The Lister Institute

Celebrating 125 years 1891 – 2016

Contents

FOREWORD

Lord Iveagh

I am honoured to be invited to write the opening lines to this wonderful publication as we celebrate 125 years of pioneering science funded by the Lister Institute of Preventive Medicine.

The Guinness family has had a close relationship with the Lister Institute for most of the Institute's existence. The fascinating story of how my ancestor, Edward Cecil Guinness, the first Earl of Iveagh, became involved in the Institute through his generous donation bears re-telling; I encourage you to discover this tale and many more stories of human generosity and genius in the pages of this publication. The 'hands on' involvement of the family continues right through to the modern era with Edward Guinness, who served on the Institute's Governing Body from 1968-2001 and, more recently, with my brother, the Honourable Rory Guinness, who is currently a member of the Governing Body.

Those of you with a strong relationship to the Lister will be aware of the superb history of the Institute, written by Lesley Collier (a great Lister hero himself) and published in 2000. You can find a PDF version of this book, *The Lister Institute of Preventive Medicine: A Concise History*, at the back of this publication. Rather than duplicate his work, the current publication brings the story up-to-date by recognising the outstanding young scientists we have funded since 1982 via Lister Fellowships and Prize Awards.

We also wanted to include a perspective from the people who support the Lister behind the scenes including Michael French, Chair of the Finance Committee, and Patrick Maxwell, who chairs the Scientific Advisory Committee. The Institute would not be where it is today without their wise counsel.

Scientific knowledge is advancing at an accelerating pace, with great attendant benefits for humankind. The Lister Institute can be extremely proud of its contribution to these advances. Infectious diseases are no longer the major killer in developed countries (although the real threat of resistance to antibiotics may change this), however, they continue to be a major cause of death globally. It is, therefore, appropriate that, while funding work on basic biology, we have fellows working on a wide range of clinical challenges including infection, cancer and genetic disorders.

I would like to give my thanks to Kate Law, current Director of the Institute, for all the time she has put into bringing this publication to life, alongside the author, Edwin Colyer, who has devoted many hours to researching the Lister's legacy and interviewing the numerous contributors. Thanks also go to Professor Cheryll Tickle for her welcome editorial scrutiny, Heidi Houlihan for support in sourcing photographs and to Simon Owen for the graphic design.

Finally, my thanks to all those who gave so freely of their time to ensure this work is a worthy celebration of 125 impressive years of the Lister. I hope it will also serve as inspiration for future generations of Lister scientists who find themselves standing on the shoulders of the many giants who came before them.

Edward Guinness, Fourth Earl of Iveagh

Celebrate our success

Alex Markham finds inspiration in the Lister Institute's long heritage of world-changing biomedical research. He believes that today's Prize Awards should support equally impressive medical advances.

Sir Alex Markham

Sir Alex Markham has been Chair of the Lister Institute's Governing Body since 2011.

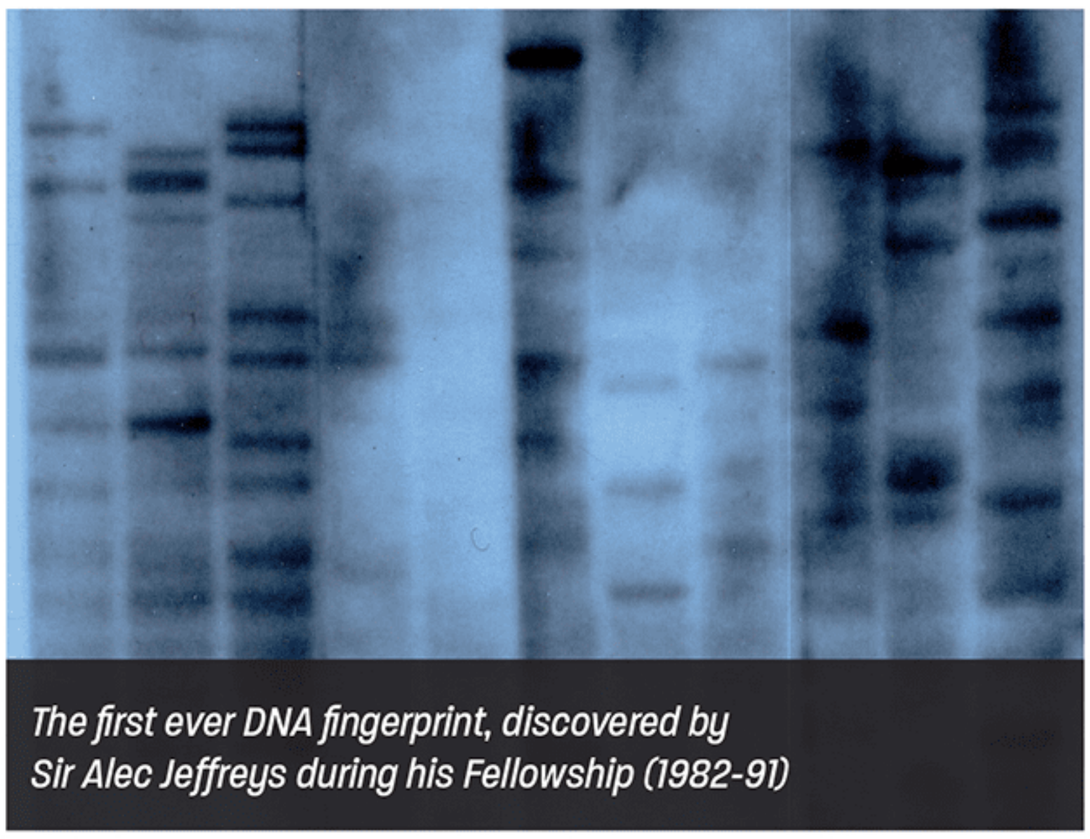
I'm delighted to welcome you to this wonderful publication, which celebrates our 125th Anniversary. It is both a privilege and a humbling experience to be the Chair of this impressive organisation. The Institute can emphatically claim significant and wide reaching impact in pushing the frontiers of scientific knowledge and its medical application since the end of the 19th century, before many of the medical advances we now take for granted ever existed.

Lister scientists have been behind some of the 20th century's greatest advances and developments in the life sciences. Within these pages you will encounter remarkable scientific discoveries and medical applications that have undisputedly changed the world and that still contribute to health and well-being today. We also look forward to further breakthroughs as the impact of research by more recent Prize Award winners begins to unfold.

When I tell the stories of the Institute's successes I'm always surprised by how little all this is known. Here is an organisation founded two decades before the Medical Research Council (MRC); an organisation whose scientists produced the UK's first diphtheria vaccine, unravelled the mechanisms of yeast metabolism, made it possible for the World Health Organization to eradicate smallpox, supplied the NHS with blood products for 30 years and discovered DNA fingerprinting. This is the stuff of legends!

Of course, many of these stories are from the distant past, although the influence of the Institute's research heritage lives on today. If you don't know our 'ancient' history, I encourage you to read Leslie Collier's wonderful tribute, *The Lister Institute of Preventive Medicine: A Concise History* (2000) which you will find on the USB memory card at the back of this publication.

For our 125th Anniversary we bring the history up-to-date. You will find many stories, for example, about what our funded researchers have achieved since the Institute launched its Fellowships Programme in 1982. We bring you recollections and insights from just a few of the 137 former Fellows and current Prize Award researchers who have benefited from our funding over the past 34 years. Their science is incredibly diverse, often impacting on medical practice, always fascinating and in many cases still in its infancy. Where will it all lead?



The first ever DNA fingerprint, discovered by Sir Alec Jeffreys during his Fellowship (1982-91)

Sir Arthur Harden in his laboratory

I actually prefer real history to metrics, but perhaps a few numbers help to illustrate the impact of our funding schemes. Among our current and ex-Fellows (the latter are now Members of the Lister) we count 85 Professors (including one Regius Professor), nine Fellows of The Royal Society of Edinburgh, seven Fellows of The Royal Society and two Vice Chancellors, not to mention hundreds of other prestigious medals, prize lectures and awards. Leszek Borysiewicz and Alec Jeffreys received knighthoods for their services to research in medicine and genetics, respectively. Sir Arthur Harden, joint winner of the Nobel Prize for Chemistry in 1929, carried out most of his research in the Institute and we can trace influential links to several other Nobel laureates. I also firmly believe that we have existing Members worthy of the Nobel Prize too!

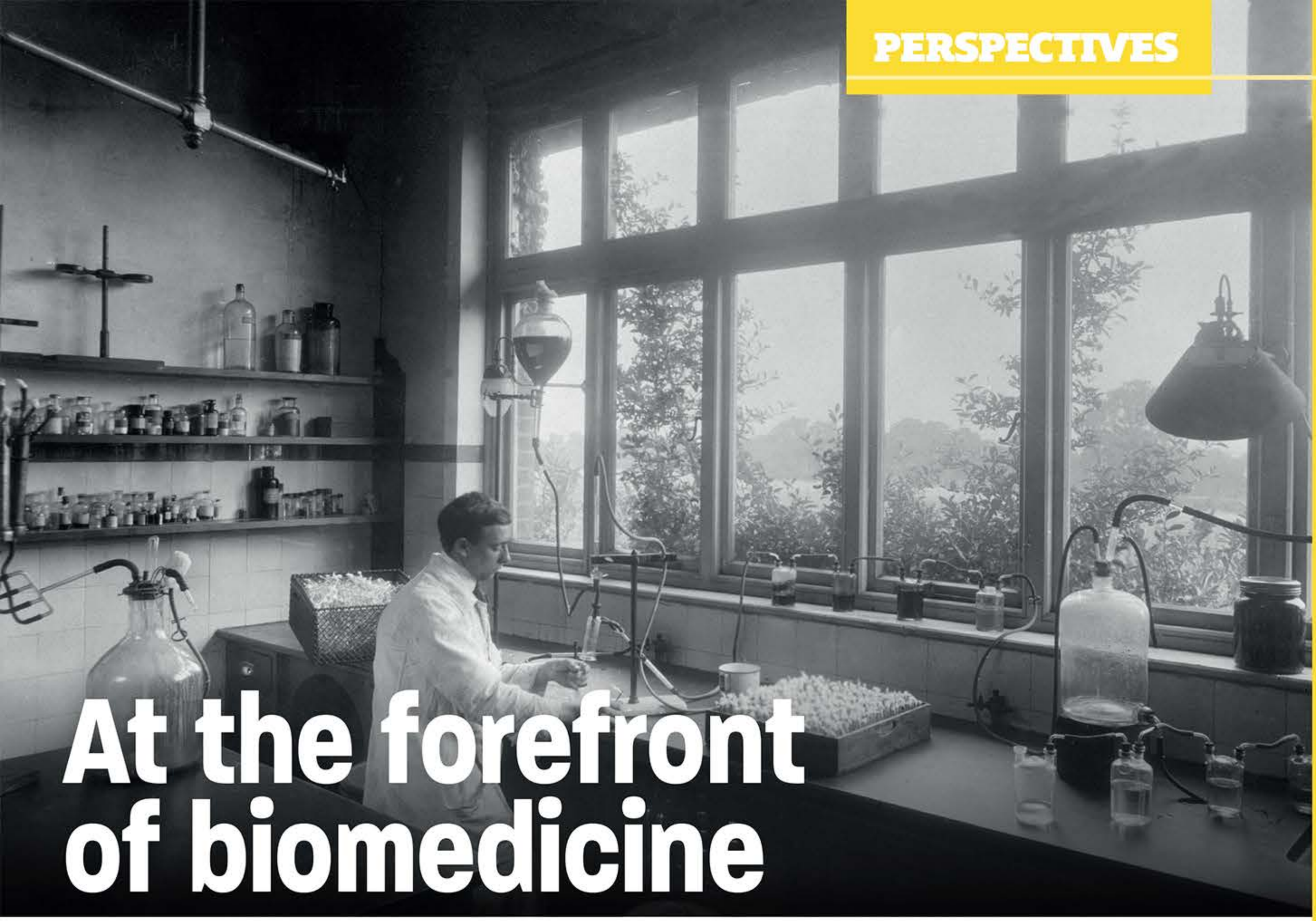
In this publication we merely offer snapshots of our work – an eclectic mix of researchers who express similar gratitude for the support that Lister funding has given them. Our present Prize Awards are around £200,000, but the recipients are no less appreciative than were the recipients of the five-year, fully salaried Fellowships. Everyone talks about how the flexibility of Lister funding gives them freedom to focus on their research, explore interesting avenues and find their feet as early career researchers. I'm delighted that through many ups and downs, the Lister has retained its historical independence; today we can offer a wonderful slice of scientific freedom to the people we fund.

As I read the commentaries in this publication I can't help but admire how the Lister is a catalyst for success. We seem to have the knack for identifying young people with potential. A Fellowship or Prize Award is more than some spending money in the research coffers; it's a vote of confidence in the person and it seems to unlock other grants and open scientific doors.

I thoroughly enjoy my trips to universities and institutes around the British Isles to meet Prize Award winners and present them with their Lister mementoes. These are splendid days of celebration, as is our annual meeting where we listen to brilliant young scientists enthuse about their work and the impact on society they hope to have. That meeting – in my opinion the best biomedical research day in the country – reinforces the sense of community and camaraderie that people often say is special about the Lister. Members offer support and advice to one another and the mentoring younger researchers receive simply by mixing with their senior colleagues is invaluable at this tough stage in their careers. Today's Prize Award winners come from right across the UK and Ireland and I think we play an important role in supporting provincial universities and integrating their excellent researchers into mainstream national activities and professional networks.

Indeed, what the Lister does – giving excellent early-career scientists some flexible funding and a support network – is hugely underdone in this country. Although we support only a small number of early-career scientists each year, we punch above our weight. The Lister Institute is unquestionably a gem in this country's scientific infrastructure.

Serge Mostowy, a 2015 Prize Award winner, with Alex Markham.



At the forefront of biomedicine

From its Victorian roots to today's prestigious annual Prize Awards, the Lister Institute has supported top scientists in their research to prevent and cure disease. Its contribution to global medical advance over the past 125 years is astounding.

It was the age of steam, commerce and Empire. An age of invention, innovation and economic growth. It saw the invention of the telephone and radio, motorcars and the movies, the London Underground and electric street lights.

Yet despite this rapid technological development, medicine in Victorian Britain still had a long way to go. Life expectancy was less than 50 with infectious disease as the top killer. Diphtheria claimed the lives of thousands of children each year and smallpox outbreaks were not uncommon. Even bubonic plague was a threat as it resurfaced in China and spread fast through Eastern Asia towards the end of the 19th century.

In 1898 the Institute was renamed the Jenner Institute, but changed again in 1903 to become the Lister Institute as it is still known today.

Scientists were hard at work, however, in their efforts to tackle disease. By the turn of the century the work of Louis Pasteur in France and Robert Koch in Germany had traction and Joseph Lister's work on antiseptics and sterilisation was finally reaching everyday clinical practice. But without a specialist centre to focus on infectious disease research, Britain risked falling behind other countries in the research effort.

The founding

The founding of the British Institute of Preventive Medicine, as it was first called, owes its conception to the then Lord Mayor of London, Sir James Whitehead. In 1889 he visited the Institut Pasteur and was so impressed by the rabies treatment it administered that he returned home to raise funds for its support. However, the plan soon became more ambitious, with Lord Lister, the prominent chemist Sir Henry Roscoe and other big names getting involved to set up this a UK equivalent. The Institute was officially inaugurated in London on 25 July 1891, just three years after the opening of the Institut Pasteur.

Fund-raising for this new Institute was slow, however. There was no tradition at the time of public subscription, but philanthropic donations – and a large bequest from an Irishman, Mr Richard Berridge, who left £200,000 "for advancing the sanitary and economic

sciences" – provided enough to purchase land in Chelsea at a discount price from the Duke of Westminster. Building work on the site commenced in 1894 and the first laboratories opened in 1898.

While the Chelsea laboratories were under construction, scientific research had already begun in earnest. In 1893 the Institute amalgamated with the College of State Medicine giving it access to existing College laboratories in Great Russell Street. Research progressed rapidly: in 1894 scientists, led by interim Director of the Institute and Pasteur protégé Armand Ruffer, successfully immunised a pony called Tom to produce antisera against diphtheria. Inoculations saved the nephew of one of the researchers and soon after the lead researcher, the neurologist and future Nobel Prize winner Charles Sherrington who was acting as Professor-Superintendent of the Institute at the time. Diphtheria remained one of the Institute's key research concerns for many years: the Institute continued to manufacture diphtheria vaccine until the eventual closure of its production facilities in 1978. Over that period, life expectancy at birth in the UK had risen by over 20 years (to 70 plus).

The Guinness connection

It took a series of coincidences to transform the early Institute into the biomedical research powerhouse it then became for the next three-quarters of a century. On a February morning in 1896, a dog bit Jim Jackson, a groom at Elveden Hall, the Suffolk estate of Edward Cecil Guinness, first Earl of Iveagh. With no treatment available for rabies in the UK, Lord Iveagh's physician immediately sent Jim to Pasteur in Paris, where he received the vaccination. Lord Iveagh had given £5000 in the initial appeal for the Institute, but the close call for a favourite member of his household staff brought his attention once again to its work. Just before Christmas In 1898 Lord Iveagh gave a staggering £250,000 (equivalent to around £20 million today) from his personal fortune, providing enough annual income to complete the Chelsea building programme, generate the salaries of staff and provide scholarships for promising researchers. Combined with the growing income from sales of sera and vaccines, the future of the Institute looked secure.

Arthur Harden received a knighthood in 1926 and shared the Nobel Prize for Chemistry in 1929.

From bacteria to blood

Since these early days, Lister researchers – first staff, now Fellows and Prize Award winners – have kept up a steady stream of ground breaking discoveries and clinical applications. The Institute has also become the proving ground for Fellows of the Royal Society, Nobel Prize winners and recipients of many other prestigious awards. A short overview cannot do justice to all the breakthroughs and discoveries of Lister scientists; a few highlights must serve to illustrate the impact this Institute has made on British biomedical research over more than a century.

In 1900 Arthur Harden began his studies of cell physiology in the new Chelsea laboratories. Here he invented a method for measuring how much CO_2 yeast produced during fermentation. Harden led collaborations spanning 30 years that discovered the first co-enzyme and how enzymes phosphorylate sugars.

In 1902 the Institute purchased Queensbury Lodge near Elstree village in Hertfordshire. With its 28 acres of land, this estate became home to the Institute's serum unit and vaccine production facilities.

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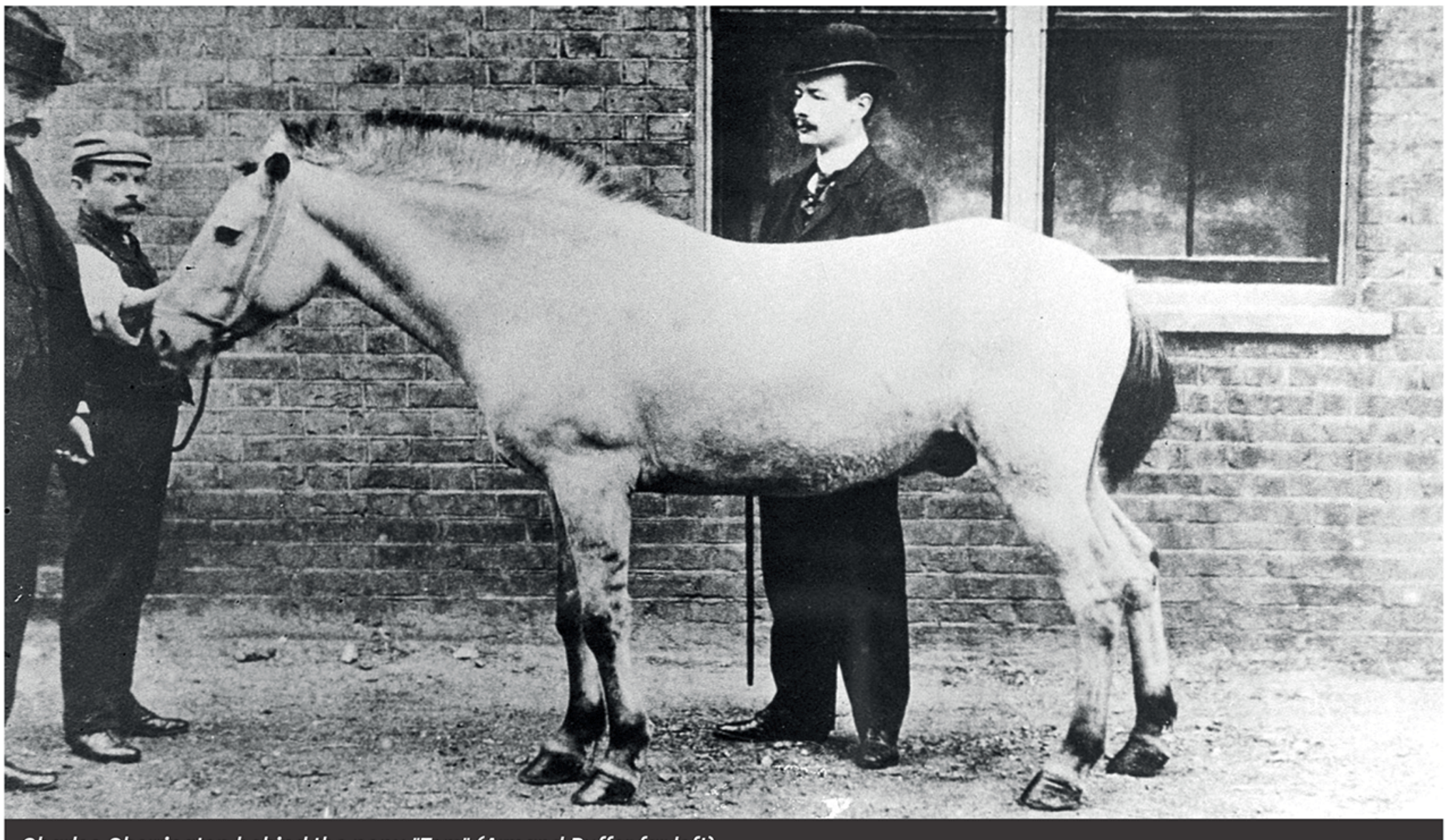

Charles Sherrington behind the pony "Tom" (Armand Ruffer far left)

The Royal Society elected Muriel Robertson as a Fellow in 1947 making her among the first women to be granted this honour.

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During World War I Lister scientists who were not called to clinical duties or the front line focused on military medical research. Muriel Robertson, for example, switched from her pioneering studies on trypanosome parasites to investigate the causes of gas gangrene which sadly killed a high proportion of wounded soldiers. Muriel helped to isolate three species of *Clostridia* and produce antitoxin serum for treatment of the condition. The Lister scientist Henry Dakin developed a hypochlorite solution, commonly known as Dakin's solution, which was used to treat wounds during and after the war until the arrival of antibiotics. The Institute also produced the UK's stocks of tetanus antitoxin for the treatment of wounded soldiers.

When peace arrived in 1918 the Institute became a bastion for fundamental medical science, with particular strength in bacteriology and a growing portfolio of research in virology. John Ledingham, who had deduced during the war that trench fever was caused by the bacterium *Rickettsia quintana* and spread by lice, led research on the pox viruses. Joseph Arkwright, great-great-grandson of the industrialist Sir Richard Arkwright, continued work on *Rickettsia* and its role in typhus. Between the wars the Lister laboratories witnessed the first isolation of rough and smooth variants of salmonella, the discovery of the curious Weil-Felix coagulation reaction (used in the diagnosis of typhus fever) and Emmy Klieneberger's discovery of non-pathogenic L-form bacteria.

World War II saw a second dispersal and redistribution of staff and activities, with a more immediate focus on vaccine production and immunisation. It was around this time that the Lister also cemented its leadership in immunological studies of blood, supported by the arrival in 1943 of Dr (later Sir) Alan Drury as Director, formerly the Chair of the MRC Blood Transfusion and allied Committees.

