupils look at research and explore issues like: what conditions might it affect? Then, how many people? Is it primary research – which gives scientists more information about how the body works – or secondary, so further down the line towards a treatment or drug? We explain that the government will fund early research – but industry will be more likely to come on board the closer a project gets to a treatment or drug. The students really enjoy arguing about what they think is best!'

An 'aha' moment

Combining science with a business outlook is sometimes an 'aha!' moment for students who have presumed science isn't profitable, or haven't previously seen a connection to business.

But the learning isn't only in one direction; school pupils can be hard to impress, and running the sessions provides useful experience for the team and for any session 'guests' from the Franklin. It can be a training ground for some of the Franklin's younger researchers to meet what Dr Higgott calls a 'brutally honest' audience! She says: 'We find it can really help our staff with their communications skills. It's not enough to speak to audiences that already know the value of what we do; it's much harder to enthuse new audiences. Having that more unsympathetic perspective makes us question ourselves as well!'

> "It's vitally important that the Franklin's work continues to be covered by the press; it's a gateway to the public. They're paying for our work, so they have a right to know what we are spending it on!".
>
> Laura Holland

A question and answer session follows every event, and feedback is valuable, with students often saying that they didn't understand where science funding comes from, or appreciate the variety of roles in the sector. Since the Franklin is publicly funded, it's vital that the public understand what we are doing.

Occasionally the sessions have led to follow up activity, such as visits and work experience for A-level students at the Franklin, during which they may work on assigned tasks, such as the synthesis of aspirin, working alongside the Biological Mass Spectrometry team with their equipment and evaluating samples for purity.

Dr Higgott concludes: 'It's quite a time commitment, but I get a lot out of it, and it's rewarding to see students' perspectives on science – and the possibility of a role in it for themselves. We love seeing the students come back for more – and hope that in time, some may end up working or studying at the Franklin.'

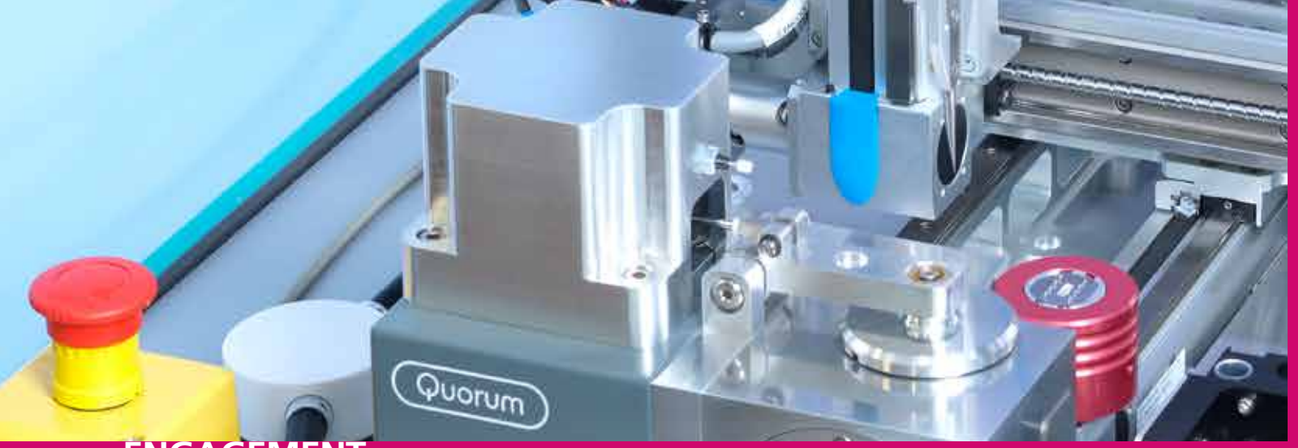
Staying in the headlines

Another important part of engaging the public is making sure that the Franklin's achievements are featured in the national and international press. Notable last year was the media coverage around the Franklin's key research into llama antibodies which had been found to have significant potential as a treatment for Covid-19.

Timed to coincide with the paper's publication in Nature Communications, the press release highlighted the involvement of Fifi the Llama, part of the antibody production facility at the University of Reading, and the communications team hosted an online media briefing, giving journalists the opportunity to question the Franklin's scientists, Professors Ray Owens, Jim Naismith and Dr Miriam Weckener live about the work.

The story captured the media's attention, and the Franklin's work was subsequently covered in high-profile national outlets – including by the BBC Online, with interviews on Radio 4 as well as the BBC World Service ; the Times, the Daily Mail, the Independent and the Daily Telegraph – and was picked up by the Press Association, leading to even more coverage. International outlets also covered the story, including the Sydney Morning Herald, Canada's CTV and Newsweek, as well as specialist publications such as Wired.

Director of Strategic Marketing and Culture, Laura Holland, said: 'It's vitally important that the Franklin's work continues to be covered by the press; it's a gateway to our funders – in other words, the public. They're paying for our work, so they have a right to know what we are spending it on!'



> “It has been fantastic to work with scientists at The Rosalind Franklin Institute; like us, they are not afraid to tackle the more challenging aspects of the cryo-EM sample preparation”.
>
> Paul Thaw, SPT Labtech

Optimised sample preparation fuels the ‘resolution revolution’

Researchers at The Rosalind Franklin Institute are working with SPT Labtech and Diamond Light Source on chameleon®, an automated sample preparation system that improves the efficiency of the cryo-electron microscopy workflow.

As cryo-electron microscopy (cryo-EM) becomes more sensitive and more widely available, biologists are increasingly drawn to this technique to solve the 3D structure of proteins. These structures are fundamental for understanding protein function, their potential role in disease and, crucially, for designing drugs that target them.

Cryo-EM involves flash-freezing solutions of proteins or other biomolecules before showering them with electrons to reconstruct their three-dimensional shape in atomic detail. Unlike X-ray crystallography, cryo-EM doesn’t require protein crystals, which can be challenging to grow and lock proteins in a single conformation. With cryo-EM, proteins are free to move around until the moment of flash-freezing so researchers can capture different conformational states that can offer a deeper understanding of their mechanism of action.

‘Thanks to improvements in hardware and software, we’ve seen a big jump in the quality of the structures solved by cryo-EM,’ says Paul Thaw, Product Manager for Integrated Structural Biology at SPT Labtech. ‘Scientists are realising that they can quickly create high-resolution models of molecules with multiple components in varying biologically relevant states, which has traditionally been very difficult to do with X-ray crystallography, either because of their complexity or inherent instability.’

What is often referred to as the ‘resolution revolution’ in cryo-EM has resulted in a steady growth in the number of structures solved by this technique and submitted to the Electron Microscopy Data Bank. In the next few years, the number of biological structures determined by cryo-EM is likely to surpass those determined by X-ray crystallography[1].

Tackling the main workflow bottleneck

Cryo-EM relies on a sample preparation method known as vitrification. This involves immobilising the biological specimen on a support, a so-called grid, by rapidly freezing it into a glass-like or vitreous state, avoiding the formation of ice crystals that can compromise the structure of the specimen.

As Dr Miriam Weckener, Postdoctoral Research Scientist in Structural Biology at the Franklin, explains, sample preparation for cryo-EM is by far the most time-consuming and difficult stage of a project. Samples need to be carefully applied to a grid, blotted and quickly plunged into liquid ethane.

chameleon® uses inkjet technology to spray tiny amounts of sample (minimum dispense volume 6nL) onto unique self-blotting nanowire grids. ‘The whole system is automated, minimising grid damage and sample waste caused by manual handling,’ she says.

