ROSALIND FRANKLIN, LLAMAS AND DISRUPTIVE TECHNOLOGY

Professor James Naismith is the Director of the Rosalind Franklin Institute and a world-leading expert in structural biology. He became Interim Academic lead at the Franklin in 2017, leading the design and specification of the building, and theme leader for Structural Biology at the Institute. In June 2019, Professor Naismith became the first full Director of the Rosalind Franklin Institute.

July 2020 marked the centenary of the birth of Rosalind Franklin, the pioneering chemist and crystallographer, our namesake.

July also saw the peer reviewed publication of our work on nanobodies directed against COVID-19. This paper is amongst the 0.1 % of most impactful paper this year and 0.02 % ever.

The Rosalind Franklin Institute has a clear mission: to develop technology that will transform the life sciences and lead to better medicines and diagnostics. A mission that is directly inspired by Rosalind Franklin's famous discovery: her 'Photo 51' of DNA fibre.

This breakthrough in the life sciences was made possible because Franklin's expertise in the physical sciences had led her to do a novel experiment. It is predominantly technology that advances the life sciences, and this was a perfect example. As Sidney Brenner, the Nobel Prize-winning biologist, put it: "Progress in science depends on new techniques, new discoveries and new ideas, probably in that order."

In 1952, biologists knew that DNA was central to heredity and physicists understood diffraction could disclose the arrangement of atoms in crystalline material. Crystalline DNA fibres diffract X-rays, so scientists knew it should be possible to determine the structure of DNA, but it still seemed an impossible task. Franklin improved on previous X-ray diffraction experiments by controlling the hydration of the fibre throughout the process. This was crucial: it meant she was able to collect X-ray patterns from separate A and B form of DNA (photo 51 is the B-form). All previous efforts had been a variable mix of both and therefore impossible to interpret.

Image courtesy of Jenifer Glynn

The rest is well-known. Jim Watson saw photo 51 and with Crick made the leap to double stranded DNA. The story is a stunning example of the transformative impact that the physical sciences, if properly directed, can have on biology. What is less well known but really deserves more recognition, is that Rosalind Franklin moved on from her work in DNA and pioneered the use of X-rays to study viruses, making a transformational impact and for which was highly praised by scientists at the time. It remains a tragedy that cancer robbed the world of her talents at such a young age.

MAKING THE BREAKTHROUGH

Yet this sort of disruptive change in science is very hard to achieve. It's not just about talented people: it relies on luck, circumstances and timing.

Think, for example, of the biologist and biophysicist, Richard Henderson. Using his knowledge of fundamental physics, Henderson spent years advocating the use of electrons for imaging biological molecules. Vindication and his Nobel prize came much later when direct electron detectors finally appeared, something Richard had long called for, triggering a 'resolution revolution' in the detail and precision of the structures that could be obtained. In two years, the entire field of structural biology had been transformed.

The Franklin was set up to increase the chances of making this kind of breakthrough: to accomplish major changes in life science by means of interdisciplinary research and technology development.

We are funded through UK Research and Innovation's Engineering and Physical Sciences Research Council, and sit at the heart of the UK's national lab in the Harwell Science and Innovation Complex, home to some of the country's leading physicists, engineers and chemists. We

draw in expertise from our ten partner UK Universities, working with them as a team and enabling them to collaborate further afield.

Our neighbours at Harwell include the synchrotron Diamond Light Source - also one of our partners- the Central Laser Facility, ISIS (neutron source) and the Research Complex.

All of this means is that we can bring people from different disciplines and organisations together with top-level technology, embedded in a campus with extraordinary depth of physics and engineering.

A NATIONAL EFFORT

In the present pandemic situation, we've been able to act as a neutral focus that can lead a national effort for our partners to get engaged in. The Franklin has been at the forefront of efforts to bring the public and private sectors together to find a way through this - something we're very proud of.