Rise and fall

With its finances under pressure after the war, external funding became the norm, with groups typically supported wholly or in part by grants from other bodies such as the MRC. The country entered another era of intense scientific endeavour and the Institute remained at the forefront of biomedical research. At the same time, demand for the Lister's vaccines began to rise; income from these products was soon supplemented by sales from a new unit at Elstree for the production of blood products.

With the arrival of the National Health Service in 1948, the British Government had determined that the UK should become self-sufficient for blood plasma and essential blood protein factors such as fibrinogen, thrombin, immunoglobulin and albumin. Lister researchers Ralph Kekwick and Margaret Mackay developed an ether-based precipitation procedure for blood protein extraction which they brought into pilot production.

By 1956 demand had reached such a level that production moved to a new building in Elstree: the Blood Products Laboratory, a department of the Institute but fully funded by the Ministry of Health. Here Lister researchers were the first in the UK to purify a clinically effective Factor VIII concentrate used in haemophilia patients. In 1963 the Blood Products Laboratory also prepared the first anti-D immunoglobulin used in a trial to prevent the sensitisation of Rh-negative pregnant women bearing Rh-positive babies, a treatment still used today. The Blood Products Laboratory eventually took over the Plasma Fractions Laboratory in Oxford. Here it developed the radio-immunoassay used nationally to screen blood donations for hepatitis B virus.

The annual weekend remains a key element in the Lister's aim to nurture early-career scientists. It provides a unique opportunity to network with peers from a vast array of disciplines alongside eminent research leaders in their field.

Walter Morgan (rear centre) meets the Queen Mother

1966 The Lister Institute Staff Photograph.
Front row (l-r): S. A. White, R. R. Race, G. G. Meynell, R. A. Kekwick, L. H. Collier, W. T. J. Morgan, A. A. Miles, W. d' A. Maycock, A. F. B. Standfast, B. G. F. Weitz, C. Kaplan, D. E. Colby, G. J. Roderick
2nd row (l-r): W. A. Blyth, A. M. Lawn, G. M. A. Gray, W. E. Parish, J. M. Creeth, F. R. Wells, W. M. Watkins, M. E. MacKay, J. M. Dolby, D. Ellis, L. Vallet, C. Shaw, H. G. S. Murray, G. S. Turner
3rd row (l-r): D. Z'Derman, P. Tippet, R. Sanger, E. J. H. Lloyd, B. A. Prideaux, R. M. Lemcke, D. G. Godfrey, M. P. Banks, M. H. malkinson, A. E. R. Taylor, D. C. Miller, C. M. G. Giles, H. D. Nunn, T. B. Philips
4th row (l-r): A. Staley, E. J. Gavin, W. P. Aston, B. Mason, V. Petrovskaya, A. S. R. Donald, S. M. Lanham, J. J. Wells, S. T. Edwards, N. C. Mahoney, W. H. Sawyer, B. I. Bristow, J. Taverne, P. Reeve
5th row (l-r): B. J. Dod, A. E. Smithm M. Kai, D. R. Body, G. B. Hay, J. C. Holt, J. M. Jones, J. M. Walsh, L. C. Robinson, A. M. Marr, B. D. Ward, G. Williamson, E. D. Wesley, F. R. Hunter, A. V Payne

Over a period of 25 years after World War II the Institute gathered momentum and attracted some of the country's leading scientists in immunology, vaccination, biochemistry and genetics. Here, for example, Walter Morgan dedicated more than 20 years to the study of blood antigens, finally publishing the structure of the A and B blood groups in 1965. The Institute also established one of the country's first research units for bacterial genetics, led by Bruce Stocker. Research continued across the spectrum of biomedicine from metabolism to inflammation. Infectious diseases were not forgotten: trypanosomiasis remained an area of expertise, but pathogens of interest included *Chlamydia*, rabies and the vaccinia virus. One of the Institute's most significant achievements during these "golden years" was Leslie Collier's successful stabilisation of the smallpox vaccine for use in the tropics. With this breakthrough, the World Health Organisation successfully spearheaded the worldwide eradication of the disease.

Closures and openings

From the late 1960s the Institute entered a period of decline. The Institute's finances took a heavy toll from the downturn in the UK economy, but it was the Medicines Act of 1968 that sounded the death knell. Having ploughed all its profits from vaccine and blood products sales into funding research – and with no protected intellectual property to fall back on – the Institute had no reserves with which to upgrade its manufacturing facilities to meet the requirements of the new legislation.

Despite its noble history, the Institute could not persuade any public funding body to provide support at that time,

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Summary of sera and vaccines prepared by The Lister Institute, Elstree

Antisera	*Bacterial vaccines*	*Virus vaccines*
Diphtheria	Diphtheria	Smallpox
Tetanus	Tetanus	Rabies
Gas gangrene	Pertussis	
Rabies	Cholera	
Scorpion	Typhoid & paratyphoid	

Aerial photograph of the Elstree site

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forcing the Chelsea laboratories to close in 1975 (the site was sold in 1980 for £2.7 million). With no new products in the pipeline and unable to invest enough in its facilities, the Vaccines and Sera Department at Elstree closed in 1978, although the Blood Products Laboratory continued its production under new National Health Service management.

But the Lister Institute was certainly not dead. Determined to remain at the forefront of research – and with significant investment capital from its sale of the Chelsea laboratories and Elstree site – the Institute launched its Fellowships Programme in 1982.

In 1991 the Lister Institute received the Oliver Memorial Fund award in recognition of its work in transfusion research. The Fund was established in 1944 to commemorate the work of Percy Oliver who set up the country's first blood donor panel. Over the years eight individual awards have been given to Lister staff or workers in Institute-hosted units.

Research Fellowships

The Fellowships gave individual researchers attractive salaries and laboratory running costs for five years, freeing them up from teaching and other university duties to focus on their research. They were awarded to stellar early-career scientists with significant post-doctoral experience. The scheme targeted researchers in the first throes of becoming independent scientists and trying to set up research groups – still the hardest time to secure funding because they have to compete head-to-head with professors and life-long researchers with established track records. At the time, the Lister Fellowships were among the very few in the country prepared to offer five years of funding on flexible terms, especially for novel projects with high degrees of risk.

In its first year the Institute awarded five Fellowships from 44 applications. Alec Jeffreys, Judith Armitage, Alex Law and Stephen Perkins are now professors while Marius Clore, known for the development of three- and four-dimensional nuclear magnetic resonance spectroscopy, is a Distinguished Investigator in the National Institutes of Health in the USA. Judith Armitage and Sir Alec Jeffreys are both Fellows of The Royal Society.

The Institute's Studentship Scheme funds undergraduates to spend a summer working in the lab of a Lister Fellow or Member.

In 1985 the Institute held its first Fellowship weekend, following the success of several informal gatherings between Fellows, Members and the Governing Body. St John's College, Cambridge, hosted the first weekend meeting, which included presentations from Fellows on their research as well as talks from invited guests. Positive feedback from the Fellows ensured the weekend became an annual event, which continues to this day.

Just a few years into the Fellowship scheme the Institute once again hit the headlines with a discovery of global proportions. In 1986 Alec Jeffreys published his discovery of DNA 'fingerprinting'. Alec had developed two DNA probes that bound to highly variable fragments in enzyme digests of DNA. Each probe produced distinct band patterns of DNA blotted from gel electrophoresis which made it possible to differentiate DNA from unrelated individuals with high accuracy.

Alec immediately recognised the application of his discovery, especially in criminal forensic investigations and paternity disputes. The Institute helped Alec to patent his technology and license it for commercial development.

Lister Prize Award

By 2002 the Fellowship scheme had funded 95 Fellowships, ranging across subjects from DNA replication to neurology, as well as some of the Lister's more traditional areas of microbiology, cell metabolism and immunology. However, despite their clear contribution to the personal development and research of leading scientists, these generous Fellowships proved difficult to sustain financially. Throughout the two decades of the scheme the costs of scientific research – and especially research infrastructure – had skyrocketed; the Institute could no longer responsibly make such long-term commitments.

Dame Bridget Ogilvie, Chair of the Governing Body (2002-2011), helped to launch today's Prize Awards.

"The Prize Awards allowed as much freedom as possible for the recipient to decide on what and when to spend the funds."

Over the first decade the Institute has allocated a total of £7.5 million to 41 Prize Award winners.

The historical change in fortunes of the Lister has arguably been a blessing in disguise. Once the Institute was home to many excellent researchers; today it focuses on nurturing talented individuals who show great promise. The Prize Award winners are all exceptional researchers, but they are at a critical stage in their careers. The Lister's financial support and mentoring from Members undoubtedly enables them to pursue world-leading research and add to the Institute's impressive history for driving medical advances around the world.

When Dame Bridget Ogilvie took the Chair of the Governing Body in 2002, she realised that the Fellowship Scheme was no longer sustainable financially. Moreover, the MRC, Wellcome Trust and other funding bodies had followed the Institute's lead and introduced their own (and sometimes more generous) Senior Fellowships.

Bridget closed the Fellowships and spearheaded efforts to reduce running costs. 'The White House' headquarters in Bushey Heath was sold and the three part-time staff, including Dr Trevor Hince as Director, switched to home working.

Now the Lister was ready for its next bold step: the launch of the Lister Prize Awards.

The Prize Award offered a one-off lump sum payment of £150,000 (currently £200,000) to a small number of scientists each year. This new scheme was simple to understand and easy to run with minimal administration and no additional long-term financial commitment for the Institute. Yet it still gave promising early-career scientists (up to 10 years post-PhD allowing for career breaks, medical training, etc) a substantial sum of money for spending on their research however they wished.

This type of "no strings attached" funding is rare in the current British system. It enables the outstanding young scientists who succeed in the Institute's rigorous selection processes to take on novel, high risk/high reward, ground-breaking research that is difficult to fund through standard peer review processes.

The Institute continues to hold its annual meeting where Prize Award winners can share their experiences of 'life after post-doc' as well as learn from the wisdom of esteemed Members and former Fellows.

Former Directors of the Lister Institute

Years	*Director*
1893 -1896	Dr M. Armand Ruffer (interim Director)
1896 -1903	Dr Allen MacFadyen (interim Director)
1903 -1930	Sir Charles Martin CMG, FRS
1930 -1943	Sir John Ledingham CMG, FRS
1943 -1952	Sir Alan Drury CBE, FRS
1952 -1971	Sir Ashley Miles CBE, FRS
1971-1972	Professor David Evans CBE, FRS
1972 -1975	Professor Walter Morgan CBE, FRS

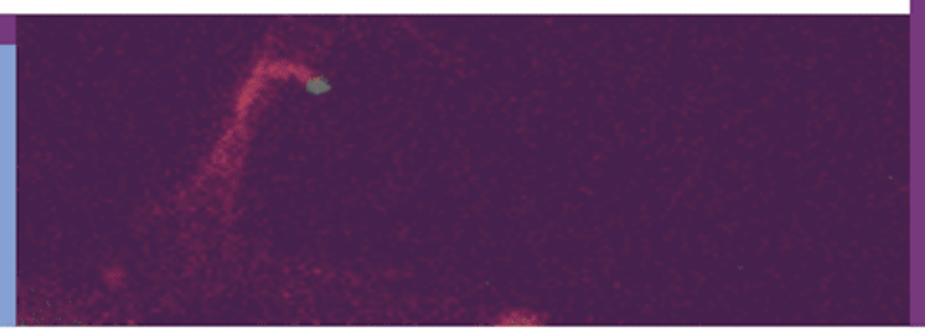
New uses for an old vaccine

PROFILE

Professor Geoffrey Smith

Department of Pathology
University of Cambridge

Fellowship: 1988–92
University of Cambridge,
University of Oxford



Geoffrey Smith is using vaccinia virus to create new vaccines and as a tool to dissect the processes of inflammation and the immune response to infection.

When Geoffrey obtained his Fellowship in 1988, his father, who was a surgeon, told him about a Lister connection: his great-grandfather, Thomas Johnstone, had been taught by Lister as a medical student in Edinburgh in the 1870s, thereafter working for him as a surgical dresser. Among the family archives is a testimonial written by Lister that supported great-grandfather Johnstone's appointment as Medical Officer for Health in Ilkley, Yorkshire.

"I knew nothing about this when I applied for the Fellowship," Geoffrey remarks. "It's a coincidence that Lister is behind my Yorkshire roots and the Lister Institute supported my early research career in England." Geoffrey was well aware, however, of the Institute's historic role in smallpox research and the manufacture of smallpox vaccine.

> "The virus is an amazing tool leading us to new discoveries about how the immune system works."

While working as a post-doc in Dr Bernard Moss's group at the National Institutes of Health, USA, Geoffrey helped develop vaccinia virus so it would produce signature proteins (antigens) from pathogens in a way to prime the immune system but not cause disease. This method of antigen expression is ideal for vaccine research. "Thanks to smallpox eradication, vaccinia virus was no longer needed for smallpox vaccination, but we still wanted to use the virus, with genetic modification, to make a vaccine against other pathogens. To improve the vaccine I wanted to understand the genes in vaccinia that affected its virulence. An application for a Fellowship to do this research seemed to fit perfectly with the Lister Institute's ambitions and research heritage."

During his Fellowship, first in Cambridge and then at the University of Oxford, Geoffrey identified numerous genes that affect virulence by influencing the immune response to infection. He has researched these genes ever since, trying to understand how they work and the activity of the proteins they encode. "My work is part virology, part immunology," he explains, "and these go hand in hand. My research has taught us not only what makes the virus virulent, but also something about how the immune system works."

Early on in his studies Geoffrey identified a secreted vaccinia protein that binds the inflammatory cytokine IL-1ß. The viral protein resembles the host cell's surface IL-1ß receptor, so outside of the cell it captures the cytokine; this prevents it from binding to the cellular IL-1ß receptor and triggering an inflammatory response. Geoffrey showed that the secreted protein prevented animals from developing a fever following infection (a normal response to infection that may restrict some pathogens from multiplying in the body).

Geoffrey chairs the World Health Organization (WHO) expert committee that oversees research with variola virus, which causes smallpox, before stocks of this virus are destroyed as mandated by a resolution of the World Health Assembly in 1996. In 2015, on behalf of the WHO, he witnessed the destruction of a batch of variola viruses that scientists had discovered at the National Institutes for Health, USA, the previous year. Samples of variola virus are still held by the Centers for Disease Control and Prevention in Atlanta, USA, and the Russian State Research Center of Virology and Biotechnology in Novosibirsk.

He also discovered that vaccinia makes the enzyme 3-ß-hydroxysteroid dehydrogenase. This enzyme is involved in the synthesis of steroid hormones, such as glutocorticoids, that are natural immunosuppressants. By making this enzyme, the virus is able to suppress the host's immune defences around the site of infection.

More recently his group discovered a new pattern recognition receptor (host sensors that detect virus infection and sound the alarm) called DNA-PK and also a vaccinia virus protein that antagonises this host defence to enable the virus to escape detection.

These discoveries have revealed that viruses do not just invade and replicate in host cells; some viral proteins also aid virus escape and spread by disrupting host immune responses. "Vaccinia is a great tool for studying immunology," Geoffrey says. "Take out any one gene and you may get a marked change in virulence, helping you to work out the function and mechanism of action of the protein the gene encodes. The virus is an amazing tool for dissecting the immune system and leading us to new discoveries about how the immune system works."

Geoffrey served on the Institute's Governing Body from 2003 to 2013. "It was an invitation I wasn't going to turn down. It's very rewarding to be able to give something back to a wonderful organisation that was so supportive and crucial to the success of my research career."

The final frontier in smallpox eradication

Without Leslie Collier's method to stabilise the smallpox vaccine, would the World Health Organization have been able to eradicate this deadly disease?

Leslie Collier was Head of the Lister Institute's Department of Virology from 1955 to 1974.

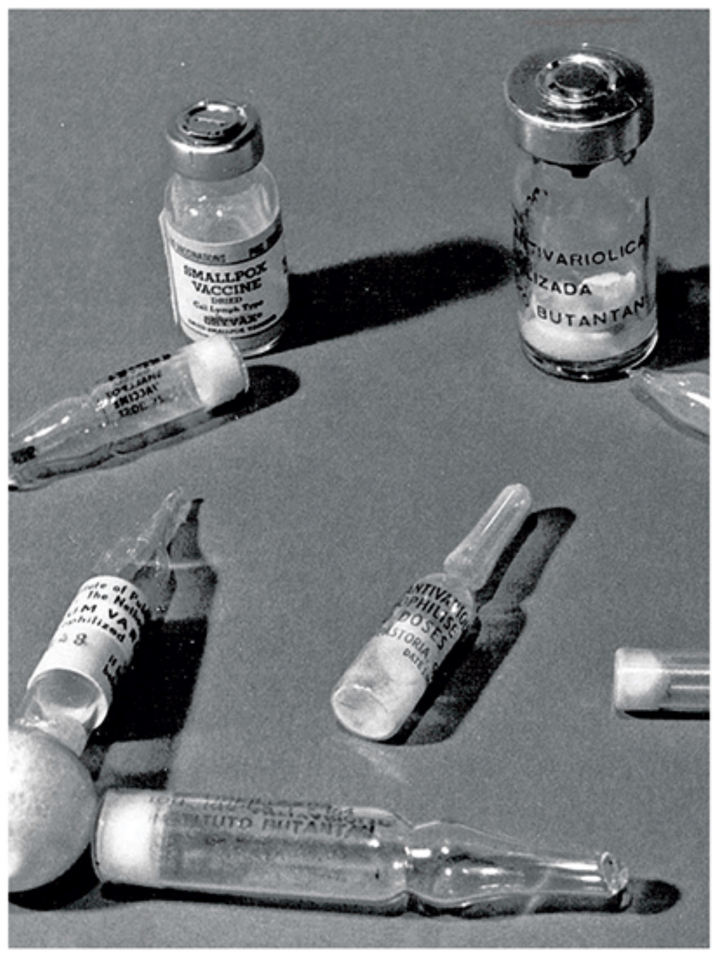
From its conception in 1891 right through to the closure of its Elstree production facility in 1978, the Institute produced and distributed almost all of the smallpox vaccine used in the UK. The Institute was responsible for holding enough reserves of the vaccine to stock an emergency vaccination programme in the event of a smallpox outbreak. In one event in 1962, Elstree issued more than two million doses within a week.

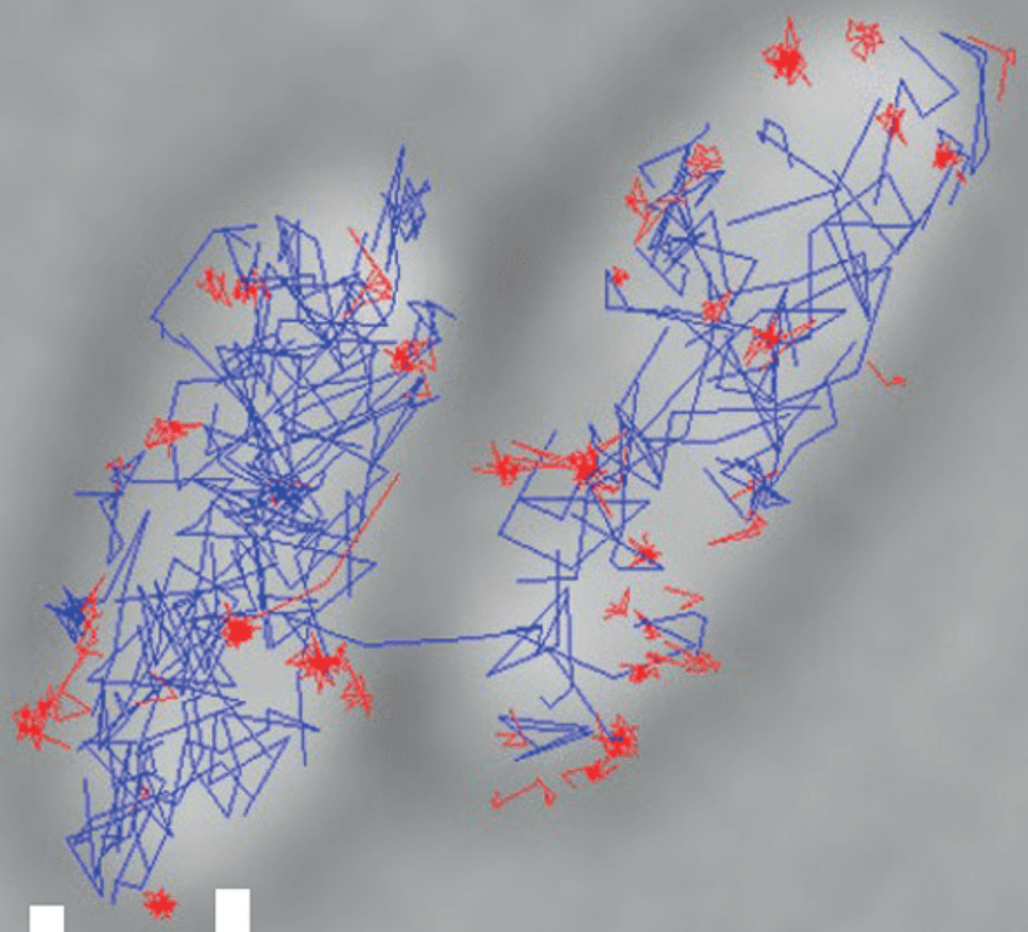
However, the Institute's most significant impact in smallpox vaccination stemmed from its research into freeze-dry methods for vaccine preservation. The original Lister smallpox vaccine, like all live preparations, was unstable at temperatures above freezing. This made it almost impossible for the vaccine to retain potency and reach many hot, remote regions of the globe where mobile refrigeration would make it prohibitively expensive.

In 1948 the Institute appointed Leslie Collier to the smallpox department. He pioneered a new freeze-dry method which gave the vaccine long-term stability. Lab tests showed the preserved product lost no potency even after two years of storage at 45ºC.

When the WHO launched its initiative for worldwide smallpox eradication, it compared five vaccines for heat resistance; the Lister product performed best and Leslie's method became standard for the preparation of all WHO smallpox vaccines. The Institute did not patent the freeze-dry method so smallpox vaccine manufacturers worldwide were free to adopt the technique.

Although the Institute may have missed out on some healthy income, its focus on open science and medical application has certainly assured its place in the history of disease prevention: the WHO officially declared worldwide eradication of the disease in 1980.





A tale of tails

PROFILE

Professor Judith Armitage

Department of Biochemistry
University of Oxford

Fellowship: 1982–85
University College London

Judith Armitage explains how her Fellowship was the start of a lifelong fascination with bacterial flagella.

Judith Armitage loves to experiment – with bugs. Since her earliest days at university she has found bacteria fascinating, especially the clever-yet-curious behaviour of the flailing "tails" that many bacteria use to swim in fluids or crawl on solid surfaces.

"For my PhD and first post-doc I worked on *Proteus*, a common human pathogen, but I quickly realised this was a difficult organism to study," she admits. "In the next door lab, though, they were working with photosynthetic bacteria and I was fascinated by how they moved. In anaerobic conditions they would swim towards light but away from oxygen. In aerobic conditions they did the opposite. I really wanted to know what was going on with this contradictory signalling."

Poor *Proteus* got dumped – Judith would take up that challenge again much later in her career – and she started applying for funding for studies on bacterial motility. "Just at that time some organisations started offering Research Fellowships along with the usual Royal Commission 1851 and The Royal Society," she recalls. "This included the Lister Institute which had recently launched its Fellowships in 1982. I applied for them all."

She was offered them all too – a certain reflection on her passion, aptitude and research vision. She decided to become one of the Lister Institute's first Fellows.