Moreover, chameleon®’s high-speed cameras allow fine control over sample layer thickness. ‘When using older semi-automated methods, you have no idea of the ice quality of the sample on the grid until you put it in the microscope,’ Dr Thaw explains. chameleon® allows researchers to discard samples that are too thick or too thin so valuable microscope time is not wasted screening unsuitable grids.

Other parameters that can be fine-tuned with chameleon® enable a very short time (54 milliseconds) for sample application and freezing, which can prevent the sample from adopting a preferred orientation or dissociating (falling apart). ‘Preferred particle orientation is a common problem for cryo-EM; if we only see a protein in one orientation, we can’t accurately reconstruct its 3D structure,’ Dr Weckener explains.

By using chameleon® to optimise sample-specific preparation and control grid quality, researchers can generate consistent results faster and with smaller amounts of sample.

Putting the system to the test

SPT Labtech have been working with researchers at the Institute on chameleon® since 2019, first on an early prototype and since November 2020 on an upgraded production-level model. ‘It has been fantastic to work with scientists at The Rosalind Franklin Institute; like us, they are not afraid to tackle the more challenging aspects of the cryo-EM sample preparation,’ says Dr Thaw. ‘They tell us what works and what aspects need improving.’

Dr Weckener has been optimising the system for different types of samples, including nanobodies in complex with the spike protein of SARS-CoV-2 that mediates viral entry into cells[2]. This work shed light on the structural basis of SARS-CoV-2 neutralization, which is aiding the development of new COVID-19 therapies.

By reaching out to Diamond’s EM user community, Weckener has been able to test samples that have proved difficult to prepare for cryo-EM on chameleon®. ‘We’ve been offering 2-day sessions during which we make a series of grids using different parameters to try to solve all sorts of issues encountered using other systems,’ she says. Some of these sessions have resulted in long-term collaborations, including one with a Korean group that is helping to optimise the grids themselves.

Dr Weckener has found the partnership with SPT Labtech very rewarding. ‘Developing new instrumentation is an iterative process; it is very gratifying that SPT Labtech take our feedback on board and that we are able to offer a support service to the community.’

Speaking about the future, Dr Thaw says that SPT Labtech plans to further develop chameleon® and a broader range of grids, as some samples may be better suited to grids made of different materials. In addition, he is keen to collate all the data produced in the process and apply emerging computational methods to build a knowledge base that will enable the cryo-EM community to adjust the sample preparation protocol according to the type of sample they are studying.

‘Ultimately, our goal with chameleon® is to democratise the use of cryo-EM by bringing vastly improved and more efficient sample preparation closer to the bench biochemistry,’ he concludes.

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Harnessing the power of citizen scientists

> “We’re looking for the uncommon. We’re really looking for the anomalies, the things that are missed most of the time”.
> Dr Michele Darrow

The Rosalind Franklin Institute’s Artificial Intelligence and Informatics (AI&I) theme and imaging teams are working with citizen scientists on a range of projects.

Working with researchers from Diamond Light Source and University of Oxford, the Franklin team is using cutting edge imaging techniques to identify nanoparticles and classify nanoparticle catalysts.

Nanoparticles are incredibly small, measuring between 1 and 100 nanometres - one thousandth of a human hair. They are used in everything from the manufacture of medicines, flatscreen TVs and agrochemicals to water purification. The research could lead to more efficient and environmentally friendly nanoparticle catalyst systems.

Dr Michele Darrow, the Franklin’s Head of Data Strategy for Cryo-Electron Imaging, said: ‘We hope that by collecting basic information about the number of individual nanoparticles, their sizes and how many of them are part of clusters we can better understand their role and make them more efficient and environmentally-friendly when they are used in agriculture and other industries.’

Using Scanning Transmission Electron Microscopes (STEM), Dr Darrow’s colleagues and their counterparts at Oxford and Diamond Light Source have taken thousands of incredibly detailed images of these tiny particles.

Although AI found and categorised many of the nanoparticles, it struggled to separate others from the background of the image and mis-labelled some clusters.

To address this, they have combined the best in machine learning with human classification – which is where the citizen scientists come in.

Send in the Zooniverse

The partners have found willing volunteer collaborators by launching the nanoparticle catalyst project on the Zooniverse. The Zooniverse is a citizen science portal with 1.6 million registered users ranging from school children to retired people. They are currently hosting more than 50 projects.

It is based on the idea that anyone with a computer and a bit of time on their hands can help move research forward. Volunteer citizen scientists help researchers to do science that otherwise would not be possible. The Zooniverse was established by the University of Oxford, Adler Planetarium and the Citizen Science Alliance – with many projects supported by the Alfred P. Sloan Foundation.

Indeed, some of those citizen scientists have already helped Dr Darrow with several health-focused projects posted on her Zooniverse Science Scribbler pages – including studying images of cells affected by the neurological disorder, Huntington’s disease and visualising cells as they are infected by a virus, Virus Factory

Citizen scientists on the Zooniverse are reinforcing the work of Dr Darrow, her colleagues and AI in an ongoing project, Placenta Profiles, which aims to explore in detail the complex structure of the placenta, starting by finding all of the mitochondria (the energy producing factories inside of cells).

Dr Darrow said: ‘How well the placenta works is related to its development and structure but that’s hard to study because there are lots of different cell types, each playing different roles and taking different forms. Placenta Profiles is giving professionals and citizen scientists the opportunity to do important work analysing the complex structure of the placenta that we can then feed back to machine learning, making it faster and better in the future.’

The nanoparticles project mentioned above, named Key2Cat, has already sparked great interest amongst the citizen scientists. Within a week of data being posted in May 2022, hundreds of Zooniverse members identified and marked around 170,000 nanoparticles and clusters on the STEM images.

The researchers used these marks to create a new dataset showing each individual nanoparticle. The team put together a few questions and asked for the help of citizen scientists again to classify the nanoparticle catalysts, before the results are again analysed by AI. The last citizen science leg of the project is ongoing now – click here to help out!

Providing the citizen scientists with the tools for the job

The Franklin is also working with the University of Oxford and University College London to develop and test out software tools so citizen scientists on the Zooniverse can add the human touch to AI analysis of large datasets. The topics range from astrophysics to ecology and the activity of proteins in human cells.

Dr Darrow says: ‘With the software tools being developed we’re looking for the lower abundance items that are not obvious. We’re looking for the uncommon. We’re really looking for the anomalies, the things that are missed most of the time.’

Oxford astrophysicists (and citizen scientists) will be the first to test out the new tools as their datasets are ready for analysis. They and the citizen scientists will analyse masses of data about objects at the farthest reaches of the Universe.

Dr Darrow, who received her PhD for imaging work around the structural basis of protein misfolding disorders, will use the tools – and the support of citizen scientists – to focus again on proteins inside the cell. For the first time, advanced imaging equipment is providing us with large numbers of high quality volumes showing proteins engaging in their normal activities within human cells.