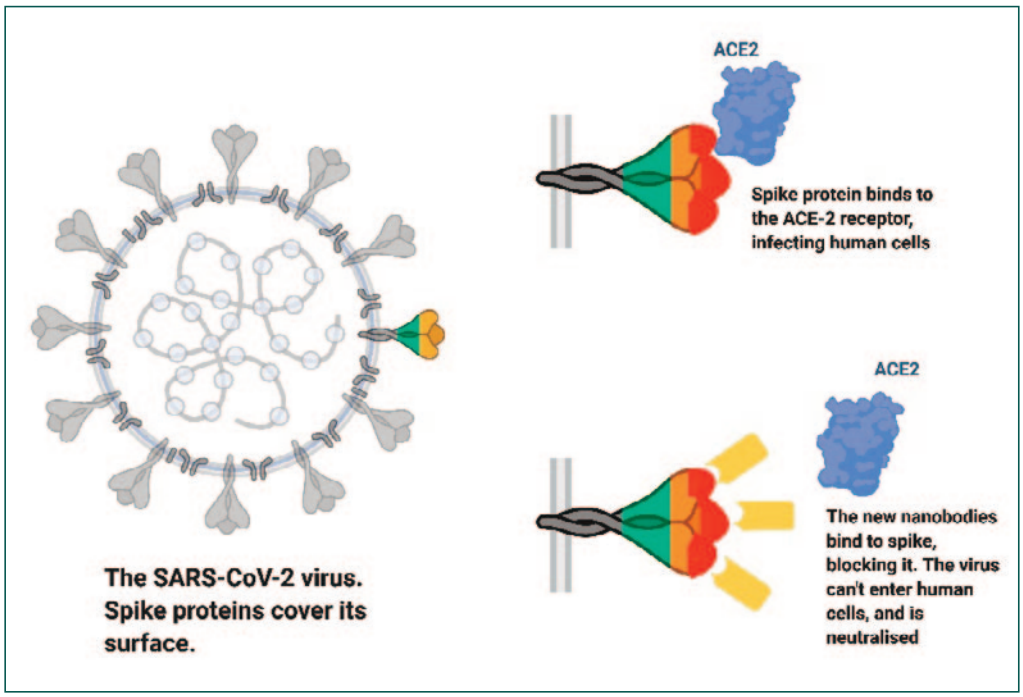
One of our most exciting areas of work relates to antibodies naturally produced by llamas and alpacas, known as nanobodies. These can be engineered in a laboratory to create nanobodies that can be used therapeutically, and also as a research tool to improve imaging of proteins. We are leading the UK's work in this field.

Working with Diamond Light Source, Oxford University and Public Health England, we have shown that these nanobodies can neutralise the SARS-CoV-2 virus in the lab. They do this by binding tightly to the 'spike' protein of the virus, working like a cap on a pen, the nanobodies stop the virus from working.

Using advanced imaging with X-rays, we've also found that the nanobodies bind to the spike protein in a new and different way to other antibodies already discovered. We have also able to combine one of the nanobodies with a human antibody and show the combination was even more powerful than either alone.

But these kinds of discoveries don't happen by chance. Some time ago, The Franklin identified nanobodies as an important technology asset for the country and started to work on them, bringing industry and academia together. One year ago, we had begun to build our nanobody lab. And when the pandemic hit, we were able to switch all that work completely over to focus on the new virus.

As Professor Ray Owens from Oxford University, who leads this nanobody work for The Franklin puts it: "This research is a great example of team work in science. We have created, analysed and tested the nanobodies in 12 weeks; and the team has carried out experiments in just a few days, that would typically take months to complete."



AN ANTIBODY COCKTAIL

There is currently no cure or vaccine for COVID-19. However, the clinical outcomes of critically ill patients have been improved by giving them with a transfusion of serum from convalesced individuals. This serum contains human antibodies against the virus - this process is known as passive immunisation and has been used for more than 100 years. However, it is difficult to identify the right individuals with the right antibodies and then to give such a blood product safely.

This is where nanobodies come in. A completely lab-based COVID-19 specific antibody 'cocktail', which can be made on demand, would have considerable advantages and could be used earlier in the stages of the disease where it is likely to be more effective.