Her idea was to identify the molecules and mechanisms driving the movement of bacterial flagella. She thought that if you could control flagella you might control infection. As she was one of very few people in the UK working on the responsive control of flagella, the Lister funding was crucial; it would have been almost impossible to get a post-doctoral position in this area.

"What I wanted to do was novel, so I knew I had to be independent," Judith explains. "UCL was happy for me to have my own space and I was very happy with the freedom to pursue my own course. I did part-supervise some students and do a bit of teaching, but this was like an honorary lectureship. It was a prestigious position so early in my career because independent research fellows were quite unusual at the time."

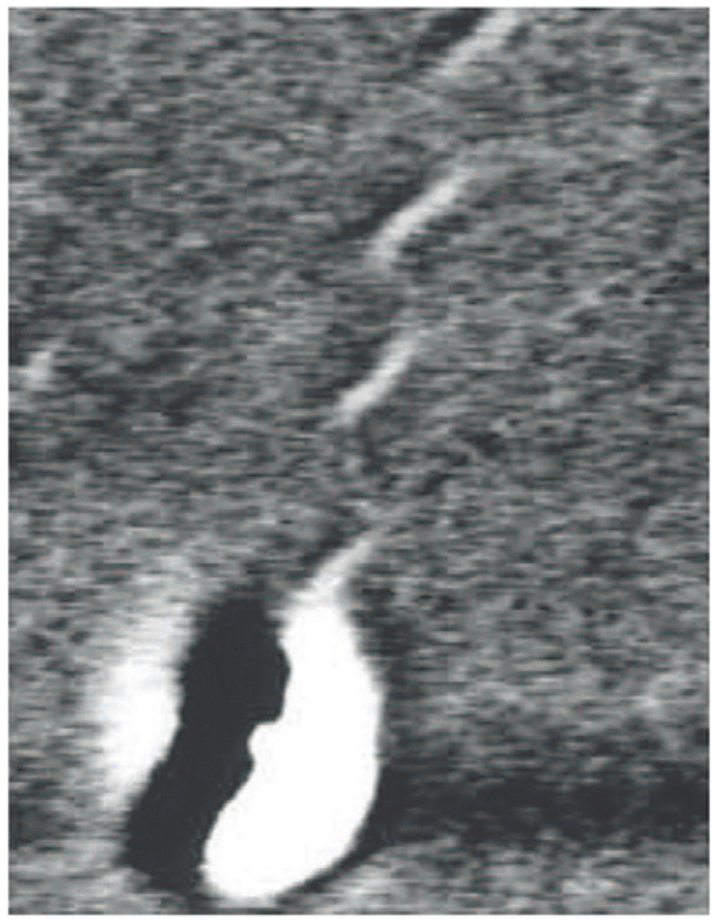
When Judith accepted a lectureship at the University of Oxford she resigned her Fellowship, but in just three years she had made some key discoveries – some so far ahead of her time that it took another 20 years for experiments to catch up with her theories. She published eight papers based on her Fellowship research, revealing important properties of the rotor and stator proteins which together form part of the 'motor' complex that drives the rotation of a flagellum. She has also shown how the bacterial cell membrane is involved in the control of a flagellum's response to environmental stimuli.

"The Lister Fellowship let me go in a direction that I wouldn't have been able to do had I been in a lab working for someone with their own agenda."

One key experiment revealed a strange lag phase when bacteria switch between photosynthetic and oxygen-driven energy pathways. She observed that in darkness, if she poisoned the oxygen-dependent pathway the bacteria would stop swimming. When she switched on the light, the bacteria started to swim again, but only after a delay proportional to the time they spent in the dark. Judith speculated that the flagellar motor dissociates in the dark; the lag occurred because the motor needed time to reassemble.

It was only the arrival of single-protein fluorescent labelling coupled with a special form of optical microscopy that showed she was right. Amazingly, proteins of the flagellum are exchanged with a pool of proteins in the bacterial cell cytoplasm, even as they spin at 1300 rpm. This discovery led to Judith's election as a Fellow of the Royal Society in 2013.

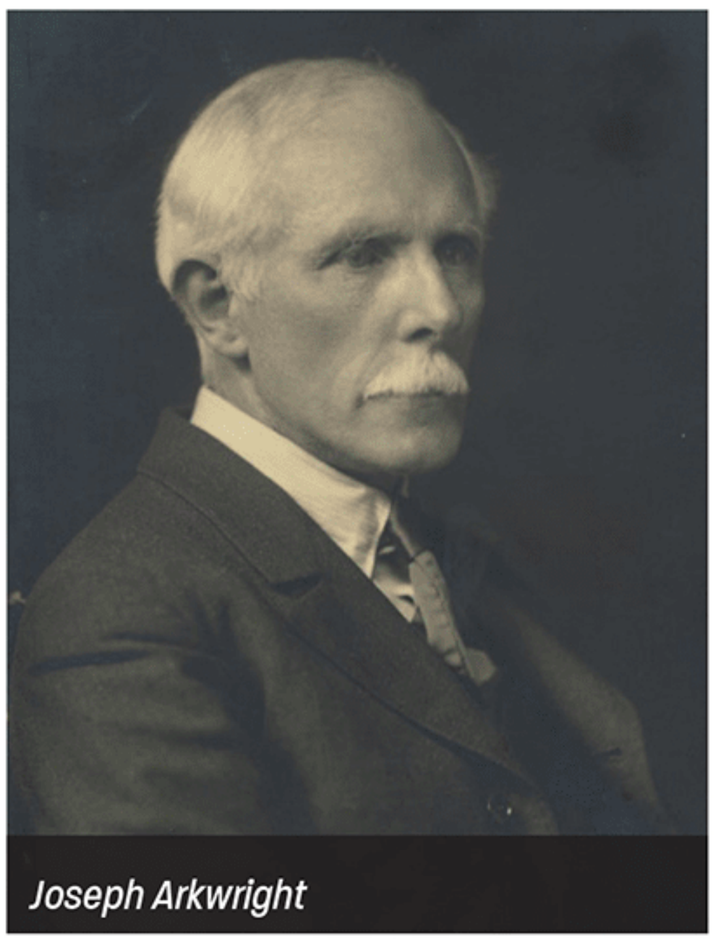
Although she still focuses on flagellated bacteria, Judith has also investigated the structure, dynamics and assembly of other bacterial microstructures, for example the injectisome. This needle-like appendage activates once a bacterium makes contact with a host cell to inject toxins into the cell and kill the host. She has also looked at the dynamic interplay between the two stator proteins of *Pseudomonas aeruginosa* that can be switched around depending on whether the cell is free-swimming or crawling on a surface.



In 2015 Judith was elected to the Governing Body of the Institute. "I feel I owe my start to the Lister. They set me on the right track and allowed me to follow that track. I felt I should give something back."

Two thousand strains of Salmonella

Lister Institute staff led research into bacterial variation and genetics



Joseph Arkwright

Joseph Arkwright – the great-great grandson of the renowned Sir Richard Arkwright who mechanised the cotton industry with his spinning jenny – joined the Lister Institute as a bacteriologist in 1906. He used Robert Koch's pure culture technique to isolate and study mutant bacterial strains.

The first to observe rough and smooth colonies in bacterial cultures, Joseph showed that colonies lost their virulence when they changed from rough to smooth; later experiments also revealed non-virulent strains lacked a key cell body antigen.

With his colleague John Ledingham, Joseph was a mainstay of the Institute's bacteriology department for more than 30 years. They were both elected Fellows of the Royal Society and received knighthoods for their services to the country, especially for research on typhus and trench fever during World War I when Joseph showed that *Rickettsia* bacteria were responsible for these infections. As part of this work Joseph bred lice for his experiments and let them feed on him through special muslin-covered boxes on his skin. He barely survived when he contracted typhus during these studies.

Decades later the Guinness-Lister Unit, built on the foundational work of these two scientists, investigated the inheritance of antigens in bacteria. Led by Bruce Stocker, this unit effectively established the field of bacterial genetics. He and Sylvia Smith became leading experts in *Salmonella* genetics and published ground-breaking work on transduction techniques, plasmids and conjugation. When the Unit finally closed in 1972 it had amassed more than 2000 mutant *Salmonella* strains.

It takes more than medicine to save lives

Professor Sir Leszek Borysiewicz
University of Cambridge

Fellowship: 1983–1987
Royal Postgraduate Medical School London, University of Cambridge

Leszek Borysiewicz, now Vice-Chancellor of the University of Cambridge, says his Lister Fellowship allowed him to refocus early in his career on his personal interest in cytomegalovirus.

During a six month visit to Gambia in the middle of his Lister Fellowship, Leszek Borysiewicz – Borys to friends and colleagues – began to appreciate that effective medicine required more than excellent research or knowledgeable clinicians.

"I had the opportunity to go to West Africa and, in its typical person-oriented approach, the Lister Institute was happy to grant me leave," Borys remembers. "Working in Gambia was incredibly challenging and exciting for developing my clinical expertise, but it did more. I learned about how to deliver healthcare when resources are limited. I think this was my first preparation for getting involved in research policy and direction. When you make daily decisions about rationing of drug use you start to see how medical research fits within a system and a broad policy context."

It would be some time before Borys would find himself spending more time in an office than a laboratory, however. Back in the 1980s he was eager for research. With an MRC Training Fellowship, he was already involved in some clinical research, but he found his hospital duties were increasingly taking up his time. "I really wanted to answer some more fundamental questions," he insists. "As a clinician, I'd seen several transplant patients sadly die because of cytomegalovirus. I started to wonder how the virus worked. Why did immunosuppression make the virus suddenly virulent and dangerous? The Lister Fellowship allowed me to refocus my interests in CMV."

Having developed an elegant way to block the expression of target CMV proteins, Borys uncovered how immune cells could recognise proteins the virus made only when it was inside the host cell. He also learned how CMV evades capture by the host's killer T-cells and lies dormant until the host immune system is down.

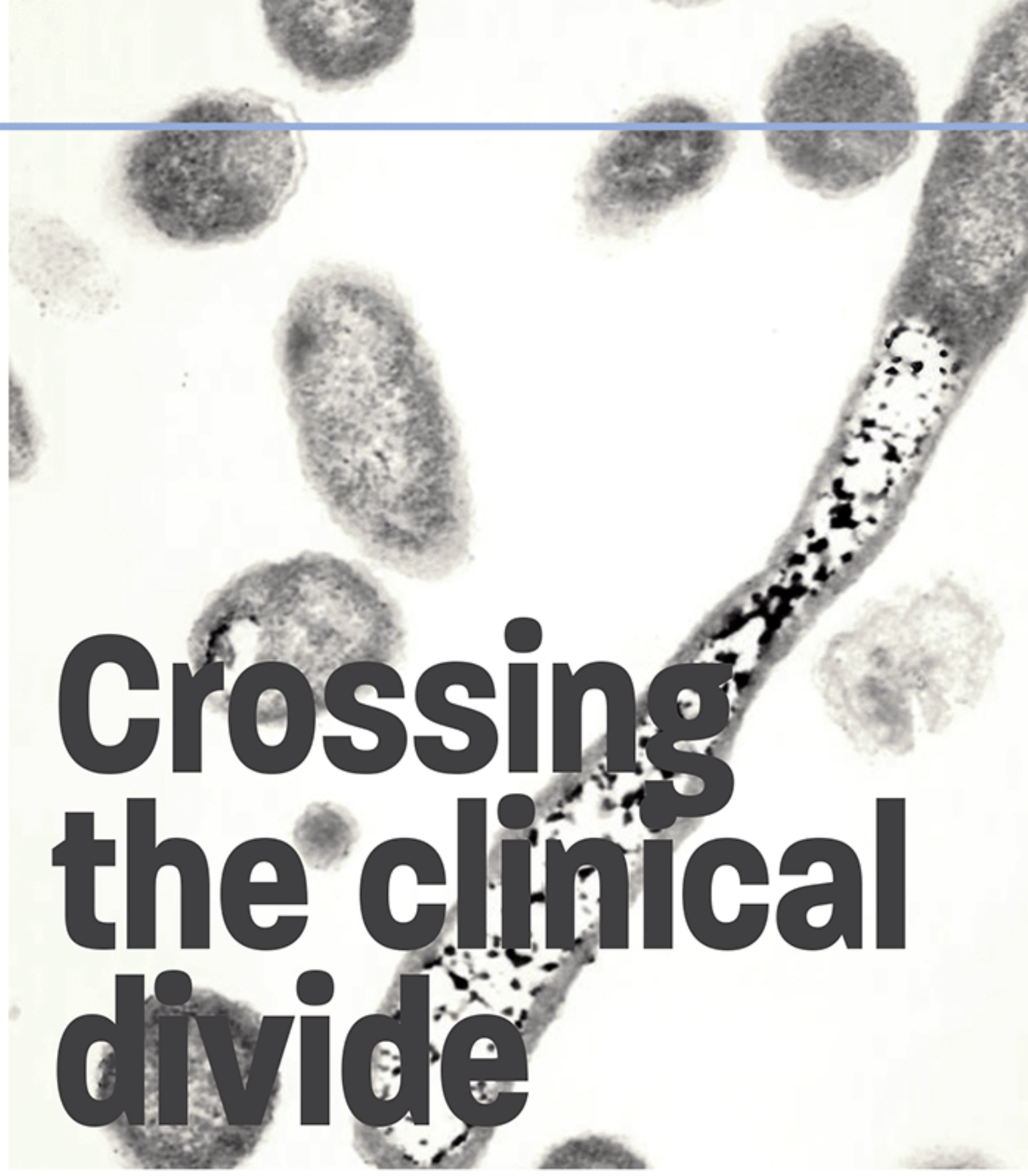
In 1991 Borys moved back to his home city of Cardiff, where he was appointed head of the Department of Medicine at the University of Wales. Here he switched to human papilloma virus (HPV) research. This virus employs similar mechanisms for persistent infection and immune evasion, so Borys could build on his earlier CMV research.

During his tenure at Cardiff, Borys began work on a therapeutic vaccine for HPV, a virus scientists had implicated with a high risk of cervical cancer. The Cardiff professorship also launched Borys into the world of research leadership. "You quickly find yourself making decisions about strategy and how you are going to invest your budget, where you will put more emphasis in the research portfolio," he notes. "But these were things I'd already experienced as a Lister Fellow and back in Gambia."

> "Investigator-led research lets ideas and people blossom."

After Cardiff, Borys became the Head of the Faculty of Medicine at Imperial College London in 2001, later promoted to Deputy Rector. In 2008, the same year he was elected a Fellow of the Royal Society, he became Chief Executive of the MRC, at the forefront of shaping and implementing national research strategy in medical and clinical sciences. Here he spearheaded the creation of MRC fellowship schemes, which he modelled on the Lister scheme that had launched his own research career 20 years previously. "One thing the Lister does is pull you in," he observes, "so you feel part of a community and supported in your work by peers and senior, eminent scientists. I felt this community aspect was important, so I copied the model, giving MRC Fellows that same sense of support and belonging. The fellowship model is now mainstream practice, but I think we should all recognise the effect of the Lister scheme on today's research funding landscape. It's not an obvious achievement, but the model is now influencing a whole generation of scientists across many disciplines."

In all his prominent roles, Borys has never forgotten the big lessons he learned during his Fellowship years. "First is the importance of focus," he states. "Excellent research requires focused researchers. Second, it is no good forcing people to do things if their heart is not in it. Investigator-led research lets ideas and people blossom."



Crossing the clinical divide

Professor Simon Kroll
St Mary's Hospital, Imperial College London

Fellowship: 1986–1991
University of Oxford

Simon Kroll describes how his Fellowship supported a transition from clinical medicine to academic research.

Simon Kroll is a rare specimen of a scientist. After receiving his first degree in Chemistry he immediately switched to medicine and trained as a doctor. Yet despite years of clinical training, there was something about fundamental research he simply could not resist.

Three years after completing his medical training he moved to Oxford to take up a clinical lectureship. "I'd made up my mind that I wanted to get into academic paediatrics and basic research," he explains. "This opportunity came up to work with Professor Richard Moxon in his new department for paediatric infectious diseases, studying *Haemophilus influenzae*, then the chief cause of bacterial meningitis in children. I couldn't turn it down."

"Colleagues shook their heads and prophesied disaster would come of leaving clinical medicine so soon. They thought I should focus on becoming a consultant," he remembers. "To be honest it made me feel rather exposed and on my own within the clinical setting."

But the Lister Fellowship came to his rescue. Just before he applied, he had spent three months in the lab of Staffan Normark in Sweden. Here Simon isolated a curious, unrepeated segment of the *H. influenzae* chromosome. This new sequence was nestled deep within a section of the chromosome known as the capsulation locus, which encodes genes necessary for the production of the bacterial capsule. The capsule is a polysaccharide coat that can surround *H. influenzae*, giving it protection from immune cell attack.

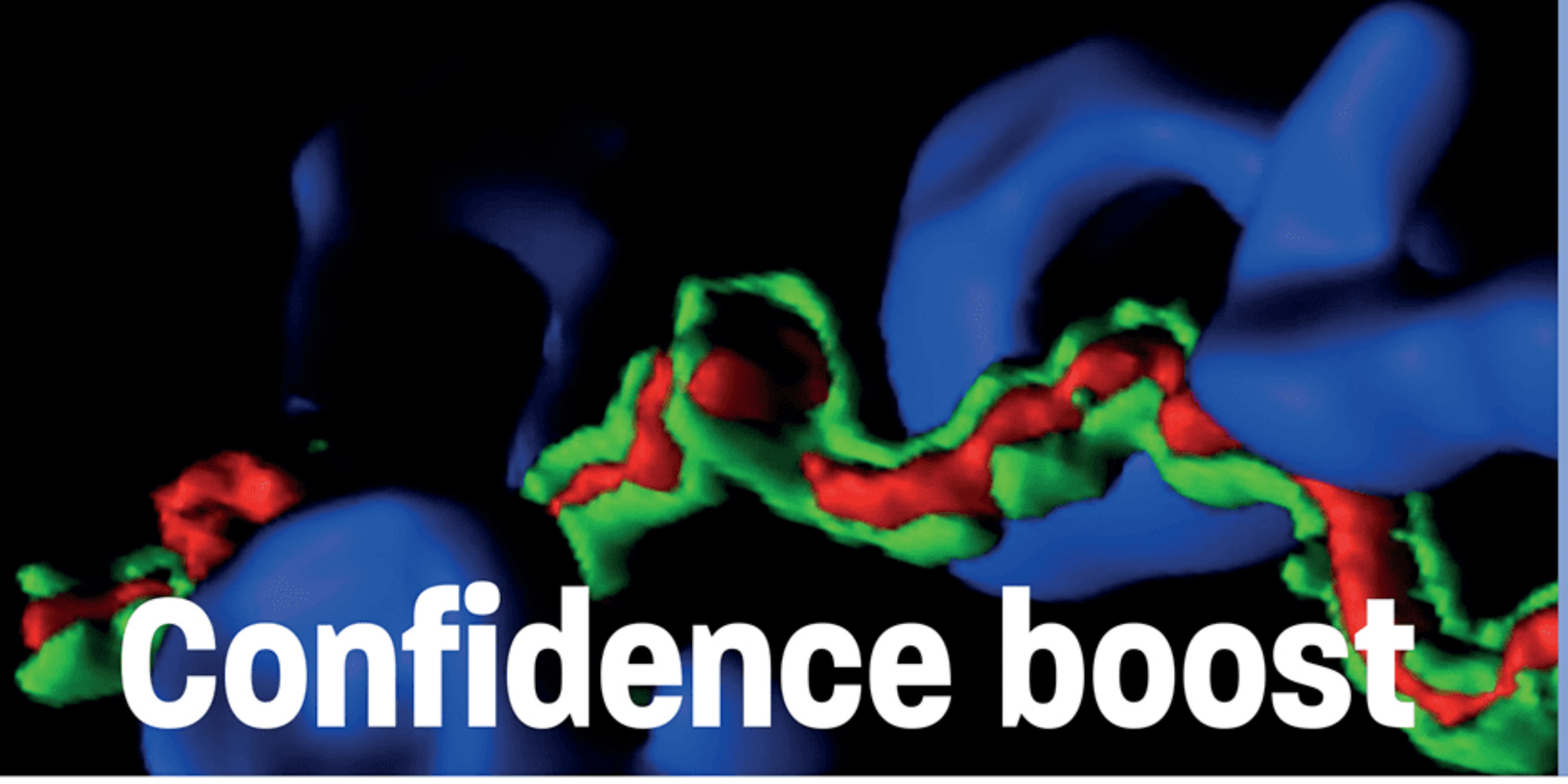
How this small segment of the bacterial chromosome might be involved in capsulation became the basis of Simon's pitch for his Lister Fellowship. He convinced the selection panel to support his research into the molecular basis of capsulation, its role in bacterial virulence and the functional aspects of the capsulation locus. Two years later his paper in the journal *Cell* presented the unique mechanism by which Haemophilus exported the capsular polysaccharide on to its surface, dependent on that short stretch of DNA.

Simon's research took him deep into the structure and genes of the bacterial capsulation locus. He showed how different Haemophilus serotypes were encoded by unique, transferable blocks of genes nested between common segments of DNA – a finding now exploited as the basis of genetic serotyping tools. He also found that the whole locus was flanked by insertion sequences, making it a so-called compound transposon. This discovery suggested that capsulation – and hence virulence – could be transferable between *H. influenzae* variants or even between bacterial species.

Simon's studies have contributed to scientists' fundamental understanding of virulence and genetic variation in this organism. Based on the structure of the capsulation locus, Simon speculated early on that introduction of a vaccine might cause a shift in strains within the population – an effect now seen in post-vaccine screening studies of *H. influenzae* in the population.

During his Fellowship Simon explored many aspects of the molecular basis of bacterial virulence, some of which he still researches today. For example, an emerging mini-epidemic of Brazilian Purpuric Fever proved to be due to a unique variant of *H. influenzae* with previously undescribed virulence genes found to occur in another major meningitis pathogen, *Neisseria meningitidis*. Exploring similarities between these two microbes, Simon identified a gene encoding an excreted copper-zinc co-factored superoxide dismutase, an enzyme previously considered extremely rare in bacteria, but which has now been identified in a plethora of species. Studies show this superoxide dismutase plays a role in virulence by detoxifying superoxide radicals generated by host immune cells; it has potential as a meningococcal vaccine target.

"I was absolutely delighted to get the Fellowship. I was probably the least qualified applicant on paper as my career had been unusual – I didn't even have a PhD at the time and while my period of research had been intense, it hadn't been all that long."



Confidence boost

Professor Jane McKeating
Institute of Biochemical Research
University of Birmingham

Jane McKeating says mentoring from former Fellows helped her become one of the UK's pioneers in HIV research.

Fellowship: 1994–1999
University of Reading

"It's scary going out on your own, independent, when you've always been under the umbrella of a big lab." This is how Jane McKeating felt before she became a Lister Fellow. "I'd just accepted my first lectureship position at the University of Reading. I really felt like a naïve post-doc."

She had completed her post-doctoral training under the mentorship of Robin Weiss at the Chester Beatty Labs. This powerhouse for HIV research established Jane's career path into virology with a particular focus on HIV. But now she faced the daunting task of creating a new research group. "It was down to me to set up the team," she recalls. "It was hard. Suddenly I had to do everything myself from writing grants, ethical paperwork to teaching undergraduates. So the Lister Fellowship made a huge difference."

With her Fellowship funding she first brought in a lecturer, Wendy Barclay, a virologist from New York. Wendy took on the undergraduate teaching commitments so Jane could focus on research. Although Wendy's primary role was teaching, she brought her significant skills and knowledge of influenza virus to the fledgling group. "Our offices were next to each other and we loved talking science," says Jane. "So the Lister funding didn't just bring a lecturer to free me up, it contributed directly to the research too. We went from strength to strength."