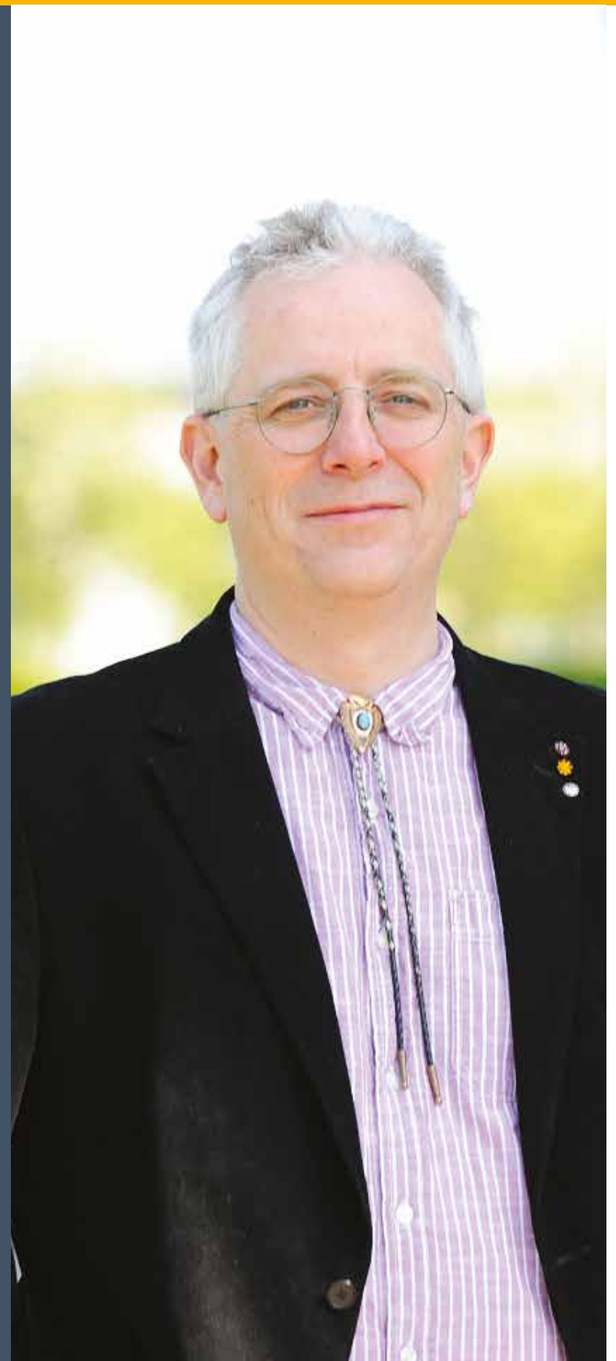
Dr Darrow explains: ‘Biochemists have been able to look at the structure of a purified protein outside the cell environment for almost 100 years but when you take the protein out of its natural environment its structure can change, so sometimes you don’t get an accurate picture.’

Using Science Scribbler projects on the Zooniverse, she will again enlist citizen scientists in the study of biological data – the basic science that could eventually identify opportunities for researching potential treatments for disease.

Strategic Report

Director's foreword

Our teams have shown great resilience and teamwork during this year. Thanks also go to our collaborators who have housed our teams across the UK, and who have been instrumental in our early success.



I am pleased to deliver this foreword. We have seen the culmination of a four year effort to design, deliver and equip our hub building - a uniquely efficient and effective space for science. When funding for the Franklin was granted in 2017, there was no team. With the support of our funders UKRI-EPSRC, campus partners UKRI-STFC and members, science and operational leads were appointed. Our building went from a blank sheet of paper to our award winning home to world class science in less than four years. This was achieved against the backdrop of a global pandemic but delivered on time, specification, and budget.

It was therefore an incredibly proud moment to bring those stakeholders together to celebrate our official opening in September 2021.

Our nanobodies work, built on the foundations of the Protein Production UK platform,has continued to deliver exceptional work which we published showing a potential therapy against SARS-CoV-2. The work has been recognised by the award of a Horizon Prize from the Royal Society of Chemistry, a place at the Royal Society summer science exhibition and further funding from Wellcome and BBSRC.

Moving labs is never easy and has placed a burden on everyone. I want to particularly praise the science and operations colleagues who fitted out and operationalised labs. All of them have shown great resilience and teamwork. Thanks also go to our collaborators who have housed our teams across the UK, and to our advisory boards who keep us on our toes.

Looking to 2022-2023, we can see the equipment now on site starting to produce important and exciting research. In Electrifying Life Sciences, our work in sample milling and microscopy places us at the global forefront of electron tomography, thanks to our collaboration with ThermoFisher Scientific and funding support from Wellcome.

In correlated imaging, partnership with JEOL has seen the delivery of one-of-a-kind instruments which will advance our aim to bring the very cutting edge of physical science to bear on life science, and in chemistry, a strategic partnership with Oxford University's pharmacology department has created a powerful partnership which will help realise our aim to deliver true in-cell chemistry. The distributed model of development in biological mass spectrometry has seen good progress, with equipment yielding results at host organisations around the UK. In the coming year, we will see migration into the hub, with progress accelerated by this important early work.

The coming year does not lack its challenges. We are committed to reducing our carbon footprint wherever we can, not only because of the climate emergency but because of the cost to us. Inflationary pressures are even stronger in science equipment and consumables. To thrive in the medium term we need capital funding and long term support; we welcome the exceptional effort made by EPSRC. The quality of our teams and the skills they develop here means that they are in high demand. Remaining an attractive employer is increasingly demanding.We have opportunities, our engagement with Industry is bearing fruit, we have in here enormously talented PhD students linked across the UK in a unique model and our reputation is increasing.

I believe that we will meet our challenges and seize our opportunities.

Professor James H Naismith FRS FRSE FMedSci

Chair's foreword

Welcome to our trustees strategic and financial report for the year 2021-2022. This year has marked our full emergence as a prestige research institute, taking our place among the constellation of exceptional UK institutes. The depth and breadth of outputs across the Franklin is exceptional, given our age and the ambition of our projects, and we start the new financial year eagerly, as cross theme work and collaborations grow from these foundations.

Our research values of adventure, novelty, engagement, and utility have all been drawn on and exemplified by the Franklin team this year, marking key milestones in occupying the stunning Franklin hub building, creating collaborations both in the UK and internationally, and delivering an efficient operations team which underpins the running of the Institute.

It was an honour to chair our opening event, and to be joined by Nobel prize winning collaborator Richard Henderson, entrepreneur Noor Shaker, industry leader Fiona Marshall and Executive Chair of our funder UKRI-EPSRC Professor Dame Lynn Gladden.

After so much disruption, taking the opportunity to celebrate our achievements, and most importantly, the tenacity, hard work and perseverance of our teams, was incredibly special.

In this year we have seen already our first out-licenced work through our collaboration with STFC and MRC-LMB, to Quantum Detectors to develop the new C100 Detector. This detector is designed to democratise low energy electron microscopy. Our collaboration with SPT Labtech has also been a great success, with their Chameleon system now out in the wider market, improving the efficiency of electron microscopy sample preparation.

In addition to technology collaborations, in the coming year we will collaborate deeply with the pharmaceutical industry in both the exploitation and co-development of our current technologies, and on the shaping and refinement of our plans. These links with industry are vital to us – it is through these links we will have the greatest impact on human health.

In 2022-2023 we expect to see the publication of further government strategy on life sciences, and the birth of the new research funder ARIA. Both will emphasise the need for the UK to innovate in technology if life science is to thrive in the long term in the UK. The signs are good – funding in life sciences innovation in the UK is at an all-time high, and large companies are continuing to invest in the UK. We believe the Franklin has a key role to play in underpinning this success and acting as a lightning rod for international investment to the UK, and as a unique source of advantage for home-grown companies from their earliest stages.

To achieve this potential, maintaining our level of ambition and optimism is vital, even against the backdrop of inflationary pressure and global economic uncertainty. Only this ambition will deliver the adventurous projects which deserve the Franklin name, and which serve to make our work globally important and distinctive.