DESIGNED AROUND SCIENCE

Our brand-new home at the Harwell campus, due to complete next year, is key to fostering that ability to collaborate. It will create a place where we can bring people together from different disciplines and those in industry,

Artists impression of the Rosalind Franklin Institute. Courtesy of IBI.

to work on areas where a factor of ten shift in technology is needed.

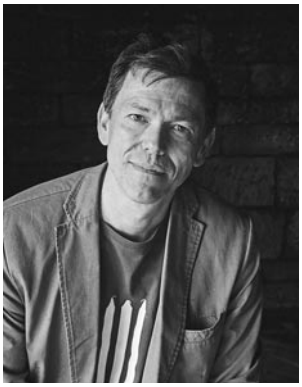
The building itself has been designed around science, providing an environment that mixes biologists and physical scientists to create something special. We have a unique electron microscopy facility, extensive tissue culture, a next generation chemistry lab and a dedicated mass spectrometry workshop. From the start we have designed features in the building to encourage collaboration and technology development. We are welcoming engineers, physicists, chemists, biologists and medics from our university partners and from industry. You could say we are increasing collisions to get a reaction.

FUNDING FOR DIVERSE PROGRAMMES

There are no 'silver linings' of COVID-19, but one outcome seems to be a recognition of how important it is to have a high-capability science base. This needs to include funding for what might seem to be esoteric programmes, such as antibodies from llamas, that subsequently turn out to be crucially important. We welcome the Government's recent R&D Roadmap announcement as a step towards this, along with the increase in public investment in research and development to £22 billion in the next five years. For the UK to become a 'science superpower' however, the kinds of disruptive discoveries we aim to foster will be more important than ever.

There's a vital role for experimenting in innovative ways with new technology. We believe that's a view Rosalind Franklin would support. □

THE SCIENCE OF COVID: LESSONS TO BE LEARNED FROM THE FRONTLINE



Professor Hugh Montgomery MB.BS BSc FRCP MD FFICM FRI
Professor of Intensive Care Medicine, UCL and Director, UCL Institute for Human Health and Performance

The Covid pandemic is a witches' brew. The recipe starts with environmental destruction, changes in animal husbandry and 'wet meat' markets abroad, mixing different species in high density and in close proximity to humans. We then add the virus itself.

Until recently, only four coronaviruses infected humans, causing generally mild upper respiratory tract disease. But in only 17 years, three more have jumped from animals to infect humans: SARS-CoV-1 (from bats/civets) in 2003, MERS (from camels) only 10 years later, and SARS-CoV-2 (which causes COVID-19 disease) seven years after that. Whilst SARS-CoV-1 and MERS were highly dangerous (killing 14% and 34% respectively of those infected), they were not hugely infectious. SARS-CoV-2 is different. It still kills 1-2% of those infected (compared to 0.1% for seasonal flu), and one in 5 of those over 80 years of age. But it is highly contagious through droplet spread (over 2m or so distance), by hand through contact with surfaces on which those droplets (and then contact with the mouth or eyes) but also (perhaps to a lesser extent) through distant aerosol carriage.

Add an incantation of 'we must all now meet again, on hols and boardroom and on plane'. Fifty-nine years ago, not a single commercial airline passenger had ever flown in a jet. By the end of 2004, two million jet passengers flew each year. In 2019, 144 flew every second.

Don't forget the inequality and poverty. The poor tend to live in close proximity. And when you do lock down, they have to go to work, often in public facing roles (care workers, shops, public transport). They are far more likely to have the sorts of diseases which make severe COVID more likely (obesity, diabetes, high blood pressure and more).

Delay lock downs, and watch as each person infects 3 more. Who each infect three. By the 10th cycle, nearly 90,000 people have been infected. Over 1770 will die. On 11th January, there were 41 cases worldwide. Eleven weeks later, there were over 4 million. By late September, there had been over 31 million.

On the frontline in Intensive Care Units (ICUs), we heard the roar of the approaching tsunami, but could not truly be prepared. This was unlike any other disease we had ever seen- affecting the lungs, yes, but also (we learned as we went along) the brain, nerves, muscle, heart,