Wendy's expertise in influenza influenced the direction of Jane's research

Cell wall under scrutiny... still

Professor Gurdyal Besra
School of Biosciences
University of Birmingham

Gurdyal Besra brings the Institute's historic research on bacterial cell walls and virulence into the modern era.

Fellowship: 1999–2005
University of Newcastle

Anecdotal evidence suggests the Lister Fellowships were crucial during the 1980s and 90s at combatting the brain drain. Lured with the promise of well paid, well-resourced post-doctoral positions in the labs of world leading experts, many top qualified PhD graduates took the trip across the Atlantic. The Lister enticed a few of them back.

Gurdyal Besra was one of those who returned. "As a researcher in the US I didn't do any undergraduate teaching, but I knew if I came back to the UK I would have to take on additional duties with a significant teaching load," he explains. "I needed a mechanism that would relieve me of these duties to kick-start my academic career. As the Lister Fellowship was the only one at the time that allowed you to retain flexibility in your academic post, it looked like the best deal."

PROFILE

on hepatitis C virus (HCV). The two researchers realised that the M2 ion channel in influenza was similar to the HCV-encoded p7 protein. They translated influenza techniques to investigate p7 and pioneered HCV research in the UK. HCV remains the primary focus of Jane's research today as she tries to understand how the virus enters the liver and evades both innate and adaptive immune responses.

At the time of her Fellowship Jane's lab was also at the forefront of HIV research. Scientists knew that HIV entered T-cells by binding the CD4 receptor, but the detailed mechanism of entry remained elusive. The ideas Jane proposed for her Fellowship funding offered a new way to study HIV-host cell interactions by using antibodies to block virus interactions with T-cells.

"We wanted to understand pathogenesis at a molecular level for improved therapies," she explains. "I believe what we were doing was unique in the UK. With no x-ray crystal structures yet published, we relied on classic virology techniques to elucidate the interaction between virus particles and host cells."

She was particularly interested in the glycoproteins of the HIV coat and how they engaged with the CD4+ T-cells. She was also fascinated by the genetic diversity of HIV and wondered how this diversity affected its ability to evade immune responses.

Her major advance during the Fellowship period was the discovery of what is now known as the second variable loop, a region of the HIV envelope protein that is a target for neutralising antibodies. She found enormous variation in this loop that she at first struggled to analyse, she admits. "Today we can look at this kind of genomic data and link sequences to biological function of the virus. At that time we simply couldn't do that. We just had to experiment and theorise."

This discovery of the loop added to growing evidence from labs around the world that HIV evolves rapidly within a host. More recent research has shown that the viral genome rapidly accumulates mutations during replication, so an HIV infected individual has a "quasi-species swarm" – a mixed population of genetically distinct variants. Understanding the impact of this genetic variability on HIV sensitivity to antiviral drugs is a question that is still being asked today.

Although Jane's research did not drive the anti-retroviral therapeutic approaches used today, it played a fundamental role in revealing the pathogenesis of the virus and the role of co-receptors in viral entry into the host cell.

Jane fondly remembers the annual dinner held for Lister Fellows and members. "Sitting among a wide range of esteemed scientists really boosted my confidenc. Everyone was so supportive and interested in my work that I gained the confidence to ask what I thought were probably really naïve questions about work outside of my field. But this experience gave me confidence to believe in myself and my work. As a junior lecturer, when you talk to a Nobel laurate it is quite special."

PROFILE

Gurdyal wanted to study tuberculosis, hoping emerging technologies and methodologies might uncover something new about the pathogen. The whole genome of *Mycobacterium tuberculosis* had only just been published, but Gurdyal was more interested in the cell wall, a structure shown by early Lister researchers to increase the pathogen's virulence.

Like his predecessors, Gurdyal believed that the cell wall was the key to infection control. "We had an arsenal of molecules that target cell wall biosynthesis," he remarks, "but very little understanding of the molecular basis for how they worked. I wanted to unravel the mysteries surrounding the biosynthesis and inhibition pathways."

"It was only after I went to my first annual Lister Fellowship meeting that I learned about the Institute's long and impressive history in the study of cell wall biosynthesis," he confesses. "I felt honoured to be carrying on the tradition and following in the footsteps of such eminent and respected researchers in the field. The flexibility of the Lister funding allowed me to do stuff not written down – experiments that I hadn't foreseen or planned."

Gurdyal's achievements come in the form of a list: a string of glycosyltransferase enzymes he identified and isolated involved in cell wall biosynthesis. He provided evidence for the involvement of more than 10 different enzymes that he studies to this day.

"At the time there were many genes in the published *Mycobacterium* genome labelled as 'unknown'. We were filling in lots of the gaps and attributing them to enzymes and annotating the genome with what the genes encoded," Gurdyal says.

One enzyme in particular caught his attention: DPRE1. This is the last enzyme involved in the synthesis of decaprenyl-phosphoryl d-arabinose (DPA), a key component of the *M. tuberculosis* cell wall. Gurdyal is currently working in collaboration with pharmaceutical company GSK to develop designer drugs that target and inhibit DPRE1 to disrupt cell wall synthesis.

"I needed a mechanism that would kick start my academic career. As the Lister Fellowship was the only one at the time that allowed you to retain your academic post, it looked like the best deal."

Excellent, eclectic and exciting

Leading the selection process for the annual Prize Awards is a privilege and a pleasure.

Professor Patrick Maxwell
Patrick Maxwell has chaired the Scientific Advisory Committee since 2012.

The Institute's Governing Board appoints the Scientific Advisory Committee (SAC) to evaluate all applications for the Prize Award each year. Our task is to identify the people and the projects that we believe will best meet the aims of the Institute. Every year we go through a rigorous process to select outstanding early-career researchers in fundamental science or clinical medicine whose research will answer important questions in biomedicine.

I have to be honest, this is a real challenge – the Committee can't possibly include world-leading experts in every aspect of bioscience and medical research. But we do our best to have depth and breadth: scientists with world-class expertise in their own specific field combined with interest and general knowledge across many subject areas. I'm privileged to steer a team of people who are all open-minded, incredibly knowledgeable and who – crucially – are comfortable comparing apples with oranges!

Our work is divided into two. Firstly, we help to shape the Prize Award scheme. Every year there is discussion about how we should deploy the available funds for maximum effect. One issue is whether we should give larger awards, or maximise the number of winners. We also consider how to balance fundamental science and clinical research, and how to allow for career breaks and ensure equality of opportunity. A key question is whether we recognise people who already have a track record of brilliant achievement or select those with unrealised potential for excellence. The former probably have lots of money already; do we reward this with some extra prestige and the invaluable flexibility a Prize Award allows, or should we give money to individuals who don't have the funding they need to get off the ground? A Prize Award could establish their career and be the catalyst which unlocks other funding streams.

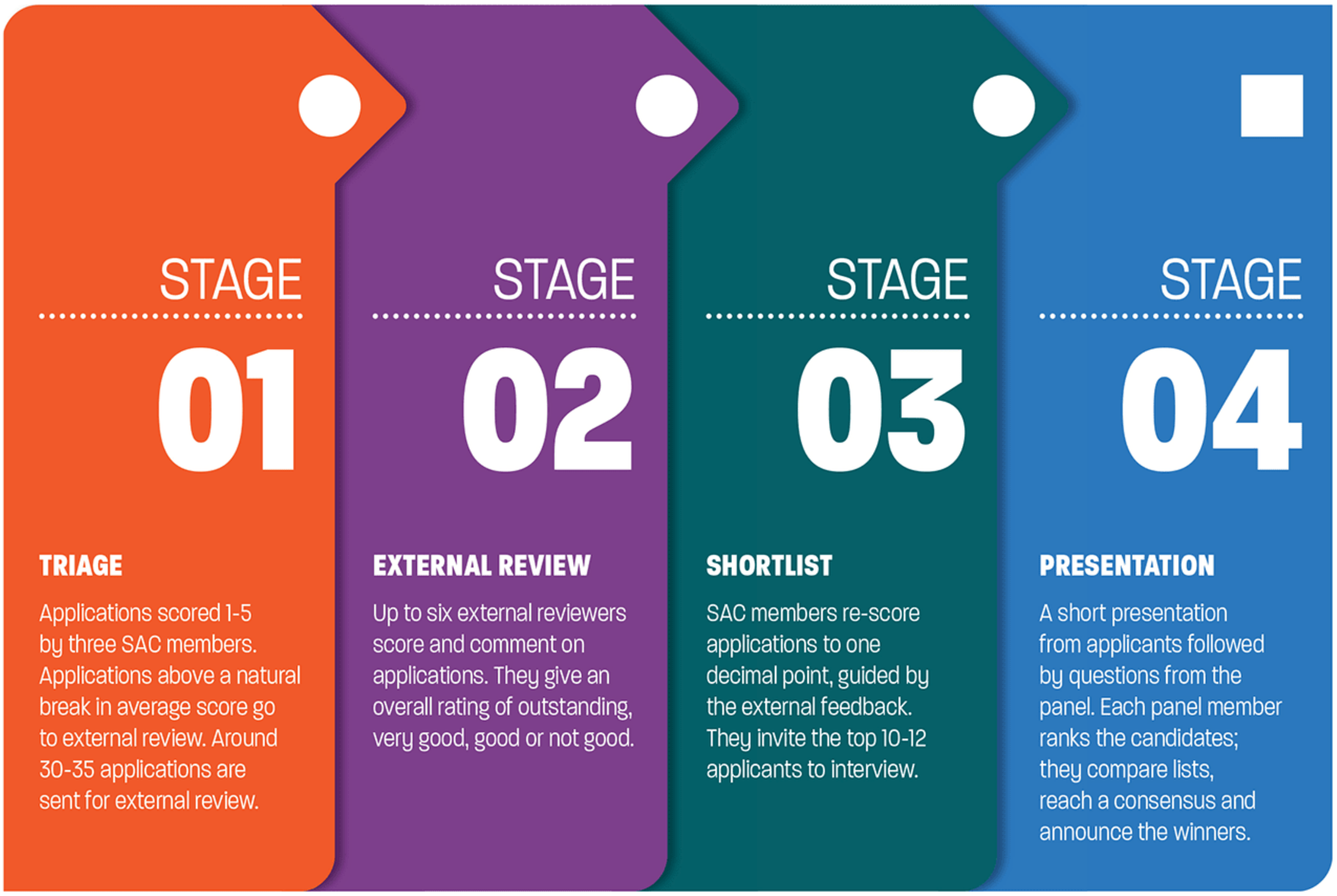
"We want researchers with imagination, flexibility and drive to deliver really excellent science."

Each year we make small adjustments - but our overall aim is always the same: to make our Prizes life-changing, both for the winners and through the eventual application of their research.

The second part of our work is selecting the Prize winners. Assessing the application is just part of the process; we also want to be sure that the researcher has the imagination, flexibility and drive to deliver really excellent science. That's why the face-to-face interview is so important. The Prize Award is as much about the individual scientist as the work they propose and you only get a real feel for someone face-to-face. If a proposal is naïve and overambitious we are quite forgiving, if a person shows sufficient promise. People who are overambitious in their early career are often the people who make the most important breakthroughs!

Thanks to the excellent contributions from all members of the SAC and many external peer reviewers, I believe we have a robust process that picks out the most deserving people and the best science. Every year during the interviews I find myself reflecting that this is one of the most enjoyable things I do. I'm looking at the brightest young people in science eyeball to eyeball. I really want them to do well in their research – and it is great to know that we are helping them on their way.

From application to award



Selection day

Former SAC member David Ish-Horowicz describes why reviewing applications for the Lister Prize Award is such a unique and rewarding experience.

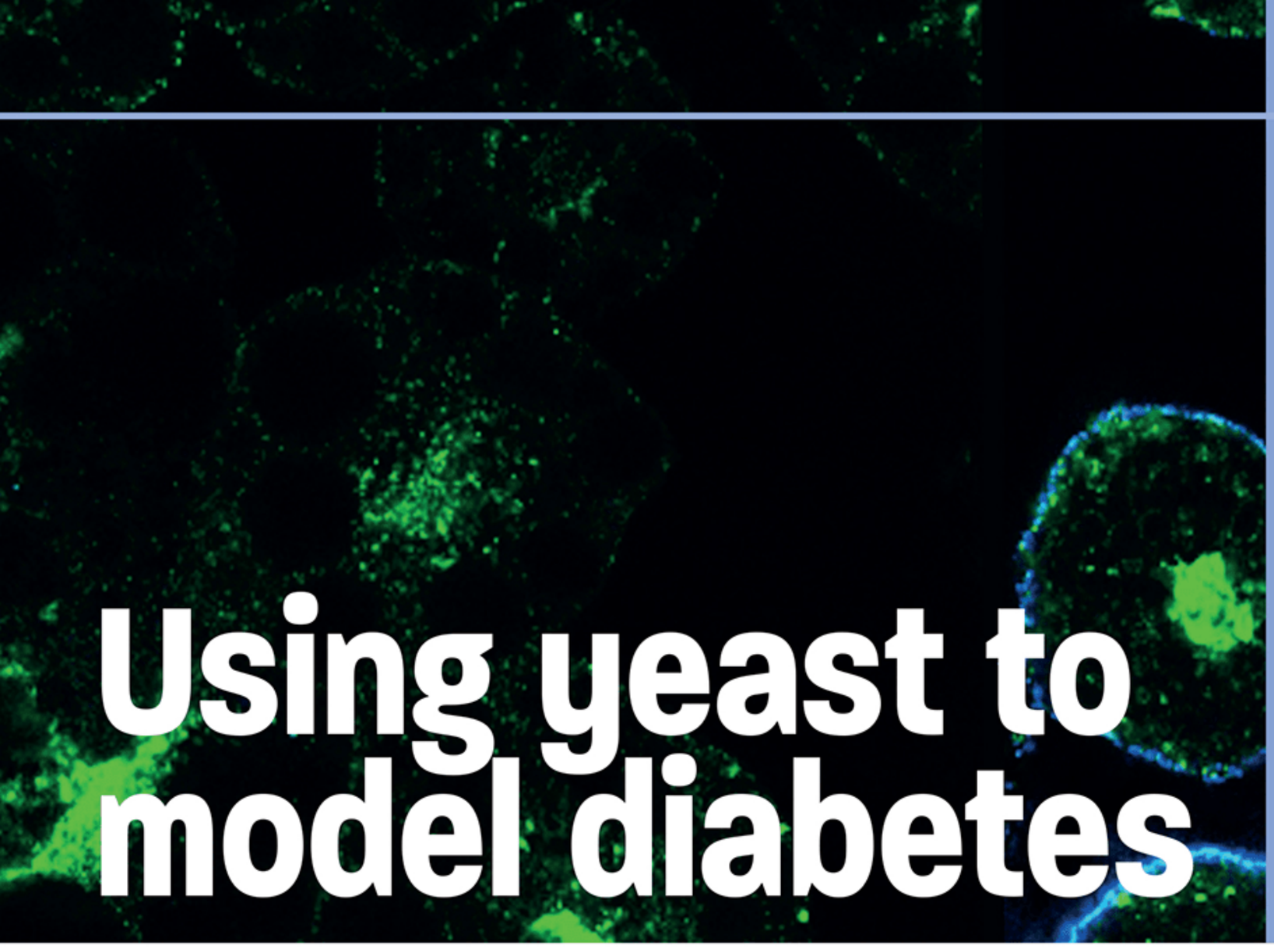
David Ish-Horowicz
SAC Member 2006-2012

Getting involved in the scientific review and selection process for the Lister Prize Award was unlike any others I've done, especially at the beginning. I was asked to join the SAC and sit on the interview panel because of my broad experience in genetics, but it was still hard work.

The interview process is a way to see how people think, to find out how critical they are about their own work and thinking. After all, any question a panel member asks is one the scientist could have thought of already. If they have, and they have answers, it is clear they are thinking well.

Our task is to select the deserving winners in accordance with the objectives of the Governing Body. We try to fund a range of topics and balance fundamental versus clinical research. We also try to give awards to people where the money and kudos will make a significant and lasting difference to their work.

Often you are comparing people doing completely different things and it isn't easy to rank people when they are so diverse. But you chew and mull it over and by the end of the day you've heard everyone else's opinions on candidates too. In the end there's a surprising level of agreement between rankings from each panel member. You can often spot the right people after their presentation, even before the questioning. If the candidate is asking a great question and seems to be the best person to crack it, that's all anyone can ask for.



Using yeast to model diabetes

PROFILE

Professor Nia Bryant

Department of Biology
University of York

Lister Prize Award: 2005

Nia Bryant discovered protein regulation by ubiquitination in mammals.

"It might seem like a crazy idea, especially to non-biologists," Nia confesses, "but gene and protein sequences conserved in mammals can be traced right back to unicellular eukaryotes like yeast. So can many of their functions."

The idea makes sense from an evolutionary perspective, however. Multicellular organisms evolved from single cells; many physiological processes in multicellular organisms retained the essential protein activity of their simple ancestors, just adding on extra layers of complexity and control.

Nia's interest in the links between yeast and mammalian cells stems right back to her early days of research. During her post-doctoral work in Australia, she studied how the glucose transporter GLUT4, which is dysfunctional in diabetes, is regulated in human fat and muscle cells by insulin. Having worked exclusively with yeast up until this point, Nia found this first foray into mammalian cell biology frustrating due to the many limitations of her cell lines. Nia thought she might be able to use yeast as a model to study human GLUT4, although the idea perhaps seemed far-fetched at the time.

When she inserted the mammalian GLUT4 gene into yeast cells, Nia discovered that the protein was regulated by a process called ubiquitination; the small protein ubiquitin binds to the target human GLUT4 and alters its behaviour.

"Other labs had suggested ubiquitination might occur in mammalian cells. They had looked hard, but not found any evidence," she explains. "What they didn't know – and what we discovered – was that in mammalian cells ubiquitination of GLUT4 is a transient process. We created versions of GLUT4 that were either never ubiquitinated or were ubiquitinated permanently, and used these to show that GLUT4 has to be ubiquitinated transiently to function properly in response to insulin in mammals."

Nia says that the GLUT4 pathway regulated by ubiquitination is a good example of additional regulatory mechanisms being introduced on top of evolutionarily conserved mechanisms.

Nia's careful management has stretched her £150,000 Prize Award to cover a decade of activity. "Generally I have used the money to extend contracts and allow people to stay in my lab. It's so frustrating when you are close to producing definitive results, only to have someone leave because a grant ends," she notes. "Often PhD students and staff are at an exciting point when contracts end, so the Lister has enabled me to keep them on and bring their work to fruition rather than give up on years of good work."

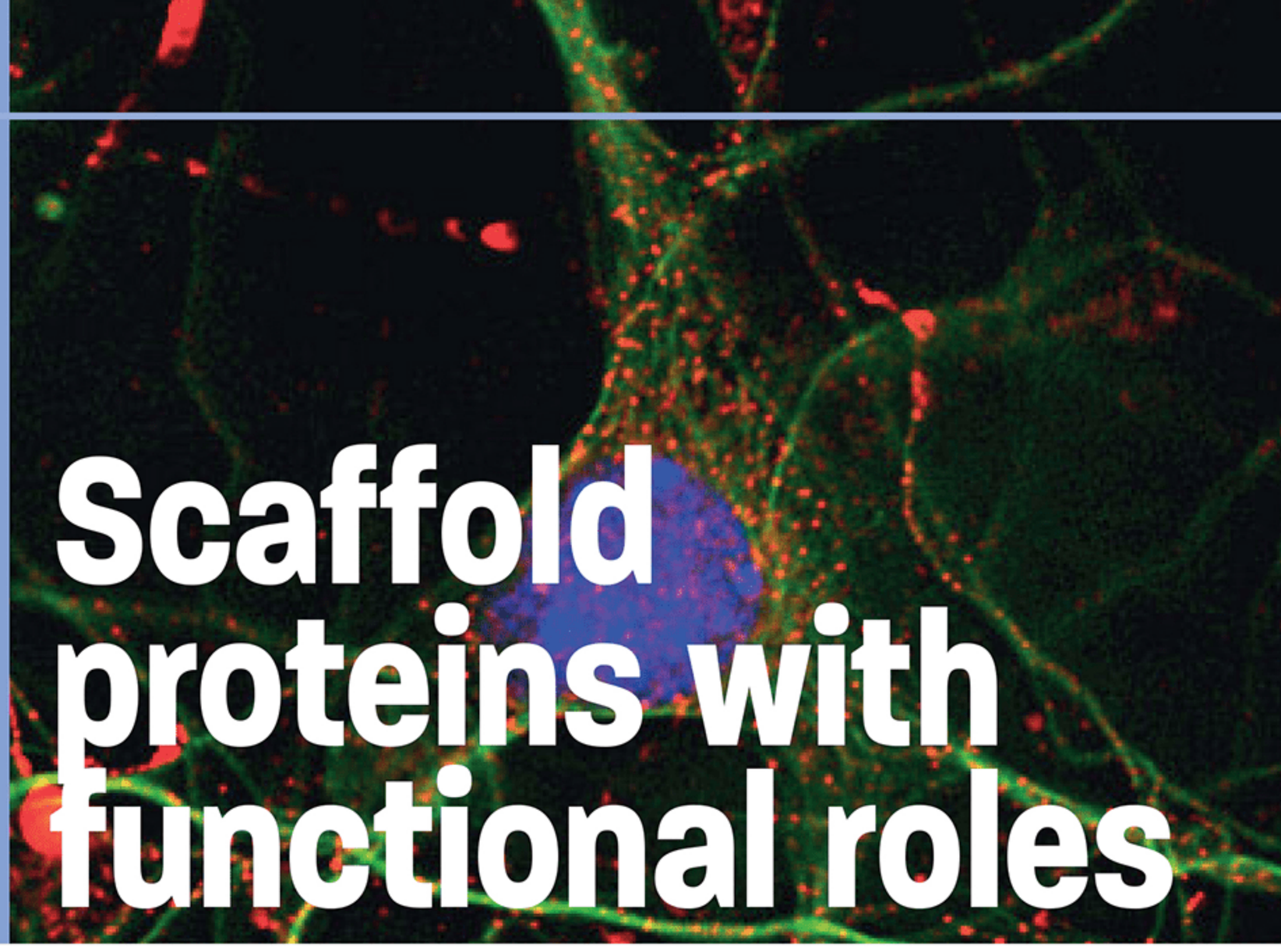
"The flexibility of the Lister funding means I haven't had to rush about and spend it quickly, not necessarily on the best experiments," Nia continues. "I've always tried to access other funds first and use the Lister as a crucial backup pot when other options fail. We've been really successful in getting funding from other sources, but I think it is fair to say that the Prize Award has given me the security to steer my group's work very efficiently and in exactly the right direction, based on our results, not just funding criteria."

Today Nia is a leading expert on GLUT4 trafficking pathways. She is currently mining published data to see whether dysfunctional ubiquitination may be the cause of type 2 diabetes in a subset of patients with this disease.

"The Prize Award has given me the security to steer my group's work based on research results, not just funding criteria."

Dr Alan Whitmarsh
Faculty of Life Sciences
University of Manchester

Fellowship: 2001–2006



Scaffold proteins with functional roles

Alan was among the first researchers to study how non-enzymatic proteins, known as scaffold proteins, integrate different cell signalling pathways.

In 2000 Alan returned to the UK from a post-doctoral position at UMass Medical Center in the USA. He had accepted a lecturer position at the University of Manchester and was keen to start his own research lab. "I thought the Lister Institute Fellowship would give me a flying start," he says.

He was right. With funding to "buy out" some of his teaching responsibilities, the Fellowship gave him more time for laboratory research and, crucially for someone in his position, time to write grant proposals that would bring in money from other sources.