Dr Vivienne Cox CBE

After so much disruption, taking the opportunity to celebrate our achievements, and most importantly, the tenacity, hard work and perseverance of our teams, was incredibly special.

Franklin strategic goals

The Franklin was conceived to deliver technologies to industrial and academic communities which will advance our ability to see life in transformative, not incremental, ways. These advances will enhance human health through the development of new drugs, improved diagnostics, and better understanding of disease. This fundamental aim underpins our three strategy strands – to deliver world class science, build a legacy to be proud of, and secure our future success.

Delivering world class science

Adventure:
Franklin projects have significant risk, balanced by significant pay off if successful

Novelty:
Franklin technologies are globally original and ground breaking in their design and application

Engagement:
Franklin projects engage multiple partners from academia and industry and there is demonstrable support for their development

Utility:
Franklin technologies will be sought after by industrial and academic communities, generating research and economic benefits

Building a legacy to be proud of

Training the next generation in collaborative science: PhD, PDRA, Placements, Public engagement

Leverage:
Optimise the effectiveness of existing government investment in science infrastructure

Become a global Centre of Excellence:
for technology development and innovation, seed a new life science cluster, and enhance the UK skills base

Value our people:
Create an environment which develops staff to their full potential, supports career progression, and centres equality and diversity in STEM

Securing future success

Diversifying income:
- recurrent funding
- earned income
- partner contributions
- external funding
- charitable donations

Foster 'many-to-many' links:
across academia and industry, acting as a national focal point

Expand global network:
Establishing international partnerships. Position Franklin on global stage

Technology maturation:
Build bridges to clinical, robust IP and commercialisation planning for appropriate technologies

Performance in 2021-2022

Our performance against our strategy is reported against KPIs. For the years 2020-2021 and 2021-2022 these goals have remained the same. These will be adjusted in the financial year 2022-2023, to enable more granular analysis of metrics and performance.

World class science:

1. The Franklin will deliver to maturity at least one 'factor of ten' initiative recognised by SAB and community in each five year period. This will be unambiguous and will have reach into our communities

Indicators of progress:

- The Electrifying Life Science programme, our flagship programme funded by a £25m Wellcome grant with industry support from Thermo Fisher Scientific is on track. Microscopes and pFIB equipment are now in the Franklin building and generating first results.
- Nanobodies against Covid – verified and published 'game changing' science has shown the huge value of our protein production platform in the face of a global pandemic. In 2022 we will continue to pursue licensing opportunities for specific agents and mature our wider platform into the community.

Securing our future success:

2. The nature of high-risk long-term research requires long-term core funding. However, we expect to secure 25 % of the operating budget for the Franklin from other sources by 2026 (direct Industry funding, auditable in-kind contributions from Industry, grants from charitable organisations and other UKRI funding).
   - Indicator of progress: We have achieved this goal for the current five-year period, with the Electrifying Life Sciences project and multiple grants across chemistry accounting for a significant portfolio of work. In future years we aim to increase the proportion of contribution across all themes.
   - In 2021-2022, the strategic focus was delivering the hub fit out – this lays the foundation for future funding success, and from this, we expect further fundraising and collaborations across all areas.
3. The Franklin will establish collaborations across the UK. We aim to secure five new multi-centre collaborations each year. We will ensure these are geographically dispersed.
   a. We have achieved this in 2021-2022 with collaborations including;
      - Bristol BioDesign collaboration – a collection of projects across themes funded by UKRI-EPSRC. These projects reflect our commitment to cross theme working and adding value to our university community.
      - Edinburgh University Studentship scheme – our collaboration with Edinburgh University brings a new PhD scheme for the UK to life, with world class first year training delivered by Edinburgh.
      - REUDI – a national collaboration to create a new Relativistic Ultrafast Electron Diffraction & Imaging facility with applications in materials and life science with Liverpool University and STFC Daresbury Laboratory.
      - A strategic collaboration with Oxford Pharmacology provides a template for University-Franklin collaborations and creates a platform for further engagement.
      - AI collaborations with UK research institutes including the Alan Turing Institute are a strong model for collaboration. Our collaboration with Birmingham on the Baskerville EPSRC funded computing project is delivering benefit to the UK and providing Franklin researchers with access to globally leading infrastructure.
4. Training and skills development in our community is essential in ensuring the success of our programmes as they mature. We will embed training programmes for industry and academic colleagues and collaborators alongside our projects at the earliest stage, with a KPI in number of individuals from both industry and academia exposed to training and learning linked to our technologies. Training will range from undergraduate projects and placements to advanced skills development for established researchers in industry and academia, to technical training for engineers and support staff. We will monitor the types and balance of training offered between different communities.

- Indicator of progress: We are proud to have participated in the HDR 10,000 Black interns programme and have hosted several final year undergraduate students on projects across several themes.

-. Internal – setting the tone for our commitment to training and development, we have taken on our first apprentice, undertaken leadership development and training across several teams, and our board has undertaken a review which will inform future training and development needs.

- Planning for leadership and management training is also underway, and will be reflected in future metric.

Building a legacy to be proud of:

5. Our goal is that every person (from student to science lead to support and professional functions) who works at the Franklin will do the best work of their career here. We will graduate ten PhD scientists a year from 2025. These students will stand out as future leaders in innovative Industries and in academia. As a KPI we will monitor the next destinations of our students.

    - Ten students started on our unique UKRI-EPSRC funded DTP programme in October 2021. These students will move into full projects in 2022 following their foundation year with the University of Edinburgh.

    -. Additionally, several students are undertaking projects at the Franklin who are based with other DTP and training schemes. These collaborations strengthen our link to the academic community and enable access to Franklin technology to a wider range of students.

6. As a dynamic research institute, we would expect to see a higher turnover of staff (around 10 % per year) as our people move on to the next steps in their careers. As a KPI we will monitor the turnover of our scientific workforce and their next destinations. At an all-staff level (including non-scientific staff) we will monitor the next steps with a goal of 90 % to have positive next destinations (employed at the same or high level, new training or personal development or desired life changes (retirement, career break).

    - Staff numbers grew from 56 to 88 in this year, not including secondees and students. Significant structural change and several short-term appointments means that turnover was artificially high in the year to March 2022, at around 24%, with turnover in operations accounting for much of this change.