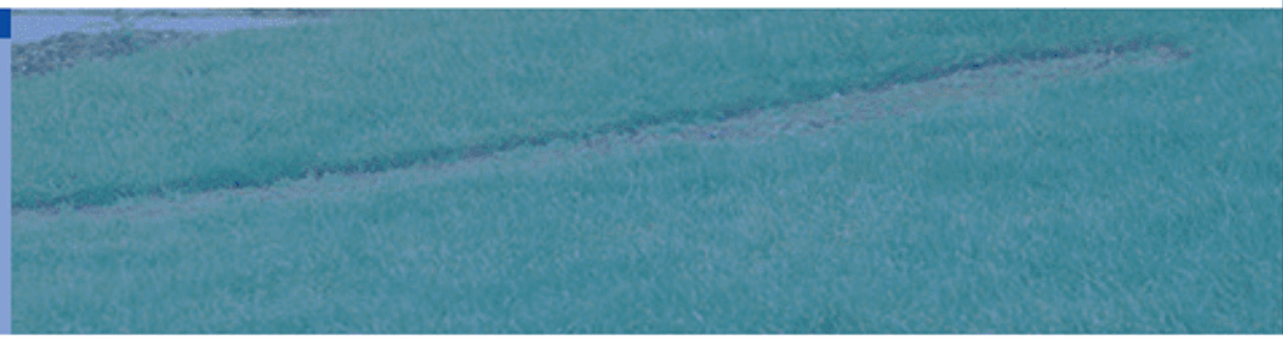
While he was in America, Alan had discovered that a mammalian scaffold protein, JIP1, was involved in regulating a recently discovered cell signalling pathway involving a family of enzymes called MAP kinases. Many studies had shown that MAP kinase pathways controlled a wide variety of cell functions, but it was less clear how the same pathway could regulate such different physiological processes. Alan's discovery was among the first to suggest that scaffold proteins constituted a mechanism of linking the pathways to specific functions.

Over the course of his Fellowship Alan characterised JIP1 and found it was a multitasker, playing a key role in integrating signals and regulating downstream effects across multiple signalling pathways. "When we first discovered it, I thought it was quite specific for a particular MAP kinase pathway, but my studies revealed how it could integrate different cell responses during development and in response to stress. My lab was the first to show JIP1 had roles in nerve axon growth that were independent of the MAP kinase pathway where it was first implicated."

Alan continues to focus on JIP1 and its role in neuron development and regeneration. Some of his latest – and surprising – research suggests that JIP1 may even play a role in the nucleus to regulate gene expression. Alan also works on signalling pathways linking mitochondrial function to nuclear gene expression and how these act to protect cells from stress and regulate ageing.

Bio Products Limited (BPL)

Created by the Institute as the Blood Products Laboratories in 1954, BPL continues to supply fractionated blood products to the NHS.



The Institute opened its Blood Products Laboratories (BPL) in a newly-built building on the Elstree estate. Although fully funded by the Ministry of Health, it was run as a department of the Institute, with a remit to research, develop and deliver the plasma-derived blood protein products demanded by the recently established NHS.

Medical advances often find their origins in military history and blood plasma products were no exception. Early in World War II, the American Edwin Cohn developed ways to isolate serum albumin from blood plasma. The extracted protein was stable for storage; medics could reconstitute the albumin as a substitute for blood plasma and give it to wounded soldiers for immediate fluid replacement.

During World War II the USA supplied most of the UK's plasma and albumin, mainly donated through the "Plasma for Britain" campaign. But after the war the British Government decided the country should become self-sufficient in its supply of blood products, not just albumin but a growing list of other therapeutic blood proteins and factors.

BPL's world-firsts include the first extraction of Factor VIII from blood for the treatment of haemophilia in patients

The success of BPL stems from the work of Ralph Kekwick and his colleagues in the Lister Biophysics Building, opened in 1937 and home to the country's first ultracentrifuge, which was used extensively in protein preparation and fractionation experiments.

Soon after the war, Ralph set up a blood filtration unit where he pioneered a new method for extracting blood proteins using ether rather than cold ethanol (which was scarce in the post-war era). A pilot plant was soon running, helping to convince the Government to invest in the industrial-scale BPL facility.

Over the course of nearly a quarter of a century as part of the Institute, BPL accomplished a number of world firsts, including the first extraction of Factor VIII from blood for the treatment

of haemophilia A. Lister scientists also developed a method to purify globulin proteins from blood for therapeutic injection. Immunoglobulin therapies were used for a variety of conditions; Lister scientists prepared the first immunoglobulin D for trials in the UK that confirmed it could prevent haemolytic disease of newborns. This condition occurs in babies with Rh-positive blood born to Rh-negative mothers.

BPL was also the first to show that some blood products – in particular Factor VIII – could be freeze-dried for stable, long-term storage. Undoubtedly, this technique was a speciality of the Elstree site as it was also used by Leslie Collier to make the live smallpox vaccines more heat stable.

In 1978 when the Lister closed its Vaccines and Sera Laboratories, BPL continued to research and manufacture blood products as part of the NHS. Until 1991 and the introduction of an internal market in the NHS, BPL provided all fractionated blood products to the NHS, using the same basic preparation techniques first developed by Lister scientists.

Indeed, some of the world's biggest blood products manufacturers indirectly owe their success to Lister. During its early days, when BPL was a world leader in blood fractionation techniques, it welcomed scientists and technicians from around the globe and taught them the processes. The Commonwealth Serum Laboratories in Australia, which sent scientists to learn from BPL, is one of the largest blood products companies in the world today with 16,000 employees working in over 30 countries.

BPL (now Bio Products Limited) is today owed by a private investment firm, although the UK Government retained a 20% stake in the company when it was privatised in 2013. Around 750 people still work at Elstree, including roughly 120 scientific staff who continue to develop production methods. BPL scientists are currently looking at other coagulation factors for rare diseases and novel applications for immunoglobulins that could have therapeutic effects in Alzheimer's disease and cancer.

Walter Morgan: research was in his blood

Walter Morgan still working at 102

During the 1930s Walter Morgan, working mainly at Elstree as a production scientist, studied the antigenic properties of polysaccharides in bacteria. Here he isolated and characterised a polysaccharide that confers the antigenic specificity of the *Shigella* bacillus. He was also among the first to suggest a complex role for antigenic polysaccharides when he showed that the *Shigella* sugar was only antigenic when bound to a particular protein.

At the start of World War II Walter moved to the Chelsea laboratories to focus on research related to the war effort. As blood for transfusion was scarce, there was little blood available from which to extract antibodies for blood group testing. So Walter helped produce artificial antigens. He combined Shigella protein with purified human blood group A and B components. These antigens produced powerful rabbit anti-A and B grouping sera used by the Navy for blood testing.

In 1942 the British Government set up the Emergency Blood Transfusion Service; Walter supported the programme with his investigations on the mechanisms of blood group incompatibility. His studies on the chemistry and genetics of blood groups, mainly the ABO and Lewis systems, continued for more than three decades.

Prior to Walter's investigations, people thought that the O antigen was the product of a corresponding O gene, but Walter revealed the presence of a genetic system, which he called H, that produced precursors of the A and B antigens as well as O.

Experiments with secreted glycoproteins in blood led Walter to conclude that the antigenic components of blood groups were carbohydrate, not protein as previously believed. Subsequent work revealed that the determinants of the H, A and B types were sugars: L-fucose, N-acetyl-D-galactosamine and D-galactose, respectively.

With remarkable acuity for experimental design, Walter carried out a series of experiments in which he removed single sugars from the carbohydrate chains of blood glycoproteins. As the chain shortened, Walter showed how specificity for one blood group disappeared, only to be replaced by new specificity. He deduced that the antigenic carbohydrate chain was built up sequentially by glycosyltransferase enzymes coded by the blood group genes.

> Walter deduced that human blood groups were determined by a carbohydrate chain built up by enzymes coded by blood group genes.

Winifred Watkins, who succeeded Walter as the Institute's Head of the Biochemistry Department in 1968, later identified these enzymes in human tissue, paving the way for an explosion of studies around cell-cell interactions and ligand binding involved in inflammatory signalling, immunology and cancer.

Charity finances

The Institute's Treasurer, Michael French, explains how a hands-on, prudent approach to money management assures the longevity of the Prize Awards and supports the community of Fellows and Members.

Michael French

Michael French has been a member of the Lister Institute's Governing Body since 2005.

It had almost become a tradition that my old firm, Coopers & Lybrand (now PwC), provided the Treasurer for the Lister. So when I retired in 2003 it came as no surprise when Peter Allen, then the Institute's Treasurer and an old colleague, asked if I would like to take over his duties. In retirement I still wanted the challenge and stimulation of the business world so I gladly accepted the invitation.

My term so far has been fascinating. Although in truth I understand very little of what the eminent scientists I meet with discuss, it is a wonderful experience just to be in the same room with so much intellectual "horsepower". It is a privilege to play a part in funding such valuable medical research and maintaining the Lister's finances so that funding can continue for the long term.

As we only receive a trickle of royalty income from licences to patents on Fellowship-funded research, we have to husband carefully the funds we already have. My main job, working with the other members of the Finance & Investment Committee, is to oversee our investments. Together we must ensure they retain their value and generate a return sufficient to fund the annual awards. As a general rule we are thus able to allocate each year at least 3% – currently around £1.2 million – of our investments for awards and running costs.

"I continue to be amazed by how much excellent science we can support by giving away £1 million per year."

The Lister costs little to run, roughly £150,000 per year including the cost of the annual Fellows' meeting (a highlight even for me as a non-scientist). With just three paid staff, no premises and much of our business and discussions being done electronically, this is a lean organisation.

We are closely involved with the management of our investments and I'm indebted to the collective wisdom and insights of our Finance & Investment Committee. We have split our capital between two fund managers who follow different investment strategies. This separation keeps each of them on their toes and avoids the danger of having "all the eggs in one basket." One firm is a large investment house with significant experience in the charity sector. The other is a boutique firm which follows the US endowment model and invests in more complex funds.

We spend a lot of time discussing investment issues with our fund managers. Although they have everyday control, we speak with them regularly to discuss their performance, on-going strategies and costs. I like to think we have a robust but collaborative relationship with them and, as a result, do our best to ensure that we get good results for the fees we pay.

I continue to be amazed by how much excellent science we can support by giving away £1 million per year. Thanks to a strong team, our assets have more than kept pace with inflation and grown from around £32 million to £40 million over the past ten years, despite turbulent markets. I think this indicates good stewardship of our endowment.

Mixing...

The annual weekend remains a key element in the Lister's aim to nurture early-career scientists.

Putting pesticides out of harm's way

PROFILE

Professor Michael Eddleston

University of Edinburgh

Lister Prize Award: 2011

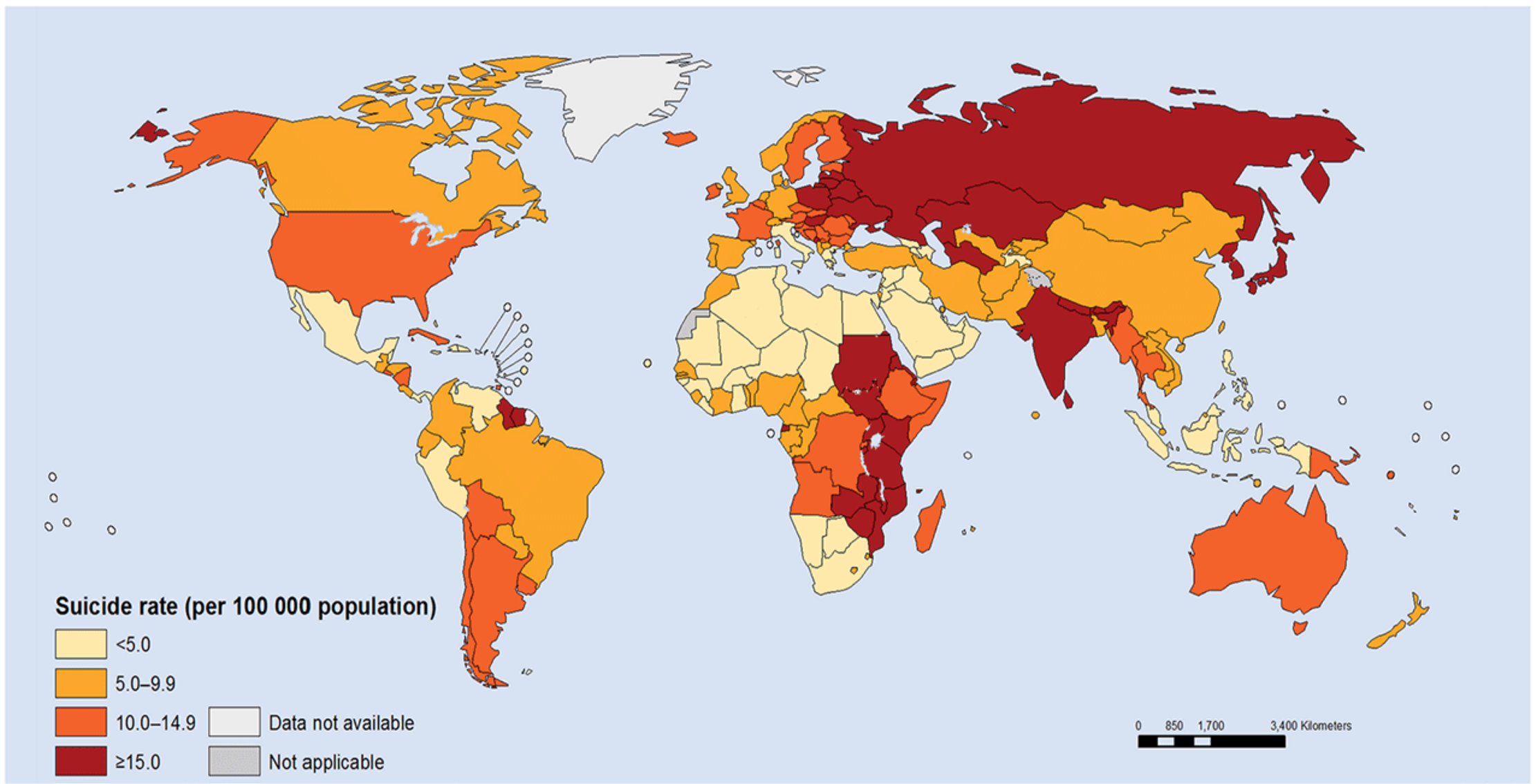
Michael Eddleston's wide ranging research is helping to reduce deaths from organophosphorus pesticide poisoning in Asia.

With a Cambridge undergraduate medical sciences degree and a PhD spent at Scripps in the USA, by 1994 Michael Eddleston looked like he was on course for life in the lab. But after much reflection, he decided not to pursue a post-doctorate in America; wanting his research to be more applied, he returned to the UK to complete his medical degree.

It was during his early clinical training in Oxford that Michael met Professor David Warrell and learned about his work on snake venom. "The idea of researching snake bites sounded pretty exciting," Michael recalls, "so I asked to join his team for the summer. He offered projects in Sri Lanka and Vietnam. As my best friend at clinical school was Sri Lankan, I chose to go there."

It was such a simple decision, but it was to change his life. "It was a quiet summer for snakes that year," he continues, "but as I stood in the hospital wards and looked around me I saw huge numbers of patients admitted with pesticide and plant poisoning. This was the chance beginning to the work I do today."

Michael learned many stark truths that summer. He heard about high suicide rates and the cultural 'norm' in rural communities to drink organophosphorus pesticides as poison, to harm themselves and commit suicide. He learned that 300,000 people die worldwide from this form of suicide every year. And he observed first-hand the tragically



Shop warning sign: "Danger - agro-chemicals available for sale"

fatal sudden respiratory failure, known as intermediate syndrome, that some recovering victims experience a few days after admittance.

Perhaps most startling was his discovery that no-one seemed to be studying any of these issues. "There were so many angles on the problem and so many ways I could see it could be tackled, but no-one seemed interested," he says.

With support from The Wellcome Trust and Scotland's Chief Scientist Office, Michael got involved in an eclectic mix of projects and programmes to reduce pesticide suicide. In the clinic he spearheaded studies to evaluate care protocols and determine the best way to give atropine, the antidote to organophosphorus poisoning.

But Michael kept coming across one major challenge: the delayed respiratory arrest. Too often he saw patients die; those who received emergency attention would have to spend 2-3 weeks in intensive care, with 50:50 odds for a full recovery.

He returned to the UK with an idea for some animal-based experiments that might reveal the cause of this respiratory arrest; preliminary research suggested that the poison affected the function of the neuromuscular junction. Although he had been working on pesticide and plant poisoning for the best part of 15 years, as a practising clinician, Michael had only carried out the equivalent of eight or nine years of full-time research since getting his PhD. He was still eligible to apply for a Lister Prize Award.

With the Prize Award funding Michael established a collaboration with Richard Ribchester in the University of Edinburgh to study the dynamics of poisoning on samples of neuromuscular tissue. Eddleston's first experiments in pigs and then mice showed remarkably that pure organophosphorus compounds had no effect; deeper investigation revealed it was the combination of compounds in the pesticide formulation that caused damage. "Organophosphorus pesticides are insoluble in water," Michael explains. "They are mixed with solvents and surfactants so farmers can dissolve the pesticide in water for application. When we took blood plasma from pigs that had been administered pure organophosphates and added this plasma to a neuromuscular junction from a mouse, the nerve impulse worked fine. But if the pigs had ingested commercial pesticide formula – pesticide, solvents and surfactants – then there was no signal transmission across the junction."

Subsequent research provided more detail on the mechanism of action: metabolites from the breakdown of organophosphates and solvents create a lethal mix which stops the contraction of the diaphragm and chest wall muscles.

A small scale trial is currently underway to see whether protecting neurotransmitter receptors in the neuromuscular junction can prevent the effects of these metabolite cocktails. Interim data, however, has not been spectacular. "Unfortunately, as a consequence of the ban on some organophosphates, the ones on the market now are much longer-lasting, sticking around for too long compared to the novel treatment we are testing," Michael observes. "Our approach may need a rethink so that receptor protection outlasts the organophosphates circulating in the patient."

Michael is adamant that the problem of organophosphorus poisoning requires a multifaceted approach – with clinical, pharmaceutical and regulatory interventions. The Lister funding has enabled him to pursue many lines of enquiry and engagement in Sri Lanka and beyond. "I'm a bit of a phenomenologist," he admits. "I look around me, I see a problem and I work out how to fix it. However, that means I get involved in lots of different studies with many people and I move back and forth between the UK and Sri Lanka all the time. I used the Lister funding to employ a projects coordinator in the UK who could organise everything for me and make sure I could keep tabs on all my activities. At that stage in my research I had so much going on; without the Lister Institute I would have had to step away from some of the projects. I couldn't have managed them all myself."

> "There were so many angles on the problem of organophosphorus poisoning and so many ways I could see it could be tackled."

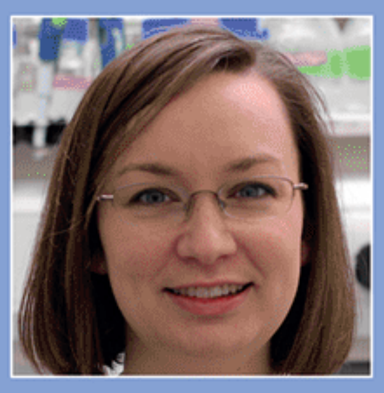
Michael has worked tirelessly with manufacturers and regulators. The most poisonous products have now been banned in Sri Lanka, typically replaced by more modern insecticides which are generally less toxic to humans. Since he started his work, pesticide suicide poisoning in Sri Lanka has fallen from 56 per 100,000 to 15, due mostly to pesticide regulation and removal of the most hazardous pesticides from agricultural practice, but also to improvements in medical practice. Mortality rates within wards for pesticide poisoning have dropped from 14% to 2%.

Based on his Lister-funded research, Michael hopes to persuade manufacturers to change their formulations as another way to eliminate intermediate syndrome; studies show that some solvents, with similar agricultural effectiveness, are safer than others. He also currently leads a large-scale study with more than 200,000 participants, funded by The Wellcome Trust, to see whether more secure and safer storage of pesticide products can reduce poisoning incidents.

> "I look around me, I see a problem and I work out how to fix it."

What's new for the next generation?

PROFILE



Dr Erica Watson

Department of Physiology, Development and Neuroscience
University of Cambridge

Lister Prize Award: 2015

Erica Watson investigates transgenerational inheritance.

"My lab is only just getting going," says Erica Watson, "but the Prize Award has been crucial in supporting my early work. It will allow me to address some risky ideas, which the usual funding programmes would probably avoid. So it's wonderful that the Lister Institute has got in on the ground floor to help me with something that could become really big."

During her PhD at the University of Calgary, Canada, Erica's supervisor, Jay Cross, gave her a mini side project to investigate embryonic defects in mice. It did not take Erica long to realise there was something odd: in this particular mutant strain she observed defects in wild-type littermates although they should have been normal. It took a while, but she eventually found that the mutation in the maternal grandparents of these mice was having an effect on foetal development.

Fascinated that developmental defects could be transmitted in wild-type mice for several generations, Erica came to England and continued her enquiries at the Centre for Trophoblast Research in Cambridge.

The Prize Award is helping Erica to continue her high-risk embryo manipulation experiments into the mechanisms of non-genetic inheritance in these mutant mice. The mutant mice she studies lack methionine synthase reductase (Mtrr), an enzyme involved in the DNA methylation process. Erica has already shown that some developmental defects persist in offspring for up to five generations of wild-type progeny, even though the original Mtrr mutation was present only in the first generation.

Preliminary results from Erica's experiments provide a few hints about her unusual observations. "The effect of the Mtrr gene mutation in the first generation is to disrupt DNA methylation throughout the genome," Erica explains. "This has widespread effects on the expression of many genes that are important for normal cell function and embryonic and placental development. We think that some of these changes in DNA methylation patterns are inherited by the next generations and thereby disrupt the expression of genes important for development independently of the Mtrr gene. It's disrupted methylation that is being passed on, not gene mutation."

Normal mouse embryo development from embryonic day 9.5 to 15.5

"Transgenerational inheritance is an emerging area of research, so my work is right at the forefront of what we know," Erica suggests. "I'm asking big questions about little known mechanisms of inheritance that are independent of DNA sequences and don't follow the normal rules of genetics. Imagine the implications if we find our diet will affect our grandchildren! Not many epidemiological studies look at the effects of our grandparents' environment. What if improvements in diet only start to make a difference two generations in the future? Suddenly public health, disease prevention and many branches of medicine take on a very different shape.

"We've only just really started looking at personalised medicine, where the genome of individual patients affects the treatments they receive. Now it looks even more complicated; we're going to have to think about how a patient's genes are turned on and off by methylation. Methylation is a dynamic process that responds to the environment. This form of inheritance helps to prepare the next generation for the environment they will be born into; it means a population can adapt faster than through genetic mutation."

"I'm asking big questions about little known mechanisms of inheritance that don't follow the normal rules of genetics."

Vitamins, nutrition and the National Loaf

The Lister Institute led post-war UK efforts to improve diets and eradicate deficiency diseases.

Through times of war and peace, Lister scientists have played an important role studying nutrition and advising the UK Government on how it should support public health through better nutrition and vitamin fortification in foods.

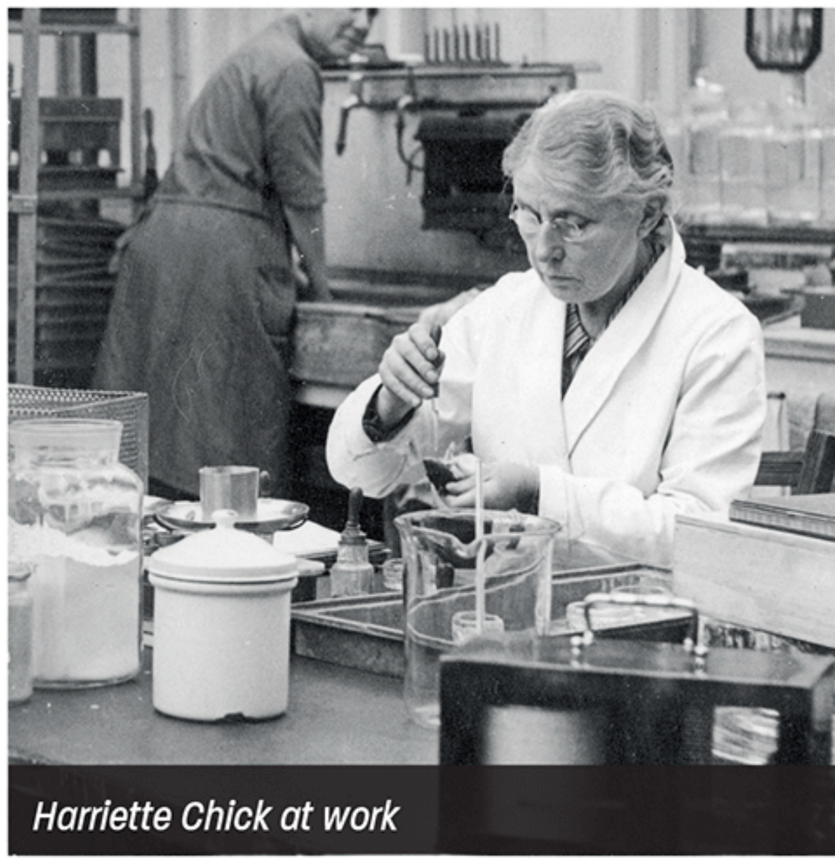
Indeed, the term "vitamin" was coined at the Lister Institute in 1912 by visiting researcher Casimir Funk, who studied a factor (later found to be vitamin B1) in rice that prevented beri-beri. During these early days, Harriette Chick also performed important work on the content of antiscurvy factor (later identified as ascorbic acid or vitamin C) in foods.

Arthur Harden complemented her work by showing that boiling vegetables in soda, a common practice during this period, destroyed vitamin C. He also devised a method for preserving the factor in food and juice concentrates.

Interest in nutrition became especially important immediately after World War I as public health had deteriorated due to rationing and poor supplies. In 1918 the Lister Institute and the Medical Research Council jointly formed the Accessory Food Factors Committee. Together they investigated nutrition-based diseases: scurvy, osteomalacia, keratomalasia and rickets. In 1919 the Committee sent three Lister women, Harriette Chick, Elsie Dalyell and Margaret Hume, on a study mission to post-war Vienna. Here they conducted controlled studies that revealed rickets could be cured or prevented with cod liver oil or ultraviolet light. This simple nutritional solution, based on solid evidence from controlled studies, started the effective eradication of rickets from European society.

During World War II, Lister scientists, led by Harriette and Margaret, who had remained on the Accessory Food Factors Committee, advised on the best way to preserve the nutritional content of staples. They focused on how to preserve vitamins in flour to make the National Loaf. This fortification programme is considered to have made an important contribution to the health of the population during the war years.

Institute scientists studied beri-beri, scurvy and rickets among other vitamin deficiency diseases. Their investigations supported national initiatives to fortify foods and encourage vitamin supplementation.


Harriette Chick at work

Cellmark

British chemicals company ICI set up Cellmark in 1986 to commercialise DNA fingerprinting. Today the company provides forensic services and DNA testing to customers around the world.

It's a reflection of the genius of former Lister Fellow Professor Sir Alec Jeffreys that it took little more than a glance at the stripes of his human DNA Southern blots for him to realise the implication – and potential applications – of his discovery. Several tests later he confirmed that the variability of DNA minisatellites could be used to identify each and every one of us.

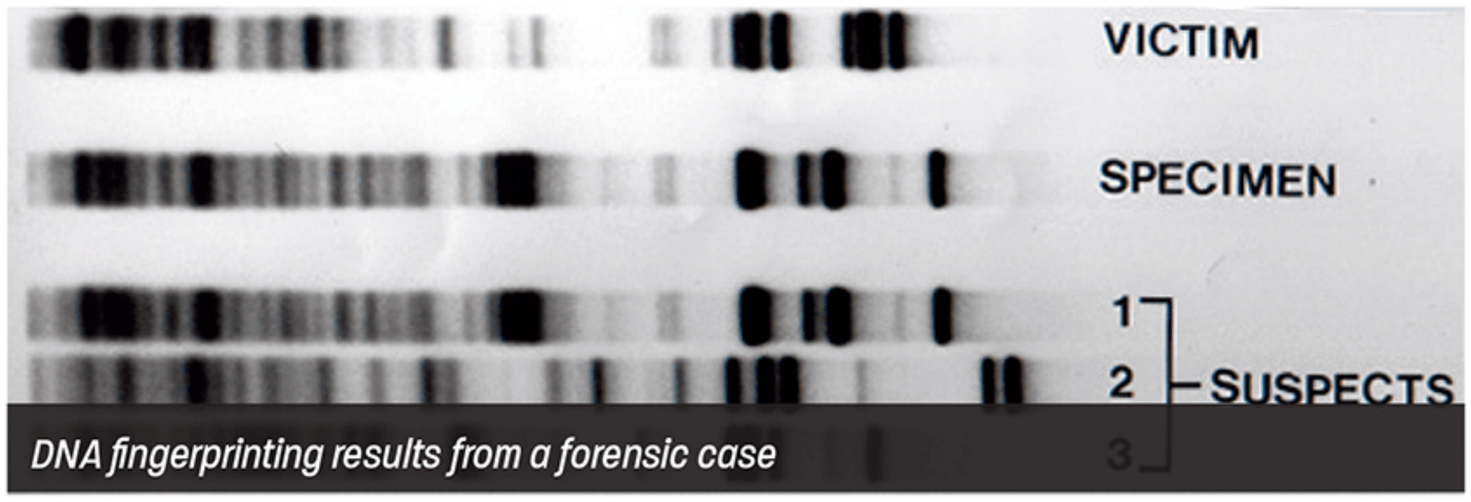
Alec had discovered that we all have a unique DNA fingerprint; just like the old-fashioned ink-and-paper smudges collected in routine police work, DNA could help to identify individuals.

Almost straightaway Alec came under great pressure for his lab at the University of Leicester to run DNA fingerprints to help solve all manner of unpleasant cases hinging on forensic evidence. But by his own admission, he realised this work was not for him. He was a geneticist, a scientist wanting to experiment and uncover the secrets of life, not dig up the secrets of murder cases and paternity disputes. It was time to license the technology for commercialisation.

> Without the Lister Institute, DNA fingerprinting would never have been born at Leicester, says Alec Jeffreys.

ICI already had an established partnership programme with the University of Leicester, so it was unsurprising that the company was given first access to the patented technology.

Alex Markham, who worked for ICI at the time, was given responsibility for launching Cellmark, a new ICI venture into the world of diagnostics. "At about the time of Alec's discovery, ICI had done some competitor analysis and realised that all their big – and better recognised – competitors around the globe had large and successful diagnostics businesses," Alex recalls. "ICI decided it needed to invest in this area and Alec's discovery came just at the right time. We realised that we could use DNA fingerprinting as our first commercial application. We would make the DNA fingerprinting technology our proof that ICI could break into the mature diagnostics sector."



DNA fingerprinting results from a forensic case

David Hartshorne was one of the first Cellmark DNA fingerprinting technical staff. "Right from the beginning there was a big focus on forensics," he recalls. With a massive team effort, Cellmark was able to open its doors for business in June 1987, just over two years after the publication of Alec's original paper.

Andy Cawood, Cellmark's first technical manager, provided all the early forensic reports for the Metropolitan Police Laboratory until they had the facilities and trained personnel to begin the work themselves. He gave the first ever DNA evidence to be presented at the Old Bailey in January 1988 in a case of incest, and also presented the first DNA evidence in a criminal trial in Australia in 1989.

In those early days, DNA fingerprinting was a lengthy process: the commercial development of polymerase chain reaction (PCR) systems to amplify DNA and provide increased detection sensitivity was still a few years away. The whole process could take several weeks, an entire forensic investigation several months. Employing 20 staff, Cellmark undertook forensic and civil paternity cases from around the country as well as overseas. The company also manufactured and sold the proprietary DNA probes that allowed DNA laboratories around the world to use the Jeffreys DNA tests. At the peak of the use of this technology in 1993, Cellmark sold probes to forensic and paternity laboratories in 40 countries worldwide.

Although the criminal cases triggered news headlines, it was routine relationship testing that touched the most lives. For example, until the introduction of DNA testing to support immigration applications to the UK, especially from the Indian sub-continent, many families were separated as they were not able to satisfy the immigration officials that they were related as claimed. DNA fingerprinting gave an unequivocal demonstration of the truth, bringing distressing separations to an end for many families.

With the arrival of PCR methods, DNA profiling started to move away from Alec's patent-protected approach. "However, the company still thrives, built on the success of the original technology." says David Hartshorne, who today is Cellmark's commercial director. "The whole concept of using repetitive sections of DNA to identify individuals is still the basis of forensic identification to this day. The technology and methodologies have moved on, but the underlying principle is still based on Alec's discovery of the remarkable and unexpected variability of human DNA."

From 20 people running gel electrophoresis in a lab, today Cellmark employs over 550 people in the UK and is part of a larger organisation that also provides paternity and forensic DNA services in the US. The company is contracted to provide forensic testing by 85% of UK police forces – not just DNA profiling but a full range of forensic services. Working with the police, today Cellmark is responsible for submitting half of all the crime scene DNA results into the National DNA Database.

"It really is a marvellous story," Alex Markham, now Chair of the Lister Institute, concludes. "A British discoverer, a technology commercialised and first used in the UK, then sold around the world. DNA fingerprinting built up a significant commercial company and brought royalties back to the inventor Alec Jeffreys, the University of Leicester and the Lister Institute. Innovation doesn't get much more satisfying than this."

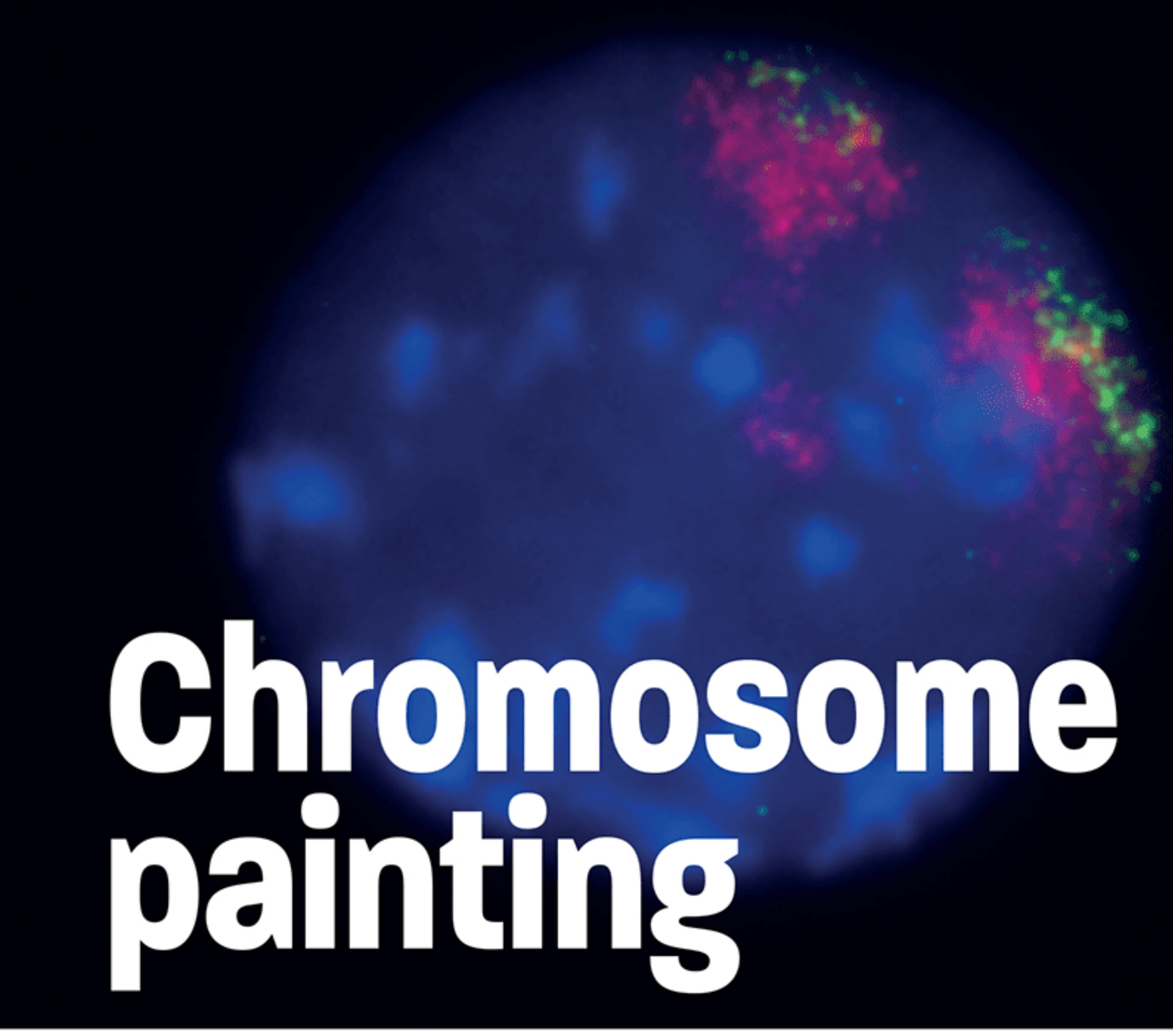
Alec Jeffreys remembers

Fellowship: 1982–91

"The year was 1982. I was a young university lecturer becoming progressively buried in teaching and administration, finding less and less time for the lab bench. Bill Shaw, a member of the Institute's Governing Body, told me about the new Fellowship scheme and its potential to provide freedom to think and research.

For me, the Fellowship was perfect. It freed up time to explore the idea of highly variable human DNA, very much a fringe project that I would otherwise never have pursued. Our accidental discovery of DNA fingerprinting in 1984 – it never actually featured in any research proposal submitted to Lister – opened up a huge new world of DNA-based identification that has now reached out and touched the lives of 50 million or more people worldwide. I pay tribute to the Lister Institute, and in particular to its Chair at the time, Albert Neuberger, and its secretary, Gordon Roderick, for their faith in me and my technology. They played a huge role in the early days to protect our intellectual property and to facilitate the commercialisation that led to the foundation of Cellmark Diagnostics.

It was a huge privilege to be a Lister Fellow for a record-breaking 10 years (given IP and commercial sensitivities, we did not dare separate), and to have remained closely associated with the Institute and its extraordinary Fellowship over the subsequent decades."



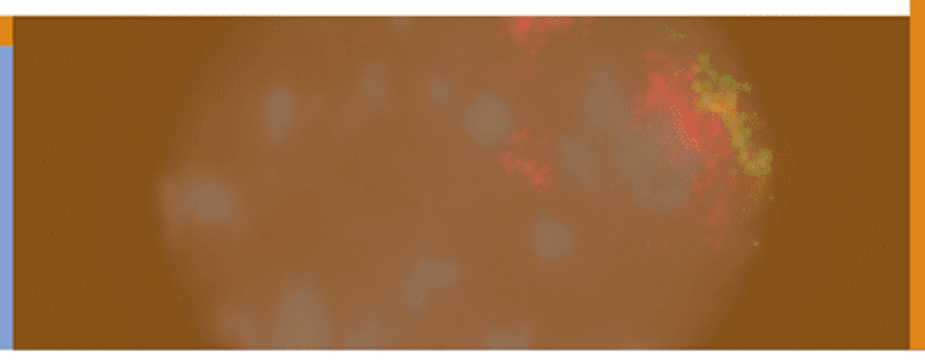
Chromosome painting

PROFILE

Professor Wendy Bickmore

MRC Human Genetics Unit
Western General Hospital
Edinburgh

Fellowship: 1991–96



Wendy Bickmore, Director of the Medical Research Council Human Genetics Unit, sheds light on the three-dimensional organisation and control of genes.

Wendy Bickmore can fairly claim to be a career MRC scientist; she has worked in MRC-funded laboratories for almost all of her research career, but it started with her Lister Fellowship in 1991. In that year she came to the end of a post-doctorate during which she had collected preliminary evidence about the non-uniform distribution of genes across the genome. "It was a side observation, but one that I found fascinating," she remembers. "In biology, there's usually a good functional reason for why things are the way they are. So why would it matter where the genes are located on a chromosome?"

She came up with an experimental technique that involved 'painting' genes and non-gene sequences with fluorescent markers. "It was a bit left field, not your standard medical research proposal, rather esoteric. But if my painting showed a pattern in the distribution of genes it would indicate some functional significance – and the mechanisms at work might just have some kind of clinical application. The Lister seemed willing to take a punt on my ideas and me as a person."

"The Lister seemed willing to take a punt on my ideas and me as a person."

Thanks to the powerful visualisation from her painting technique, Wendy was able to publish a key paper only halfway through her Fellowship that revealed how large tracts of DNA don't contain genes at all. But this finding just led to another question: if genes are not randomly distributed along the chromosome, is DNA randomly distributed in the cell nucleus? Does it matter where the DNA for a gene is spatially located within the nucleus?

Using the same kind of DNA painting methods, Wendy showed that the sections of chromosomes containing protein-coding genes tended to sit towards the centre of the nucleus, whereas the edge of the nucleus was enriched in 'gene deserts'. At this time scientists assumed that the gene deserts in the genome were just lengths of junk DNA, but Wendy's work showed these tracts might be important for gene regulation by influencing their spatial organisation within the cell's nucleus.

At the end of her Fellowship Wendy moved seamlessly to a position as an MRC scientist, still working on gene and chromatin distribution in cells. Building on her early research, she developed a way to manipulate the three-dimensional positioning of DNA within the nucleus, concluding that the movement of a gene towards the nuclear membrane can effectively switch it off.

Over the years Wendy has provided some crucial insights into how the packaging of genes plays a role in their expression and function. She recently discovered that an epigenetic mechanism for keeping a gene switched off in development involves packaging up genes so tightly that they cannot be read properly.

She is now working on the problem of how genetic switches act to turn genes on at the proper time and place in development. These switches are often a long way away on the chromosomes from the genes that they control. "All the complex information that leads to a gene turning on is somehow being fed to a tiny piece of remote DNA. But what information is controlling that switch? How does it influence the way DNA folds and where the gene locates within the nucleus?" Wendy asks.

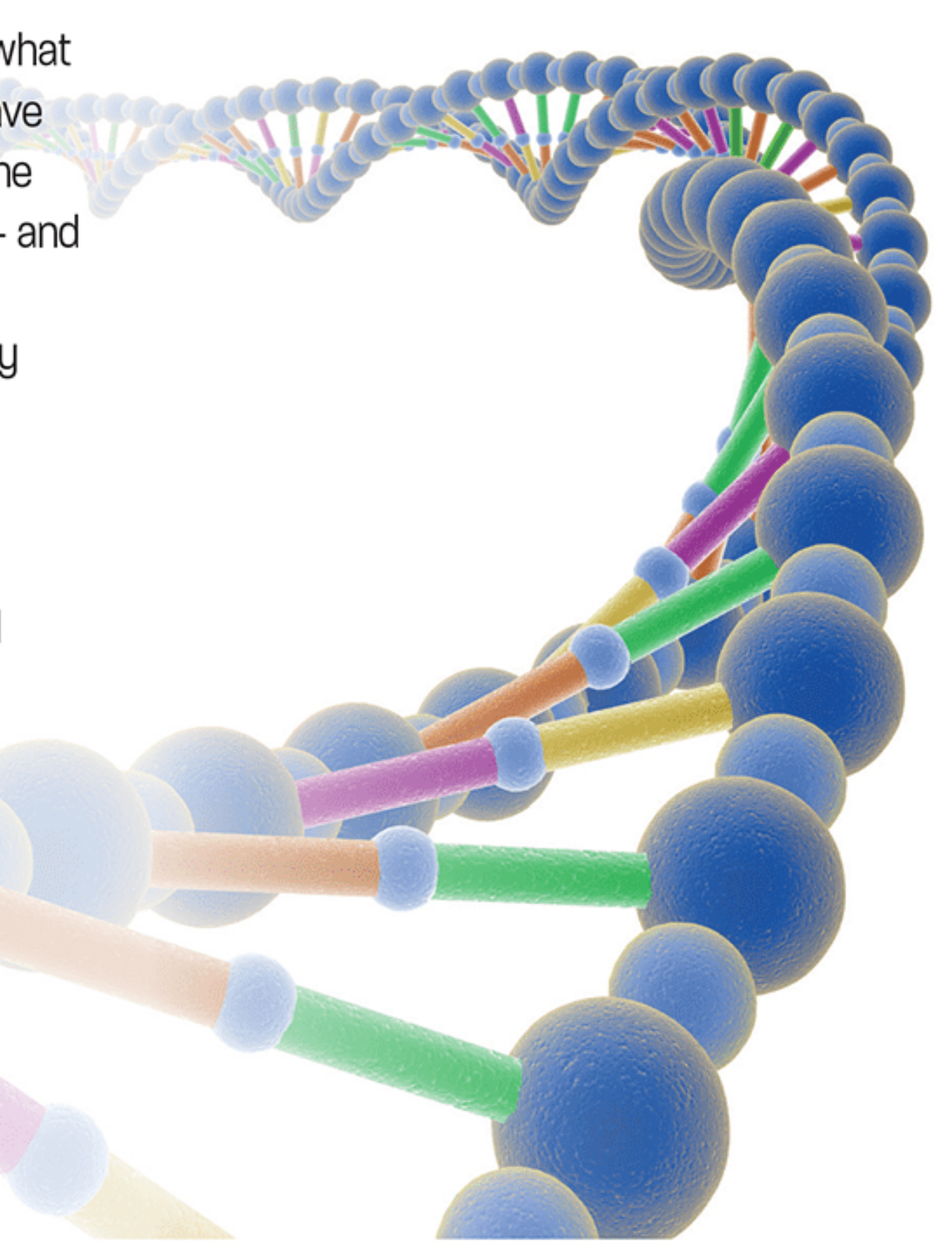
Wendy, who was elected to the Lister's Governing Body in 2015, now runs the same unit in which she carried out her Fellowship. "As a marker of esteem and quality, my Fellowship helped me enormously in securing a tenure in the unit," she says. "It was tremendous, especially as through the Lister and the annual meeting I got exposure to an enormous breadth of science that really broadened my outlook."

She argues that the flexibility which came with the Fellowship was an important complement to grants from the larger funding bodies, including the MRC itself.

"For most grants you have to say how you will spend every penny, though in truth you have no idea how you will spend the money in three or four years' time. Obviously there is a close alliance between what the Lister funds and what the MRC does, but it was great to have independence and flexibility within the Fellowship. Because the Lister was – and still is – run by a very small number of people, it can respond very quickly and add enormous value to people."

"Today the Prize Award can help researchers pursue work that gives them the preliminary data they need to land bigger grants from the MRC. There's still good synergy between the two organisations," she adds.

The MRC Human Genetics Unit has hosted four Lister Fellows. Their work continues to shape the unit's on-going research in chromosomes, gene expression, and medical and developmental genetics.



Proudly independent and a perfect partner

Throughout its history the Lister Institute of Preventive Medicine has worked in close partnership with the Medical Research Council.