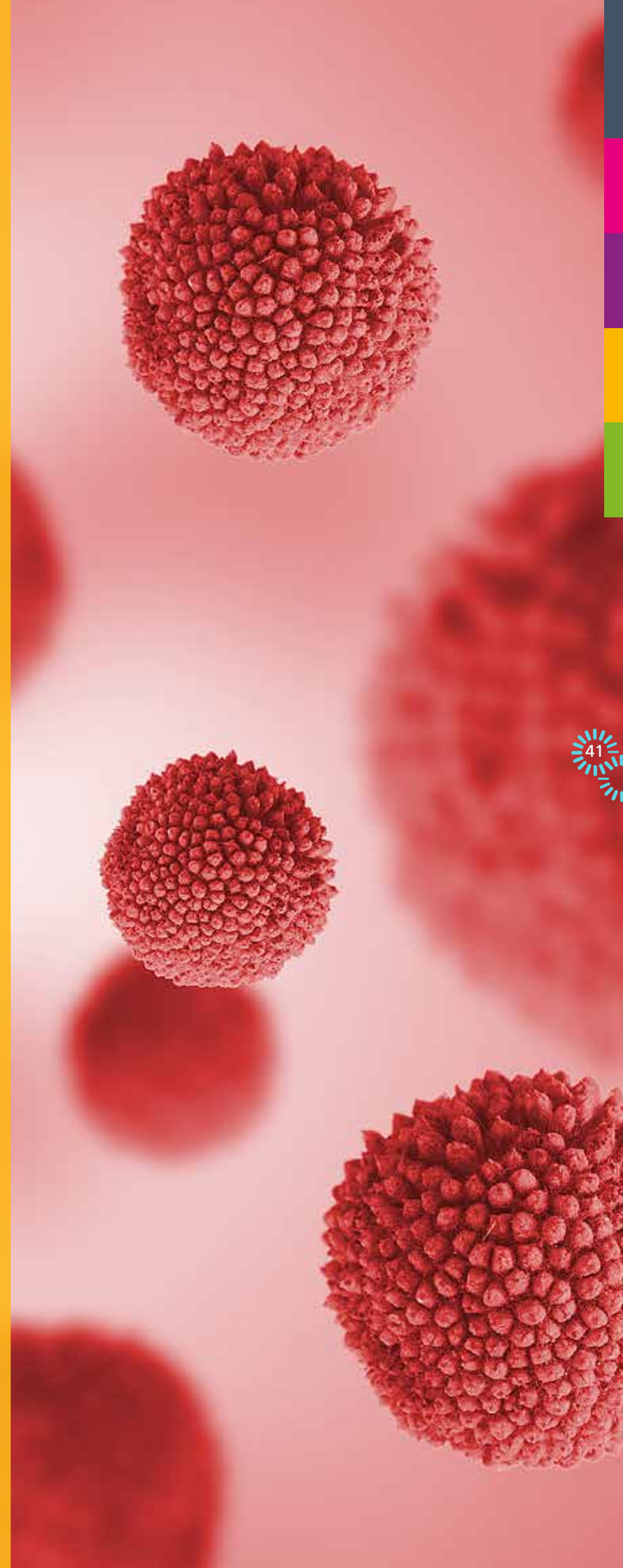
Our goal is that every person (from student to science lead to support and professional functions) who works at the Franklin will do the best work of their career here

Our goals in 2021and progress

In 2021-2022 we will fully occupy the Hub building, bringing together under one roof the technologies developed across our five themes.	**STATUS: ON TRACK**	Four of our five themes have fully occupied, with equipment in biological mass spectrometry migrating in during the coming year.
In operations, we will scale our systems and teams to support the science delivery.	**STATUS: ON TRACK**	The operations team have grown, with key recruits into senior roles. Systems continue to be scaled.
Science themes will prioritise cross theme activity and collaborations as technologies enter the development phase.	**STATUS: ON TRACK**	Strong indicators of success have been seen in this area, with internal major collaborations resulting in publications including on the chemistry and structural biology of covid-19.
Ideation and engagement will begin for the beyond state-of-the-art technologies proposed in our next phase.	**STATUS: ON TRACK**	Building on our initial phase two proposal, we continue to engage communities with our vision.
We welcomed our first cohort of PhD students in October 2021. These students will be the first of a long-term scheme, graduating researchers with national collaborators into interdisciplinary roles in academia and industry. Their skills in using and developing imaging tools in life science will make them a huge skills asset for the UK.	**STATUS: ON TRACK**	Ten students started as planned, and we anticipate partnering with six awarding partners in the first year to transfer students onto final projects in 2022-2023.
We will start maturing our phase one technologies – identifying routes to commercialise, transfer into national asset or develop further within the Franklin or a partner lab.	**STATUS: ON TRACK**	Commercialisation of our nanobody agents against covid-19 is in train, with training and development plans in place to maximise the national and international impact of our protein platforms. Our Chameleon project, a partnership with SPT Labtech in sample management for cryo-EM, is now mature and has entered national use.

Future plans for 2021-2022

- We will move our Electrifying Life Sciences project to fully operational status with the pFIB and microscope equipment on site, working on samples of increasing complexity and scale
- We will occupy the final labs remaining in the hub, with equipment in our mass spectrometry theme migrating into the building from partner organisations
- Our BioCOP project will initiate build, with first results expected by the end of the year
- We will focus our efforts on cross theme collaborations, working towards imaging more complex and relevant samples, including tissue level imaging
- Planning will continue for our next tranche of technologies
- We will collaborate with industry across our themes, with distinctive offers for industry at different scales and sizes, generating genuine benefits for the UK life sciences community
- We will focus on international collaborations and impact, maximising the benefit of the Franklin to the UK
- We will work to secure the future of the Franklin, particularly for new capital projects, working closely with our funders UKRI-EPSRC and the UK government and with other potential funders



2021-2022 highlights

Science News

People and community news

April 2021

Our prototype secondary ion mass spectrometer, developed with Ionopktika, moves to Oxford University for the next phase of its development

Led by Ben Davis, an international team solve a 20 year mystery on the function of LanCL proteins, pointing to breakthrough findings on the role of protein damage

June 2021

Ruska, an electron microscope capable of time resolved electron microscopy, becomes the first major equipment to arrive at the hub

July 2021

The C100 detector, developed by the Franklin in collaboration with STFC, is licensed for development to market by STFC spin out company Quantum Detectors

Dorothy, the ThermoFisher Scientific Titan Krios microscope adapted for electron tomography as part of our Electrifying Life Sciences project, arrives at the Franklin

Michael Grange, new group leader in electron tomography joins, strengthening our leadership in the field

Michael Grange, pictured far left, with ELS team

May 2021

The lease for the Franklin Hub is signed, marking a major milestone in the Institute's story, and enabling research to migrate to its new home on the Harwell Campus

August 2021

In AI, funding is granted from the Alfred P Sloan foundation to develop citizen science tools to highlight interesting proteins within the cell

We welcome our first interns to the Franklin, as part of the 10,000 black interns programme

Vaccine minister Nadhim Zahawi hosts the inaugural event at the Franklin alongside 100 guests, celebrating five years of the HealthTec cluster at Harwell.

September 2021

Our second major nanobodies paper is published, showing the transformative potential of an inhaled nanobody as a highly effective therapy against covid in animal models

Our nanobodies work generates international media interest for the second time, bringing Fifi, our llama based at University of Reading, global fame!

Our hub building officially launches, opened by Professor Dame Lynn Gladden, Executive Chair of UKRI-EPSRC. Science Minister George Freeman also visits to mark the opening of the hub.

October 2021

Our first cohort of students began their studies at the Franklin. The ten students joining from diverse backgrounds, will form the foundation of a major new PhD programme in interdisciplinary science

December 2021

The Franklin announces a strategic collaboration with the Pharmacology Department at University of Oxford, bringing together researchers in next generation chemistry and pharmacology

Our nanobodies work features in the iconic Royal Institute Christmas Lectures

January 2021

Vivienne Cox, the Franklin Chair, is awarded the title of Dame in the New Year's Honours

March 2021

BioCOP arrives for assembly at the Franklin

February 2021

The Franklin co-hosts a community workshop on pandemic preparedness with UKRI-STFC, iiCON and other partners in Liverpool

The Franklin welcomes our first international visiting scholar, Professor Dave McComb, to collaborate with colleagues in structural biology and correlated imaging

Hub update and sustainability

We were proud to officially open the Rosalind Franklin Hub building in 2021, with a launch event for stakeholders, colleagues, and collaborators.