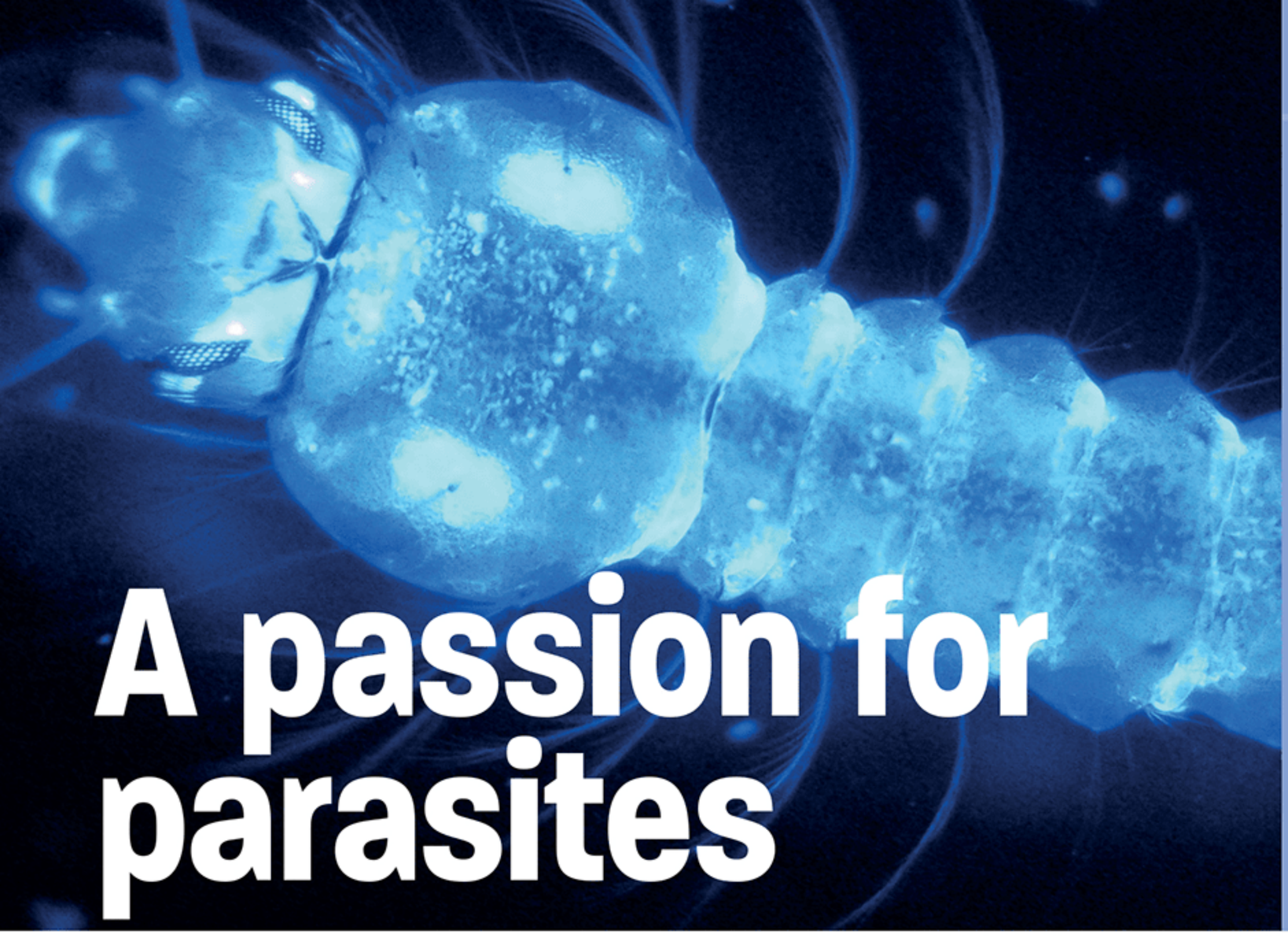
The Institute's close relationship with the Medical Research Council (MRC) dates right back to 1911 and the founding of the MRC's precursor, the Medical Research Committee. At this time some members on the Lister Institute Governing Body advocated a merger between the organisations. When the idea went to a vote in 1914 the decision to remain independent was only passed by a slim majority.

Since that time, however, the Institute has remained fiercely independent, but never insular. Indeed, relations between the Institute and the MRC have always been harmonious. William Bulloch, one of the founding members of the MRC was Chair of the Lister's Governing Body for 10 years from 1931. Over the years the two organisations have participated in many joint research and advisory activities, for example the post-World War I Accessory Food Factors Committee (with its ground-breaking studies in Eastern Europe) and the large-scale clinical trials of whooping cough vaccine in the late 1940s.

More recently, 11 former Fellows carried out their research in MRC laboratories; five Prize Award winners currently work in MRC institutes or laboratories. Former Fellows have also sat on high-level MRC committees and advisory boards including the MRC Council. Between 2008 and 2010 former Fellow Sir Leszek Borysiewicz served as Chief Executive of the MRC.

Ties between the two organisations grew especially strong when Sir Alan Drury, Chair of the MRC Blood Transfusion Committee and responsible for setting up the UK's blood transfusion services, became the Institute's Director in 1943. Under his command the Institute began a period of intense blood-related research within the new, joint Lister-MRC Blood Products Research Unit. Researchers from both organisations enjoyed remarkable levels of scientific cross-fertilisation, which have seldom been bettered even with today's focus on interdisciplinary research.

Relations between the Institute and the MRC have always been harmonious.



A passion for parasites

PROFILE

Professor Paul Eggleston

Faculty of Natural Sciences
University of Keele

Fellowship: 1987–95
University of Liverpool,
Liverpool School of Tropical Medicine

Nearly 30 years after his first genetic experiments on mosquitoes, Paul Eggleston thinks he is finally close to a modified insect that cannot transmit the malaria parasite.

Like thousands of post-doctoral geneticists around the world, Paul Eggleston found himself working with *Drosophila*. This fruit fly is a classic model for genetic experiments; it is quick and easy to breed and open to genetic modification with a host of laboratory tools and techniques. It is only a fly, but it offers so much scope for exciting experimentation!

But Paul was already thinking: what if you could do all this genetic manipulation in other insects? More importantly, what if you could modify pests or carriers of disease? Could you engineer mosquitoes so they couldn't transmit malaria, he wondered.

"I was based at the University of Liverpool, but I also worked as a research associate at the Liverpool School of Tropical Medicine. I started to moonlight down there as much as possible," he says. "I wanted to see how we could use the tools of *Drosophila* biology to tackle seemingly intractable problems, for example to interrupt the transmission of malaria.

"The mosquito, not *Drosophila*, became my true passion. But like most academics I was snowed under with tutees and teaching, so I applied to the Lister Institute for a Fellowship so I could focus on my mosquito work. I had a strong background as a geneticist and I proposed to move the fruit fly tools and techniques sideways into mosquitoes."

Paul laughs when he looks back at his naïve assumption that a mosquito was 'just another insect' like *Drosophila*. "We really wrestled with every single aspect. Whatever tool or technique we tried, no matter how easy it was in *Drosophila*, it was a challenge with mosquitoes," he admits.

His ambition was – and remains today – to find ways to kill or disrupt the life cycle of the malaria-causing *Plasmodium* parasite during its time within the mosquito host. During his Fellowship he researched many aspects of mosquito genetics in parallel. "We were trying to develop new tools for genetic manipulation of live mosquitoes, but I wanted to be ready for the parasitology once we got the tools to work," he explains. "My studies ranged from looking at the use of mobile elements for genetic manipulation through to injecting DNA into live mosquito embryos. I also tried to understand the controls of gene expression and the localisation of mosquito protein expression. It was a busy time with experiments on many fronts."

It was a frustrating time too and Paul acknowledges it might look as if he drew blanks for nearly a decade. "Yet without this intense period of fundamental research we would have never made the breakthroughs that occurred soon afterwards. The Lister Institute saw the potential of my work and funded the groundwork. They were ahead of the game."

One of the biggest challenges Paul faced was to find a mobile genetic element he could use to insert DNA into the mosquito genome. He expected the transposable P element in *Drosophila*, which easily pops in and out of the fruit fly genome like a cassette tape, to work just as well in mosquitoes, but it failed. He tried mobile elements discovered by many other research groups, but the search to find one that actually worked in mosquitoes took much longer than he had anticipated.

Progress in understanding the controls of gene expression went more smoothly as he quickly discovered the promoter region for trypsin. This peptide is expressed specifically in the mid

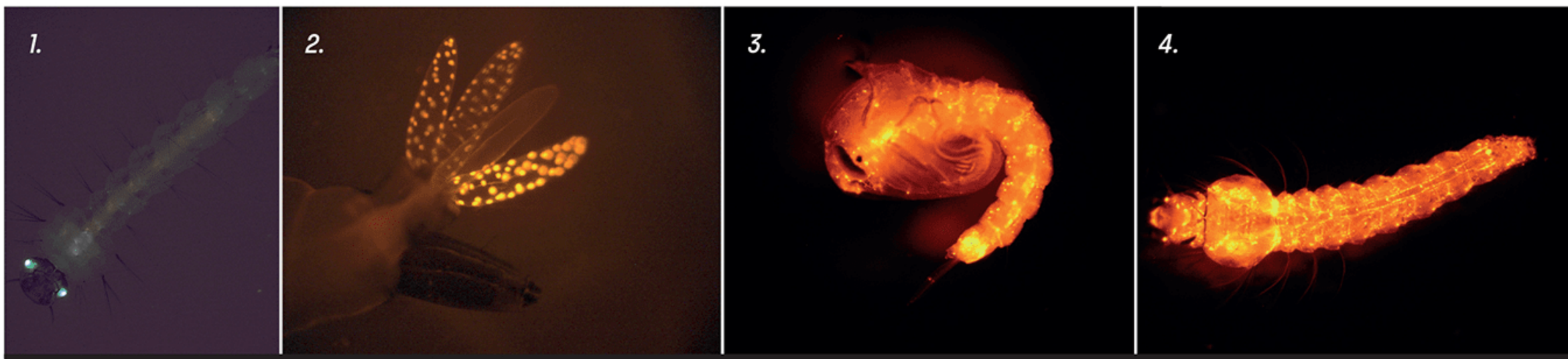
gut of the mosquito, so Paul thought he might use it to control expression of a *Plasmodium* toxin to attack the parasite soon after the mosquito swallowed a blood meal.

Paul also developed a procedure to insert modifying DNA into mosquito embryos without killing them. Again, this was far trickier than *Drosophila* work because mosquito larvae live in water. After much trial and error, he found a way to prevent catastrophic pressure changes inside the embryonic cells. His system for injecting the posterior region of live embryonic mosquitoes is still widely used in labs today.

Paul confesses that it has only been in the last few years that he feels like the work he started with his Lister Fellowship is finally coming to fruition. "Today we can make designer mosquitoes, modified exactly how we want them, even down to where in the genome we will insert our DNA. We can control expression and switch proteins or toxins on and off at key sites as we wish. Now we are just trying to refine all our approaches so we can make a mosquito incapable of transmitting the parasite. It's exciting to think that at last we could be on the brink of the breakthrough."

"The Lister Institute saw the potential of my work... They were ahead of the game."

Paul is working with scientists across Africa who will need to support field trials of his malaria-resistant mosquitoes. "I couldn't just come along and release them," he explains. "Research is built on collaboration. The development of genetically modified mosquitoes needs to involve everyone concerned including citizens, scientists and regulators."



Genetically modified mosquito larvae expressing fluorescent marker proteins

Tropical disease and the developing world

From its earliest days at the peak of the British Empire, the Lister Institute conducted a significant amount of research on tropical diseases.

In 1905 Edward Minchin was appointed Chair of Protozoology, endowed by the Colonial Office, and he investigated the complicated life cycle of a trypanosome parasite in wild rats and fleas. This model of transmission via an intermediate host was confirmed soon after in 1907 by Muriel Robertson, who revealed the role of leeches in trypanosomiasis in fish.

Just before the turn of the century scientists had also implicated the role of tsetse fly in the transmission of African trypanosomiasis (sleeping sickness). Muriel Robertson travelled to Uganda where she worked out the life cycle of the parasite, travelling around by bicycle to take samples from cattle grazing in the bush. Studies on sleeping sickness stopped at the outbreak of World War I and did not resume until 1947 as part of wider work to identify the feeding habit of tstetse flies. Identifying the sources of blood meals in the intestines of flies, Lister staff at this time were able to suggest that sleeping sickness could be controlled by eliminating the flies' preferred feeding animal from an area to break the life cycle of the trypanosomiasis parasite.

Muriel Robertson also studied trichmonas infections, studying *Trichomonas foetus* for two decades to uncover its immunopathology. She was elected as a Fellow of the Royal Society in 1947, one of the first women to receive this honour. Although she officially retired in 1948 she continued working at the Lister until 1961.

Muriel Robertson fishing for leeches

Cancer research that's Cizzling hot

PROFILE

Dr Dawn Coverley

Department of Biology
University of York

Founder and Chief Scientist,
Cizzle Biotechnology

Fellowship: 2002–07
University of York

Dawn Coverley is commercialising the fruits of her Lister Fellowship research.

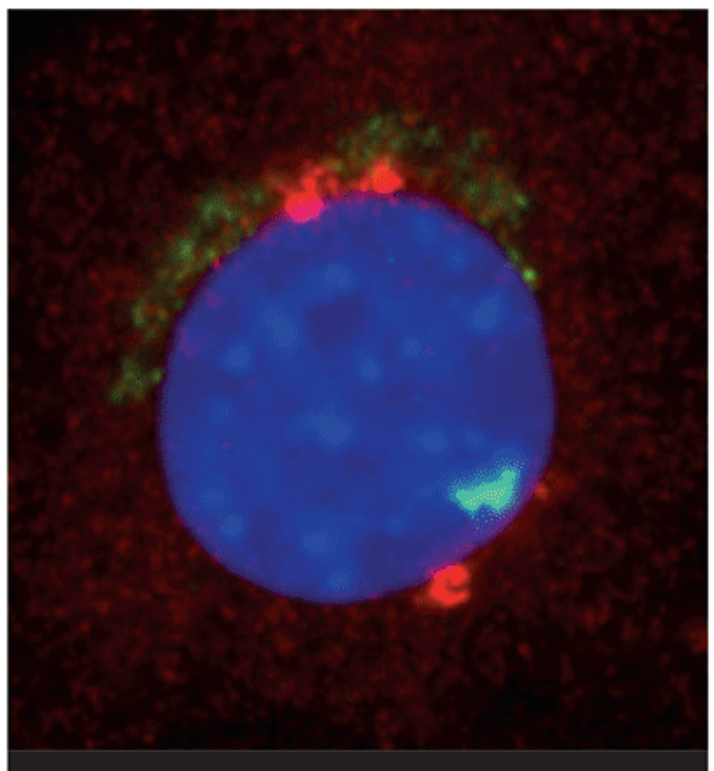
Dawn Coverley remembers being taught by Alec Jeffreys. Firmly in the limelight following his discovery of DNA fingerprinting, Alec was one of her favourite lecturers. "He was exciting and inspiring to listen to," she recalls. "The way that his discoveries were being applied made me realise that everything going on in labs had potential to make a difference in the real world. You never know if what you discover could change people's lives."

Could Dawn now follow in Sir Alec's footsteps with more commercially successful research?

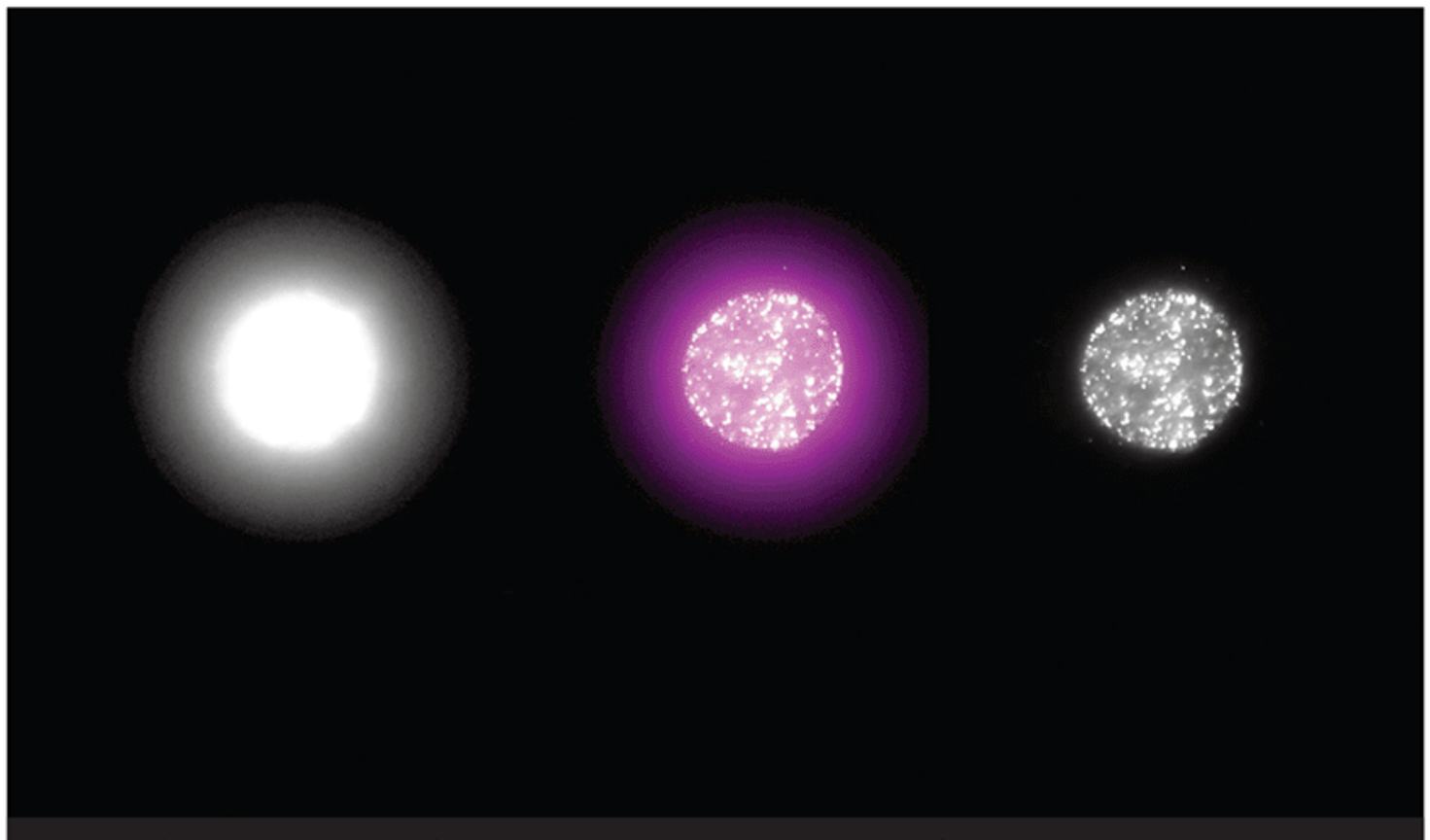
In 2005, mid-way through her Fellowship, she founded Cizzle Biotechnology to exploit some key research findings for clinical applications.

Her Lister Fellowship focused on the control of DNA replication. As a research associate she had already identified a protein, CIZ1, that helps to control the initiation of DNA replication. With her Lister Fellowship confirmed, she secured a position in the University of York where she began to characterise CIZ1 and its function in replication control.

Her laboratory work soon revealed the protein came in many variants – 28 at the last count, she says. "We were particularly excited because some specific variants were uniquely associated with cancer cells. We validated the b-variant CIZ1 protein as a biomarker for lung cancer and a candidate target for novel therapeutics. If you could develop a selective molecule against b-variant you could selectively stop the replication of cancer cells. It was theoretically feasible, but the steps to translating my



Nucleus of a mammalian cell showing DNA (blue) and tubulin (red) with CIZ1 (green) at the X chromosome at the edge of the nucleus.



Loops of DNA emanating from a nucleus (left). Machinery for DNA replication within the nucleus (right). Overlay, with DNA in pink (centre).

findings into clinical products were huge."

Nevertheless, the potential of b-variant CIZ1 for both cancer treatment and diagnosis was evident. With support from the University of York and the Lister Institute, Dawn formed Cizzle, and soon raised finance from several investors, especially Yorkshire Cancer Research, which now has a majority stake in the company.

"Being a member of the Lister Institute gave me confidence to go down this commercial route," Dawn acknowledges. "Knowing about people like Alec and talking to them about their experiences helped me to focus on deriving impact from my work."

Today Cizzle is developing a presymptomatic screen for lung cancer. Remarkably, b-variant CIZ1 is detected in the plasma of patients with lung cancer, even at the earliest stage of the disease. The protein is extremely stable in blood, so there is no problem with transportation and storage of samples before they get to the hospital diagnostic laboratory. Cizzle scientists are also investigating whether b-variant could help clinicians make decisions about patients who are found to have small lung anomalies in CT scans. Preliminary studies also suggest that CIZ1 may play a role in some paediatric cancers, although whether the protein is found in the blood is not yet known.

It has been a slow journey, Dawn admits, but she struggles to contain her sense of relief and excitement about recent and rapid progress. "It takes a long time to get from what you know works in the laboratory through proof of concept to something that complies with all regulations so you have a product to sell. We developed a monoclonal antibody for b-variant quite quickly, but for an ELISA assay that works on standard hospital lab equipment we need two antibodies. At last I think we've finally got it. I'm excited we might be able to progress to the next step," she says.

"You never know if what you discover could change people's lives."

The Institute family in Dundee

Meet the Lister Fellows and Prize Award winners at the University of Dundee.

Julian Blow is the patriarch of the Lister family in Dundee. He is an unashamedly enthusiastic champion for the Lister Institute and every year he encourages post-docs and early-career life science researchers to apply for the Prize Award.

Crowned Jenner Centenary Fellow, Julian received his fellowship in 1991 whilst working at the Imperial Cancer Research Fund Clare Hall Laboratories in Hertfordshire, now part of the Francis Crick Institute. Soon after the end of this Fellowship he secured a senior lectureship at the University of Dundee where he has since become the Director of Research for the School of Life Sciences.

"The Lister Fellowship was instrumental for my career," he says. "It gave me a great network of peers in a wide range of disciplines with whom I could discuss ideas. It really enabled me to build my network and it was absolutely crucial in bringing me to Dundee. Funding from the Lister Institute is a huge vote of confidence in your abilities as a talented scientist."

It is the intangible benefits of prestige and networking – perhaps more than the money itself – that make Julian such an eager advocate for the Lister. "In the dark days of setting up a research group, if I hadn't got the support of my peer group in the Lister I might have given up," he admits. Now he tells his story to younger colleagues and does his best to help them join this fellowship.

To illustrate their everyday closeness, Prize Award winner Vicky Cowling (2011) squeezes into Julian's office to talk about her own experiences as a member of this local Lister elite. It is clear they know each other well.

They have labs in different areas of research, but as life scientists they work in the same building on campus, so they often see each other on the corridors, in the café and at meetings and seminars. Sometimes the contact goes deeper. Julian has collaborated directly with Prize Award winner Tomo Tanaka (2005) on several studies as they are both looking at mechanisms of DNA replication. Knowing that Daan van Aalten was also a Prize Award winner (2007) makes it easier for colleagues to do drug screening. "There's a really collegiate atmosphere here, but still the fact we are all Lister Fellows is quite helpful in initiating discussions and for forming good collaborations," Dan insists.

Julian Blow
(1991-96)

As a Lister Fellow I investigated how DNA replication is controlled, and in particular how the so-called replication licensing system ensures that DNA is not re-replicated in a single cell cycle. I developed an assay for replication licensing and showed that a protein complex had to be loaded onto DNA to license the origin for a single initiation event. I also discovered that a range of different cyclin-dependent kinases could all drive replication initiation. In many ways I am still working on these questions.

A current issue in my lab is to understand how cells ensure that the genome is completely duplicated. It appears that cells license many more origins than they actually use; they also have backup mechanisms for completing replication even when replication forks, where the original strand splits apart and two copies are formed, have irreversibly stalled.