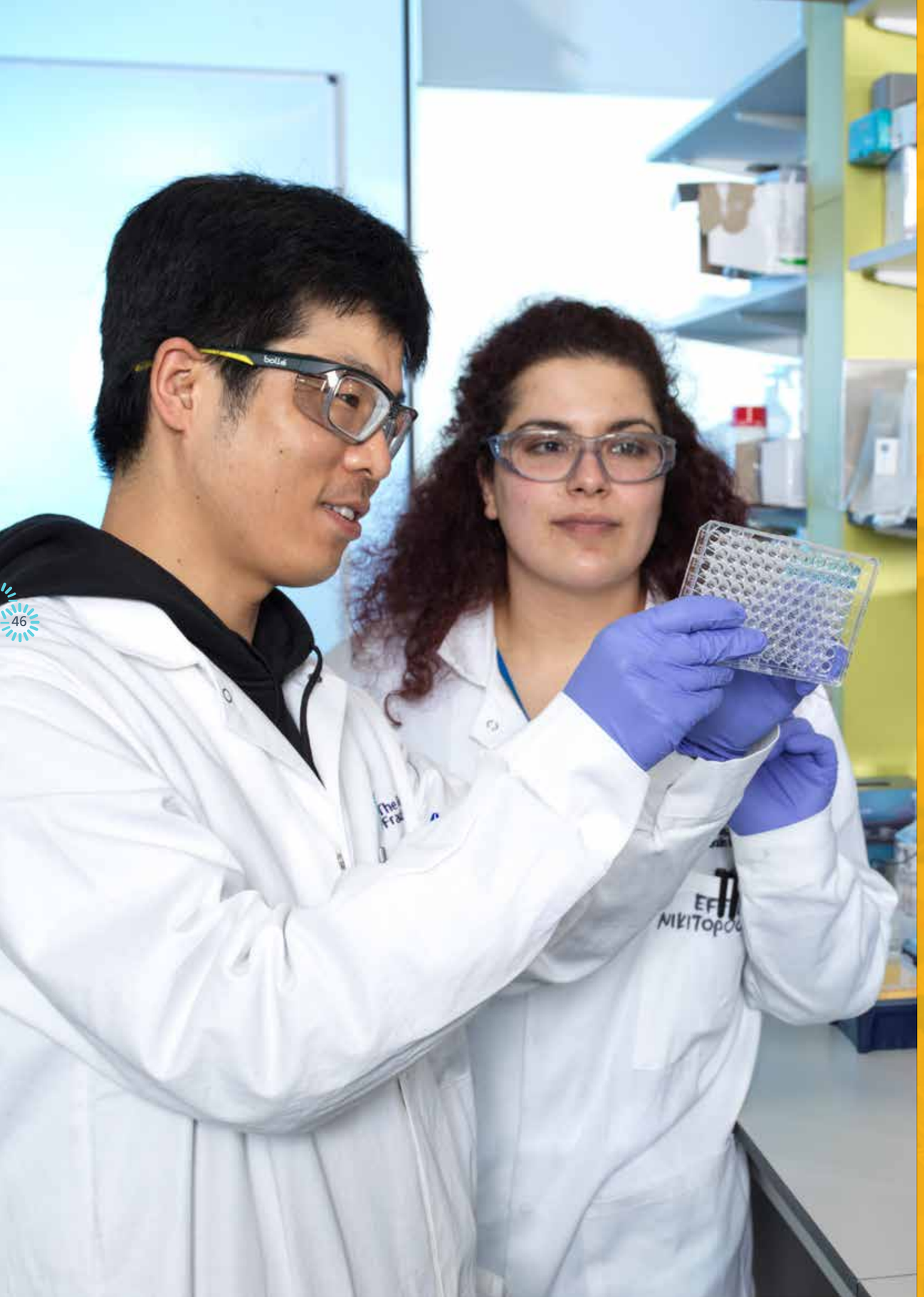
The Hub building, handed over from contractors Mace to our landlords STFC in January 2021, was occupied in May 2021, following the successful signing of a lease for the building. Research activity migrated from the Research Complex at Harwell, and labs at Harwell, Oxford and Diamond Light Source which housed our protein production UK, structural biology, chemistry and correlated imaging teams.

Fit out works commenced immediately on occupation, with complex enabling works required ahead of the installation of advanced microscopy equipment on the ground floor, and across labs in chemistry and structural biology. These works were project managed by the Franklin building team, working with external suppliers and our landlord UKRI-STFC. The successful completion of these fit out projects has been instrumental in allowing science to start on these major projects.

Equipment installation across all themes commenced, with Ruska and Crewe, microscopes in our CI theme, being installed by manufacturer JEOL, and microscope 'Dorothy' (after renowned crystallographer Dorothy Hodgkin) being installed alongside the sample milling equipment 'Franklin' in the structural biology theme with ThermoFisher Scientific. In chemistry, our collaborative work with Leeds came to fruition with the installation of the High Throughput Discovery laboratory.

The building achieved its 'very good' BREEAM rating for sustainability before opening, and work is ongoing to monitor energy use and environmental impact as part of a site wide effort. The Franklin benefits from efforts made on the Harwell campus to reduce the carbon impact of science, including extensive solar panel installation, and efforts to encourage green transport.

Fit out works commenced immediately on occupation, with complex enabling works required ahead of the installation of advanced microscopy equipment on the ground floor, and across labs in chemistry and structural biology



Equality, diversity, and inclusion

Our diverse staff:

Our staff composition by gender is 50% male, 45% female, and 5% preferring not to disclose. This mix varies slightly between science and operations (greater than 50% female in operational roles). Males are overrepresented in the most senior roles in science, a position which although represents the community as a whole, is not a position we are comfortable with. We will be investing in leadership development for female staff in science and revisiting our benefits package during the course of 22-23 to ensure we are offering both an attractive place to work in addition to offering exceptional career opportunities. Our Executive Group is 4:7 female:male membership, again reflecting the overrepresentation of males in senior science posts.

> We will be investing in leadership development for female staff in science and revisiting our benefits package during the course of 22-23

Ethnic diversity data for existing staff will be reported in 2022-2023 as staff numbers grow to enable meaningful reporting. We recognise that in science, institutional racism and social inequality present significant barriers to black staff and other people of colour in the workplace. By working alongside schemes such as the 10,000 Black Interns scheme, we hope to offer opportunities to staff early in their careers. We also follow best practice in not using the umbrella term BAME, and proactively advertising our PhD and other opportunities to black and minority societies and groups. Our best practice in PhD application process, including a no-CV approach and extensive pre-application guidance, can be extended to other processes.

Equity in pay:

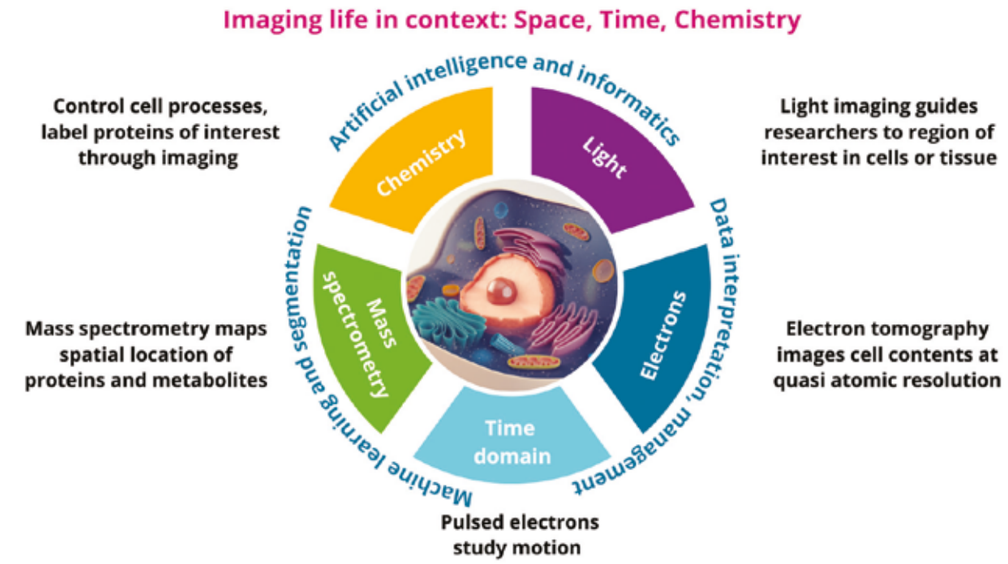
Equity and equal pay are examined annually, with internal adjustments made where required. Our relatively flat structure means that our pay ratios (the gap between the highest and lowest paid members of our team) are lower than often seen in academia and the private sector. In times of high inflation and increasing pressure on living costs, this fairness is important to us, and is essential if we are to recruit skilled people into our organisation.

International staff:

As a science organisation, we welcome many international staff to the Franklin. Our HR team support transition to the UK and UK life, and this work will continue in 2022-2023. We hope to take advantage of the campus environment further to enable staff to access cultural and language groups which will further aid in settling in and helping international staff and students to excel.

Objectives and activities

The Rosalind Franklin Institute is devoted to addressing important challenges in life sciences through the development and use of innovative technology. Many of our challenges relate to our ability to see the structures of life more clearly; from novel imaging techniques which will allow us to see better into living systems, to the atomic detail of a drug binding with a target protein. This ability to visualise the inner workings of life, and to draw new understanding from this, is one of the reasons we are named in honour of Rosalind Franklin.



In our first phase, we have described our mission as 'seeing life in context' through the five dimensions of space (x,y,z), time, and chemistry.

Our charitable objectives

The charitable objects of the Rosalind Franklin Institute are for the public benefit:

1. the furtherance of education, including without limitation in the fields of the physical sciences, engineering, health and life sciences by means including

a. conducting research and publishing the useful results of such research;

b. collaborating and exchanging knowledge with universities, industry, charities and other not-for-profit organisations, the state and other relevant bodies; and

c. public engagement through educational outreach activities, in each case with a view to advancing the state of our collective knowledge and understanding of such fields of study;

2. the promotion and preservation of human health, including without limitation by furthering the progress of scientific discoveries and new technologies arising from research into therapeutic treatments, drugs, diagnostics, other technologies and/or information resources by conducting its own research and development activities and by means of collaboration with universities, industry, charities, the state and other relevant bodies.

Income

The income of the Rosalind Franklin is derived from grants from UKRI, administered by the Engineering and Physical Sciences Research Council (UKRI/EPSRC) and grants awarded by other bodies for specific research projects and collaborations. Income is also generated through project based industrial collaborations. Future income may include further income from industrial collaboration, and income from licence revenue.

Structure, governance and management

The Rosalind Franklin is governed by its Board of Trustees whose members are also its Directors.

Of the Board members, six Directors are drawn from Member organisations on a rotation basis, with nominees selected for their ability to bring appropriate skills and experience to the Franklin board. Independent directors are drawn from industry and allied fields and are selected for their unique skills and experience.

The terms of board membership are set out in our governing Joint Venture agreement.

To ensure good governance in line with best practice, and in line with the Charity Governance Code, as updated in December 2020, a board effectiveness review was undertaken in 2021-2022, with the structure of the review underpinned by Its seven principles of Organisational Purpose; Leadership; Integrity; Decision Making, Risk and Control; Board Effectiveness; Equality Diversity and Inclusion; Openness and Accountability. The results of this review, supported by further skills analysis, will form the basis for future training and development for the Board, and will inform the recruitment of future trustees.

Recruitment and appointment of Trustees

The members of the Board who served during the year and up to the date of the Report are listed on page 55. The Members of the Board are Directors for the purpose of company law, and Trustees for the purpose of charity law. Under the Joint Venture Agreement and Company's Articles, Independent Board Members are elected to serve on the Board for a period of three years. The Board seeks to recruit a diverse membership. Periodically, they consider the skills mix of the Board as a means of succession planning. Other than our Independent Non Executive Chair, Board Members do not receive fees or other remuneration as Directors and Trustees but are entitled to recover expenses as outlined in the notes to the Accounts.

The induction programme seeks to inform Directors of the strategic priorities through a schedule of meetings and briefing documents as appropriate. As per our governance there is an annual rotation of Member Directors and as we receive feedback from 'retirees' we will review and refine this process, taking into account the skills mix and results of the recent Board Effectiveness review.

Organisational structure

The Rosalind Franklin has a clear organisation structure with documented lines of responsibility and authority and that sets out the composition of each group and committee within the structure. Member Representatives represent the interests of the member organisations. Their role is to ensure that the institute is delivering strong partnerships with its members and delivering its aims. Collectively, they drive the direction of The Franklin. The Joint Venture Agreement sets out several decisions that are reserved for the Members and those matters that are delegated to the Board, Institute Director and Executive Group. The Members appoint the external auditors.

Members of the Rosalind Franklin Institute

- University of Birmingham
- University of Cambridge
- Diamond Light Source
- University of Edinburgh
- Imperial College London
- University of Leeds
- Kings College London
- University of Manchester
- University of Oxford
- University of Southampton
- University College London
- UKRI-STFC

Structure explained

The Board – have primary responsibility for the Franklin (Joint Venture Agreement and Memorandum and Articles). The Board is responsible for setting the aims and strategic direction of the Franklin. They monitor risks, approve the annual business plan, budget and expenditure targets, and monitor the financial results (actual and forecast). The Board has final approval of funding bids and the resourcing of projects. UKRI/EPSRC may nominate a representative to attend Board meetings as an observer, but such representative will not be a Director.

The Board meets four times a year to monitor the operations of the Franklin and there is regular contact with Board Members in between meetings. During the financial year 2021-2022 the Board oversaw all of the organisation's finances and activities.

Three subcommittees were established by the board prior to this reporting year; The Value for Money Panel, Remuneration Committee, and the Audit and Risk Committee.

The Strategic Advisory Board also advises on the direction and development of scientific themes via the board.

The Value for Money Panel – The Value for Money Panel considers all major funding proposals prior to them being considered by the Board. They assess their viability and value for money. Only proposals with the support of the Executive Group and relevant Theme Advisory Panels are submitted to the Value for Money panel which is chaired by the Institute Director. Recommendations from the Value for Money Panel are presented to the Board of Trustees for final approval. Remuneration Committee (RemCom) - has oversight of the preparation of policies and procedures in respect of salaries, emoluments, and conditions of service of employees of The Franklin and as they relate to Equality and Diversity, performance reviews and personal development.

Members of the Remuneration Committee

Professor Ewan McKendrick (Chair), Dr Gillian Burgess, Professor Andrew Livingston

Audit and Risk Committee – is responsible for audit, finance and risk management. They review The Franklin's internal controls, risk management processes and compliance with funding and reporting requirements. They monitor the work of the external auditors and the resulting financial statements and receive and review the annual audit report.