Tomo Tanaka
(2005)

I study the process called chromosome segregation, whereby new daughter cells inherit a complete and identical set of genetic information when a cell divides. Errors in segregation lead to cell death and various diseases such as cancer and congenital disorders. For proper chromosome segregation, thin filaments called microtubules interact with a region of each chromosome called the kinetochore. Supported by the Prize Award, I purchased an advanced microscope system, which enabled my team to analyse dynamic kinetochore-microtubule interactions in great detail. We discovered how this interaction initially forms and how errors are resolved to establish correct interaction. Our study has made a great contribution to understanding this fundamental cellular event.

Daan van
Aalten (2007)

The Lister Prize Award allowed me to explore a new direction in the lab. Using the Prize I uncovered the molecular mechanisms of adding sugar units to proteins, specifically the process known as O-GlcNAc modification. This reversible process is similar to protein phosphorylation and is used to regulate protein activity. I used my findings to develop O-GlcNAc transferase inhibitors. My Lister-funded work led to two significant five-year awards; we are now investigating how this modification is involved in neurodevelop-ment and neurodegenerative disease.

Vicky Cowling
(2011)

My group's research specifically looks at what controls the type of proteins which are made in cells and how this changes when cells become cancerous. We want to find out new ways of starving cancer cells by preventing them making protein. The Prize Award was invaluable because it allowed me to respond instantly to my lab's needs – some-thing that is really important in translational research where there may be an urgent medical need or commercial pressures to develop something quickly. The funding helped me start a project working with the Dundee Drug Discovery Unit, screening for small molecule drug precursors which could stop proteins being made in cancer cells.

Pride and heritage: The Guinness connection

Science writer Edwin Colyer meets Edward Guinness, distant cousin of Lord Iveagh and a member of the Institute's Governing Body from 1968 to 2001.

We opted for a working lunch and moved immediately to the small dining room. Sitting together at the end of the table, I slid my water glass to the side, pulled out my fresh notebook and prepared to enjoy the meal and memories.

With his fork hovering over the cheesy potato bake, Edward told me that over more than four decades of service to the Lister Institute he had attended a good few dinners. "As Lord Iveagh's representative I was often expected at official functions," he explains. He recalls one particularly fine affair with a distinguished Colonel Seifert. According to Edward, this well-known architect and property man was a vital help in arranging the sale of the Chelsea site in the late 1970s. Edward also fondly remembers the gala dinner held at the Royal College of Surgeons in 1991 to celebrate the Institute's centenary. "I was asked to propose a toast to our distinguished guests. A long list of the great and the good attended that day and I was worried I might miss someone out."

The guests of honour were Baroness Hooper from the Ministry for Health; Alderman Sir Hugh Bidwell, a former Lord Mayor of London; and Professor Maxine Schwarz, the Director of the Institut Pasteur in Paris. Together these three encompassed the Lister's great heritage – its connections to London and Paris and its major contributions to British medicine and public health. "And my toast," says Edward holding his glass aloft, "kept the Guinness family involvement alive."

Back in 1896, Edward Cecil Guinness, First Earl of Iveagh, gave £250,000 to the newly established Lister Institute, but it came with a caveat: a seat on the Governing Body plus the right to appoint two nominees around the table too. Under revised articles of constitution, today Lord Iveagh retains his right to a seat or he can appoint a representative.

With his lunch now cold, we move onto apple pie as Edward travels back to his earliest Lister days. He stresses that fancy dinners were actually rare, then just as now. Joining in 1968, to replace Guinness family member Paul Channon MP (who stood down due to his ministerial commitments in government), the Institute was just entering a period of decline. These were dark days of failing funds, the closure of the Institute's research facilities and the end of its vaccine and sera production.

Edward had been nominated by Lord Iveagh's second representative on the Governing Body, Rob McNiele, then Managing Director of the Park Royal Guinness operation. The Institute

Edward's last project for the Institute was to act as Editor in Chief for Leslie Collier who wrote *The Lister Institute of Preventive Medicine: A Concise History*. "Around the time of our centenary we felt that an official history was desperately needed," says Edward. "We wanted something we could give to newly appointed Fellows so they would appreciate the heritage and exceptional success of Institute researchers over the decades." Seeing the book through to its publication in 2001, the project took Edward beyond his 75th birthday, considered the normal retiring age for members of the Governing Body.

wanted to set up a staff pension and sick pay scheme; Rob believed that Edward could support the process as he had spent years in personnel management. "I couldn't possibly begin to understand all the erudite science and papers," Edward admits, "but they thought I could guide some of the personnel initiatives. Of course I was happy to help."

Although he is only a distant relative of the Iveagh lineage (the first Lady Iveagh was the sister of his grandfather), Edward spent his entire working life in the brewing industry. He worked his way up from Junior Brewer in Park Royal when he joined in 1945 – "I was given gumboots and overalls and cleaned out the brewing vessels", he says – to Chairman and Managing Director of Harp Lager and eventually Vice Chairman of Guinness Brewing Worldwide.

"Once we'd set up the staff benefits schemes I thought my work was probably done," Edward modestly suggests, "but by then it was apparent that the Institute was heading for difficult times. Professor Albert Neuberger, who was the Chair of the Governing Body, wasn't going to let me go so easily! It was becoming clear we would not get the external support we desperately needed to supplement the income from the foundation capital. We would no longer be able to pay staff wages, pensions and redundancy payments; we had to close."

"For an institution as well funded and well known as the Lister Institute, this was humiliating," Edward recalls. "Elstree was turning over £1 million per year and the Wolfson Foundation had just funded construction of a new wing at Chelsea Bridge Road. It was an awful, painful decision, but we had no choice."

The eventual sale of the Chelsea and Elstree sites generated substantial funds that allowed the Governing Body to continue the Lister's mission. Although the discussions among the Governors must have been protracted and intense, Edward gently blows them aside. He sips his coffee and states simply that the Fellowship Programme was the best possible way to continue the Institute's work in keeping with the traditional wishes of Lord Iveagh.

"I think the involvement of Lord Iveagh and the Guinness family has given the Institute solidity and continuity over the years," says Edward. "Mycology is important in brewing and Guinness has always embraced science and technology. There's this sense of common ground between the family and the researchers, even if today the science is way beyond anything an outsider like me can comprehend."

"Dare I say the Guinness connection has sometimes helped the Institute stay grounded?" he wonders. "Our business and commercial perspective has helped the Institute in different ways over the years. In my time, we got a lot of help from Rob McNeile when we worked with the University of Leicester and ICI to patent and commercialise Alec Jeffreys' DNA fingerprinting. Guinness had a lot of experience in world patents and Rob helped us get a head start in this respect. Maybe our presence adds a bit of balance and stops everything getting too focused on the science?"

"Within the Guinness family, among those most interested in science, I think there is a sense of pride that we are involved in leading medical research and have contributed to some of the most significant clinical developments of the 20th century. Sometimes I've been the public face, sometimes I've helped pick up the pieces behind the scenes, but I'll always feel this has been worthwhile."

Rory Guinness

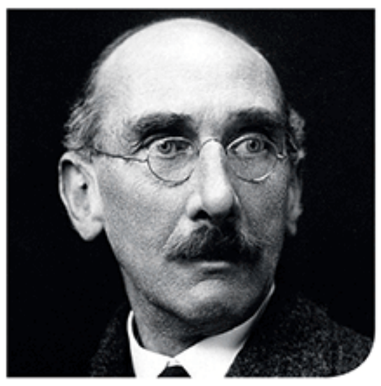
Lord Iveagh's brother, Rory Guinness, carries on the family tradition. He has served as Lord Iveagh's representative on the Governing Body since 1998. He serves on the Finance & Investments Committee where he offers his market knowledge and investment experience to help the Institute actively manage its financial assets. "Working for such an august and noble institution is a great honour," he says. "Every year I am bowled over by the candidates that the Scientific Advisory Committee chooses.

Apart from being amazing scientists at the start of the prime of their career, they are invariably charming people."

Colonel Richard Seifert helped with the sale of the Lister's Chelsea laboratories in the 1970s.

Ten outstanding scientists

01

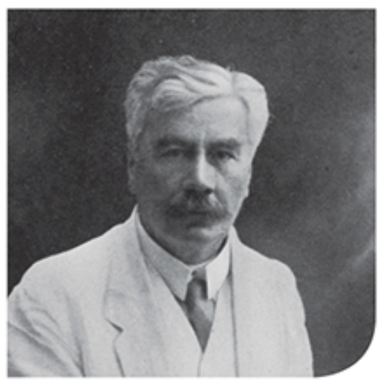


Professor Sir Marc Armand Ruffer

First Director of the Institute. Supported development of UK's first diphtheria vaccine. Pioneer of palaeopathology.

Alex Markham says: *"I'm biased as an admirer of Ruffer because diphtheria nearly killed my own mother!"*

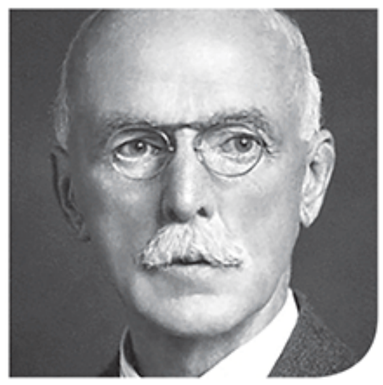
02



Sir Charles James Martin FRS

Director from 1903. Oversaw work proving rats spread bubonic plague (which killed 12 million people in India in the 30 years to 1926). Significant contributions to understanding of the disease pellagra (niacin deficiency), a problem affecting 3 million Americans between 1903 and 1940 leading to 100,000 deaths. Also expert in snake venom and the physiology of the duck-billed platypus!

03



Sir Arthur Harden FRS

Awarded Nobel Prize for Chemistry in 1929 for elucidating many of the steps in glycolysis, by which glucose is metabolised to produce energy in the form of ATP. Discovered the first co-enzyme and investigated how enzymes phosphorylate sugars. Immortalised in the annual Harden Conferences of the Biochemical Society.

04

Dame Harriette Chick

First female holder of the Jenner Memorial Research Studentship in 1905 (23 years before full female emancipation) and still an honorary staff member in 1970. Chick and Martin were among the first to conceptualise the idea of protein folding, even before WWI. One of a handful of scientists worldwide to show that rickets could be prevented with cod liver oil and sunlight, both sources of vitamin D.

05

Professor Walter Morgan FRS CBE

First studied bacterial antigens, then switched to blood. Spent 25 years dissecting the structures of the A and B blood group antigens, some of the most important basic medical research ever described. He retired in 1968, but returned as Director in the 'dark days' from 1972-75 as the Institute faced up to closure. He died aged 103 in 2003.

Alex Markham says: *"He inspired me as a medical student when I met him while he was still working in the MRC Clinical Research Centre at Northwick Park Hospital."*

06

Professor Winifred Watkins FRS

Worked with Morgan and succeeded him as head of department on his retirement. Her work laid the basis for an understanding of the roles of carbohydrate cell surface structures relating to inflammation, tumour progression and metastasis.

07

Professor Leslie Collier

His freeze-drying method of vaccine production allowed the World Health Organization to launch its global smallpox eradication campaign in 1967.

Alex Markham says: *"He also made a wonderful contribution as the Lister's centennial historian."*

08

Professor Sir Alec Jeffreys FRS

Discovered that each individual has unique patterns in their DNA, leading to the development of DNA fingerprinting.

Alex Markham says: *"This has been one of the most fundamental discoveries in human genetics in recent decades."*

09

Professor Rosa Beddington FRS

Combining traditional embryology techniques with molecular genetics, she made fundamental discoveries in the genetic and molecular controls and processes of mammalian development. She was awarded her FRS in 1999.

Alex Markham says: *"A remarkable career sadly cut short in her scientific prime."*

10

Professor Holger Gerhardt

His outstanding research into the mechanisms of angiogenesis (particularly how the process of new blood vessel growth is hijacked by tumours) resulted in a permanent appointment at the Cancer Research UK London Institute. In 2014, he was appointed to his current Chair in Berlin where his laboratory is a major contributor across the Max Delbruck Centre, the Charite Hospital, the German Centre for Cardiovascular Research and the Berlin Institute of Health.

Alex Markham says: *"I could pick almost any of our Fellows or Prize Winners, but Gerhardt reminds me of the fact that many successful research careers are based on an enthusiasm to study and work in a wide variety of the most stimulating academic centres, a tradition always fully embraced at the Lister Institute in its heyday.*

"It is gratifying to see one of our more recent Fellows again upholding some of the Lister's traditions and representing us with such distinction in Europe."

The history of the Lister Institute

1891
- Incorporation of the British Institute of Preventive Medicine

1893
- Purchase of Chelsea site
- Amalgamation with the College of State Medicine

1894
- Establishment of the Serum Department at Sudbury, Middlesex
- Building starts on Chelsea laboratories
- Lister runs evening classes in bacteriology
- Production of UK's first therapeutic diphtheria antitoxin

1897
- First UK isolate of plague bacillus
- Arthur Harden joins Institute

1898
- Donation of £250,000 from Lord Iveagh
- Opening of first laboratories in Chelsea

1901
- Charles Martin elected Fellow of The Royal Society

1902
- Purchase of Elstree site as for serum production
- Special cancer research laboratory established

1903
- Lord Lister becomes President
- Charles Martin Director of institute
- Renamed the Lister Institute of Preventive Medicine
- Radium bromide shown to be ineffective against advanced cancer

1904
- Harden publishes discovery of co-enzyme A
- Cancer laboratory closed

1905
- Proof that rat fleas carry bubonic plague
- Harriette Chick and John Ledingham join the institute
- Edward Minchin begins studying life cycle of trypanosome parasite in rats and fleas

1906
- Joseph Arkwright joins institute
- Edward Minchin appointed to first Chair of Protozoology, endowed by the Colonial Office

1907
- Harriette Chick begins extensive work testing foods for antiscurvy factor (vitamin C)
- Arthur Harden devises a method for preserving ascorbic acid in concentrates

1908
- Publication of the Chick-Martin test and Chick's laws of disinfection
- John Ledingham appointed as chief bacteriologist
- Discovery of fructose 1,6-bisphosphatase by Harden and William Young

1909
- First production of scorpion antiserum
- Muriel Robertson joins Department of Protozoology as junior assistant

1911
- Muriel Robertson studies life cycle of trypanosomes in tsetse flies in Uganda

1912
- Visiting researcher Casimir Funk coins the term 'vitamines'

1918
- Establishment of the Accessory Food Factors Committee with research conducted by the Institute and MRC

1920
- Joseph Arkwright investigates picornavirus (causes foot-and-mouth disease)
- Arkwright isolates rough and smooth variants of Salmonella
- Establishment of the National Collection of Type Cultures, financed by the MRC and curated by the Lister
- Harriette Chick, Muriel Robertson and Elsie Dalyell establish that UV light and cod liver oil can prevent and cure rickets

1921
- John Ledingham elected Fellow of the Royal Society

1922
- Walter Morgan studies medicinal chemistry at West Ham Municipal College with Harden as tutor

1926
- Joseph Arkwright elected Fellow of the Royal Society
- Walter Morgan joins the Institute

1927
- Charles Martin knighted for services to research

1928
- Walter Morgan begins to characterise the antigenic component of Shigella

1929
- Arthur Harden shares Nobel Prize for discovery of co-enzyme A

1930
- Sir John Ledingham leads early work on pox and herpes viruses
- John Ledingham Director of Institute

1932
- Harriette Chick awarded CBE

1933
- Emmy Klieneberger (later Klieneberger-Nobel) leaves Nazi Germany and joins the Lister staff

1934
- Klieneberger and Ruth Lemke characterise mycoplasmas and related infections

1935
- Klieneberger names "L-form" bacteria lacking cell walls after the Lister Institute

1936
- First ultracentrifuge in UK installed in Biophysics Department for protein and virus purification

1937
- Joseph Arkwright knighted

1939
- Accessory Food Factors Committee advises UK Government on preservation of vitamin content in flour used to create the National Loaf during the war

1940
- Walter Morgan begins work on biochemistry of blood antigens

1943
- Alan Drury becomes Director

1944
- Establishment of the joint Lister-MRC Blood Products Research Group

1946
- Participation in ground-breaking MRC field trials of pertussis vaccine in 30,000 children in the UK
- MRC Blood Reference Laboratory moves into Chelsea facility

1947
- Development of ether precipitation for large-scale production of human immunoglobulin from blood
- Muriel Robertson elected a Fellow of The Royal Society
- New studies into sleeping sickness led by Bernard Weitz

1948
- Leslie Collier joins Smallpox Vaccine Department

1949
- Harriette Chick appointed Dame of the British Empire for service to medical research
- Weitz and colleagues travel to East Africa to test blood meal samples from tsetse fly guts in mobile laboratory

1950
- National Collection of Type Cultures passes to the Central Public Health Laboratory

1951
- Leslie Collier develops freeze-dry method for heat-stable smallpox vaccine

1953
- Guinness-Lister Unit established to pioneer bacterial genetics
- New smallpox laboratory at Elstree

1954
- Blood Products Laboratory opens at Elstree

1955
- Leslie Collier appointed Head of new Department of Virology
- Leslie Collier and colleagues confirm infectious nature of trachoma blinding disease
- Elstree tests 56,000 blood meal samples from 50 species of mosquito. Results show DDT reduces Anopheles preference for human blood

1960
- First isolations of Chlamydia

1963
- Bruce Stocker appointed first Guinness Chair of Microbiology

1965
- Walter Morgan publishes the structure of human blood group antigens A and B

1966
- Institute employs a total of 56 scientific members of staff

1968
- Leslie Collier appointed Deputy Director of the Institute

1970
- Income from UK sales of DTP triple vaccines reaches £1 million

1975
- Closure of Chelsea laboratories

1978
- Closure of Vaccine and Sera Laboratories in Elstree

1979
- Sale of Elstree site to Department of Health

1980
- Sale of Chelsea site for £2.7 million
- Klieneberger-Nobel receives the Robert Koch Gold medal

1982
- Appointment of first five Lister Research Fellows

1984
- Fellow Alec Jeffreys discovers DNA fingerprinting

1985
- First annual Institute weekend meeting

1986
- Alec Jeffreys is first Fellow elected a Fellow of The Royal Society
- Alec Jeffreys publishes his first paper on DNA fingerprinting

1987
- Cellmark opens for business in forensic DNA fingerprinting

1990
- The Institute and ICI jointly receive Queen's Award for Technological Achievement for commercial development of DNA fingerprinting

1991
- Centenary dinner held at The Royal College of Surgeons, London
- Tenth Chair awarded to a former Fellow

1994
- Former Fellow Alec Jeffreys knighted

1998
- Study ranks Lister institute 12th in UK for acknowledgements in peer-reviewed journals

1995
- Institute headquarters moves to Bushey Heath

1999
- Former Fellow and embryologist Rosa Beddington elected a Fellow of The Royal Society

2001
- Former Fellow Leszek Borysiewicz knighted for services to vaccine research

2002
- Closure of the Fellowships scheme

2003
- Former Fellow Geoffrey Smith elected Fellow of The Royal Society

2005
- First Prize Awards (£150,000)

2008
- Sir Leszek Borysiewicz elected Fellow of The Royal Society

2013
- Former Fellow Judith Armitage elected Fellow of the Royal Society

2015
- Forty-first Prize Award (total of £7.5 million since 2005)

2016
- Institute celebrates its 125th anniversary

KEY
- Lister people
- Lister event
- Lister research
- Lister impact

Images and illustrations

p2 top banner: Sir Alex Markham, courtesy of Medical Illustration Services, Leeds General Infirmary

p2 bottom: courtesy of Alec Jeffreys

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p10 banner: a lawn of cells that has been infected with a strain of vaccinia virus engineered to express the green fluorescent protein. The green dots are virus particles and the cell nuclei and cytoplasmic virus factories are stained blue, credit: Michael Hollinshead

p10 top right: courtesy of Geoffrey Smith

p11 left: from a Telegraph obituary, unknown source

p11 right: Smallpox vaccines, credit: Pan American Health Organization

p12 banner: traces of static (red) and dynamic (blue) C-ring proteins in the *Yersinia enterocolitica* Type III secretion system, courtesy of Judith Armitage

p12 top right: courtesy of Judith Armitage

p13 top right: *R. sphaeroide*s with polar flagellum, credit: Judith Armitage

p13 bottom left: courtesy of The Royal Society, Godfrey Argent Studio

p13 bottom right: culture of Salmonella bacteria, credit: Tatiana Shepeleva/Adobe Stock

p14 top left: human cytomegalovirus-infected human endothelial cells. Multicolor Immunofluorescence (IF). Blue: DAPI = cellular DNA. Green = GFP (green fluorescence protein). Red + Magenta = two different viral proteins. Captured with a Zeiss LSM510 laser scanning confocal microscope, credit: Joerg Schroeer/Princeton University Art of Science

p14 below: courtesy of Leszek Borysiewicz

p15 top right: transmission electron micrograph of mutant *Haemophilus influenzae* type b cell blocked for capsule polysaccharide export, courtesy of Simon Kroll

p15 below: courtesy of Simon Kroll

p16 top banner: pseudo image of the HCV tight junction receptors in human liver, courtesy of Jane McKeating

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p16 bottom banner: a scanning electron micrograph of *Mycobacterium tuberculosis* bacteria, credit: Stewart Cole/EPFL via medicalxpress.com

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p20 top right: courtesy of Nia Bryant

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p26 banner: a patient in Anuradhapura Hospital after ingesting the organophorphorus insecticide dimethoate, credit: Michael Eddleston

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p27: a warning sign inside a shop in Sri Lanka: "Danger - agrochemicals available for sale", credit: Michael Eddleston

p28 banner: mouse embryo and placenta at embryonic (E) day 10.5, courtesy of Erica Watson

p28 top right: courtesy of Erica Watson

p28 bottom: normal mouse embryo development from embryonic (E) day 9.5 to E15.5, courtesy of Erica Watson

p29 left: National Loaf advert, from artsawardvoice.com

p29 right: Hariette Chick in conservatory animal house at Roebuck House c. 1939, from the Wellcome Library, London

p30: interpretation of DNA fingerprints in the early days of the technology (David Hartshorne in foreground), © Cellmark Forensic Services

p31 left: © Cellmark Forensic Services

p31 right: Sir Alec Jeffreys, courtesy of PLoS Genetics

p32banner: visualising the spatial organisation of chromosomes. Fluorescence *in situ* hybridisation image showing the spatial segregation of the gene-coding (red) and non-coding (green) portions of a specific pair of chromosomes in the nucleus (blue), credit: Shelagh Boyle/MRC Human Genetics Unit

p32 top right: courtesy of Wendy Bickmore

p33: double helix, credit: Benjamin Albiach Galan/Shutterstock (Image ID 17004592)

p34 banner: genetically modified *Anopheles gambiae* larva expressing enhanced cyan fluorescent protein (ECFP) throughout the body, courtesy of Paul Eggleston

p34 top right: courtesy of Paul Eggleston

p35 top image strip: from left to right: *Aedes aegypti* larvae expressing enhanced green fluorescent protein (EGFP) in the eyes and optic nerves. *Aedes aegypti* larvae expressing DsRed2 fluorescent protein in the nuclei of anal papillae cells. Genetically modified *Anopheles gambia*e pupa expressing DsRed2 fluorescent protein throughout the body. Genetically modified *Anopheles gambiae* larva expressing DsRed2 fluorescent protein throughout the body, courtesy of Paul Eggleston

p35 middle right: tsetse fly, credit: Geoffrey Attardo/Yale School of Public Health

p35 bottom right: from the Wellcome Library, London

p36 top banner: left: Loops of DNA, anchored at their bases, emanating from a nucleus from which most components have been extracted. Right: Machinery for DNA replication is held within the nucleus. Centre: Overlay, with DNA in pink, credit: Rosemary Wilson

p36 top right: courtesy of Dawn Coverley

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