Members of the Audit and Risk Committee

Mr Stephen Dauncey (Chair), Professor Stephen Caddick, Professor Peter Smith

Strategic Advisory Board – has been established to advise the Franklin, via its Board, on the development and implementation of the research and development strategy of the institute. Members are independent experts from academia and industry, both national and international. The Board met for the first time in February 2020 and reviewed the current direction and future for each theme. An annual cycle of meetings is now established, with the SAB contributing significantly to the scientific strategy of the organisation.

Members of the Strategic Advisory Board in 2021-2022:

- Professor Sabine Flitsch, Manchester University (chair)
- Professor Molly Stevens, Imperial College London
- Professor Sabine Flitsch, University of Manchester
- Dr Tom Muir, Princeton University
- Dr John Pollard, Bayer
- Professor Iain Styles, University of Birmingham
- Professor Vicki Wysocki, Ohio State University
- Professor Dwayne Miller, University of Toronto (resigned Dec 2021 following appointment as Franklin Distinguished Visiting Fellow)

Theme Advisory Panels – each theme has a panel of international experts from across academia (both member and non-member organisations) and industry who contribute to the development and review of the roadmaps, technology, and funding proposals for each theme.

The day-to-day management of The Franklin has been delegated to the Institute Director who works with the Executive Group to deliver The Franklin's operations, activities, and projects.

The Executive Group – the Group is made up of the senior operations team and the science directors. They consider developments across the themes and form part of the decision-making in advancing proposals to the Value for Money Panel. They are responsible for implementing the agreed strategy and policies and report on performance to the Board.

At the Franklin we are passionate about being a great place to work, creating our own identity which is forward thinking and collaborative in our approach to all we do

Executive Group membership

Institute Director and Director of Structural Biology	James Naismith	Seconded from Oxford University
Chief Operating Officer	Paul McCubbin	Employed Rosalind Franklin Institute
Director of Next Gen Chemistry	Ben Davis	Employed Rosalind Franklin Institute
Director of Correlated Imaging	Angus Kirkland	Seconded from Oxford University
Director of Artificial Intelligence and Informatics	Mark Basham	Employed Rosalind Franklin Institute
Co-Director of Biological Mass Spectrometry	Josephine Bunch	Seconded from National Physical Laboratory and Imperial College London
Co-Director of Biological Mass Spectrometry	Zoltan Takats	Seconded from Imperial College London
Head of Technology	Gwyndaf Evans	Seconded from Diamond Light Source
Financial Controller	Caroline Rudman (Employed May 2021)	Employed Rosalind Franklin Institute
Director of Communications and Culture (up to Jan 2022), Director of Strategic Marketing (Jan ’22 onwards)	Laura Holland	Employed Rosalind Franklin Institute
Director of Human Resources	Lydia Armes	Employed Rosalind Franklin Institute

Remuneration policy

At the Franklin we are passionate about being a great place to work, creating our own identity which is forward thinking and collaborative in our approach to all we do. We like to keep things simple, recognising our people for their efforts and keeping our pay and benefits package competitive but appropriate for a largely government funded Institute. Our people come from a variety of organisations both public and private and it is important to us that we can attract and retain talented people whilst also building and developing high performing and diverse teams.

Reflecting this ethos, we have introduced two major changes to remuneration in 2021-2022. A new process for annual pay increases which recognises contribution and performance in addition to a cost-of-living component has been introduced. Manager recommendations are balanced internally for affordability and approved by the pay committee, a new internal panel which considers both the recommended annual pay increases and meets quarterly throughout the year to consider in year changes, internal promotions, role changes, or retention issues. The committee also considers the results of regular external role benchmarking and equity reviews.

The new annual pay review enables staff and managers to reflect on performance throughout the year, objectives for the year ahead, and training and development needs. The pay committee ensures fairness and transparency in remuneration of staff across the Franklin.

Risk management

Effective risk management is central to the role of the Franklin Board in providing strategic oversight and stewardship.

Led by the Institute Director and the Chief Operating Officer, the Executive Group is responsible for reporting and managing risks, ensuring they are assessed and mitigated in accordance with our risk policy. Risks are detailed using an organisation-wide risk register which offers a rating score, pre and post mitigation. Significant risks are reported formally to the Audit and Risk Committee and Board as they have the ultimate responsibility for risks.

Examples of risks that the Rosalind Franklin Institute currently faces include;

1. Failing to realise the vision of the Franklin institute and capitalise on early gains made across our themes due to a lack of capital funding
2. External inflationary pressures and economic downturn increase running costs to the extent science delivery is compromised
3. Failure to validate our technologies with diverse communities, preventing us from maturing our work appropriately
4. Failure to maintain adequate reserves. Given the nature of the work undertaken at the Franklin, delivering complex programmes over long timescales, our ability to maintain robust reserves to deal with unexpected costs associated with running the facility to the standard required to house our state-of-the-art equipment is essential. We expect to encounter the need to urgently upgrade, adjust or repair equipment. Adequate reserves are essential to deal with such developments without threatening the financial viability of the institute.
5. Lack of leadership resilience in key roles – risking key projects and delivery

The Board seek to ensure that risks are mitigated, so far as is reasonably possible by the actions to be implemented and noted in the register. The mitigation for risks noted above includes;

1. To realise the core mission of the Franklin – to create beyond state-of-the-art technologies in life science, capital funding on an ongoing basis is essential to maintain our leading position and our distinctiveness as a partner adding value to our eco-system. Additionally, iterative ongoing development of existing technologies, and basic enabling capital (fit-out and maintenance capital) are required. Routes to both funding types are in discussion with our funders UKRI-EPSRC, and alternative routes to funding for major new projects are in discussion more broadly. This is one of the most serious risks faced by the Franklin.
2. Historically high inflation across all cost catagories is a broad, global issue from which we are not immune. We are engaging with our funders and landlord on how to best mitigate this pressure both individually and as part of our community.
3. Working closely with our communities through outreach and engagement, and by building an attractive environment for collaboration, we will work proactively to showcase our technologies to validate across multiple domains. Refining our KPIs will enable enhanced tracking and evaluation of validation and impact.
4. Working to our stated reserves policy, created and implemented by the board, this is a key metric for the trustees and is kept under continuous review.
5. Succession planning and development in both operations and science teams, with additional work in leadership development and planning for high achieving staff. This is an ongoing risk carried over from 2020-2021

Legal and administrative information

Our Directors

The Directors of the charitable company are its Trustees for the purposes of charitable law

- Dame Dr Vivienne Cox CBE (Chair)
- Dr Gillian Burgess
- Professor Stephen Caddick
- Professor Helen Cooper
- Mr Stephen Dauncey
- Professor Nora de Leeuw
- Professor Mathias Gautel
- Dr Barbara Ghinelli
- Professor Ewan McKendrick
- Professor James H Naismith
- Professor Nigel Titchener-Hooker
- Dr Anthony Wood (resigned 28/3/2022)
- Dr David Rees (appointed 23/5/2022)

Dr A Wood resigned from his post on 28/03/2022. No new trustees were appointed during the year.
In accordance with the company's articles, a resolution proposing that Richardsons be reappointed as auditor of the company will be put at a General Meeting.

Charity number	1179810
Company number	11266143
Registered office	Rosalind Franklin Institute Building R113 Rutherford Appleton Laboratory Harwell Campus Didcot Oxfordshire England OX11 0QX
Auditor	Richardsons 30 Upper High Street Thame Oxfordshire, OX9 3EZ
Bankers	Barclays
Solicitors	Keystone Law 48 Chancery Ln, Holborn, London, WC2A 1JF

> Our teams have shown great resilience and teamwork during this year. Thanks also go to our collaborators who have housed our teams across the UK, and who have been instrumental in our early success.

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