Medical research on the front line

How a century of wars has shaped MRC discoveries

Millennium Medal winners 2013
Greg Winter and Philip Cohen's healthcare revolutions
Inside the ‘Nobel Prize factory’ of the future

Scientists have begun moving into the new £212m MRC Laboratory of Molecular Biology (LMB) building in Cambridge, ahead of the building’s official opening later this spring.

A decade in the planning, the X-shaped glass and steel edifice will house 600 scientists, providing the 21st century facilities needed to allow this prestigious MRC institute – often dubbed the ‘Nobel Prize factory’ – to take its research forward.

At the heart of the building is a rooftop cafeteria, giving researchers all-important opportunities to hook up during coffee breaks and share ideas. Bespoke sculptured towers carry vibrations and noise away from sensitive lab equipment, and ‘interstitial’ spaces between floors will allow maintenance work and lab reconfigurations to be carried out without disruption to the scientists’ work.

On page 18 we bid a fond farewell to the building occupied by the LMB for the last 50 years by taking a tour of the basement room that Professor Brad Amos has worked in for three decades. And look out for a feature on the importance of coffee break culture in science in the Summer edition of Network, published in June.

Cohen and Winter awarded 2013 MRC Millennium Medal

Sir Philip Cohen and Sir Greg Winter were awarded the MRC’s Millennium Medal in February, which recognises MRC scientists for outstanding research which has made a major contribution to wealth creation and the improvement of health and quality of life.

To mark the MRC’s Centenary, two medals were awarded this year at an event hosted by Rt Hon Dr Vince Cable MP in the House of Commons.

As former Director of the MRC Protein Phosphorylation Unit in Dundee, Sir Philip established the Division of Signal Transduction Therapy - a major collaboration between the MRC, the University of Dundee and six of the world’s leading pharmaceutical companies (see feature on page 18).

Based at the MRC Laboratory of Molecular Biology in Cambridge for much of his career, Sir Greg’s work to develop therapeutic monoclonal antibodies has revolutionised healthcare and they are now used in up to a third of all new drug treatments (see feature on page 12).

Sir John Savill commented: “The MRC is proud to award this year’s Millennium Medal to Sir Philip and Sir Greg. It is with great pleasure that I, along with the MRC’s Council, can recognise those that have contributed significantly to the transformation of healthcare and the advancement of the way the research community collaborates and innovates.”

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This Easter you’re invited to take part in an egg-themed online video game which will advance MRC research into the circuitry of the brain. The first of the MRC’s live research projects to celebrate our Centenary, the great egg hunt involves watching footage of nematode worm C. elegans laying eggs. This circuit is controlled by a neurotransmitter called serotonin — the same molecule that affects human brain states that impact mood, appetite, and aggression.

“So if we observe a mutant that lays more or fewer eggs than normal, this is a hint that something has gone wrong in the egg-laying neural circuit or muscles which could have far reaching implications, maybe even teaching us something about genes involved in depression in humans.”

There are thousands of genes without a known function and screening for worms with egg-laying defects is time consuming. Because human vision is still by far the best method for detecting egg-laying, mass public participation can make a genuine and valuable contribution to neuroscience research.

Take part from Thursday 28 March by visiting www.zooniverse.org or www.centenary.mrc.ac.uk

A new scheme, CRACK IT Solutions, has been launched to allow academics to showcase to industry partners their ideas for reducing, refining and replacing the use of animals in research.

CRACK IT Solutions is run by The National Centre for the Replacement, Refinement and Reduction of Animals in Research and its aim is to make connections between academia and industry to speed the translation of new ideas and methods into practice. For more information see the case study below or visit the scheme’s website at www.crackit.org.uk

As part of CRACK IT Solutions, scientists from the University of Manchester have developed technology for mass-producing human heart stem cells called hPS-CM cells, and have made them suitable for use in various standard tests used in industry to screen for drug cardiotoxicity.

The test may offer a clearer and earlier answer as to whether drugs are cardiotoxic than could be gained by testing in mouse, rat or guinea pig heart cells. Furthermore the cells are substantially cheaper to produce than normal commercially-produced hPS-CM cells. The Manchester group is now seeking partners in industry to complete development of the model and test it against their libraries of compounds known to cause heart damage.

See more solutions at www.crackit.org.uk/share/crackitsolutions

**Case study: A better test for heart toxicity**

Many drugs fall at the final hurdle of drug development because, during clinical testing, they turn out to be damaging to the heart (cardiotoxic). Relying on the use of animal models doesn’t always accurately predict the effects drugs will have in people, and drug development dead-ends like these cost the pharmaceutical industry millions of pounds every year.

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Explore Milstein’s healthcare revolution

As part of our Centenary programme we’ve launched an online exhibition about the enormous contributions made to modern healthcare by MRC Laboratory of Molecular Biology (LMB) scientist César Milstein.

Milstien and LMB colleague Georges Köhler won a Nobel Prize for the technique they devised in 1975 for producing unlimited numbers of individual, or monoclonal, antibodies. Through Milstein’s photographs, notebooks and writings, the exhibition explores how this seminal discovery moved from his laboratory to transform the treatment and diagnosis of over 50 major diseases, including cancer and arthritis.

The ability of antibodies to bind specifically to substances is a powerful tool in medical research and it’s used for everything from tissue typing for organ transplants to home pregnancy tests. The research of Milstein, Köhler and LMB scientist Sir Greg Winter, who worked out a way to make mouse antibodies more suitable for medical use, has generated a £55 billion diagnostics and therapeutics industry (see feature on page 12).

Dr Lara Marks of King’s College London, who put together the exhibition for the MRC, explains: “This exhibition highlights the part medical history. It tells the story of how Sir Peter’s war time childhood initially sparked his interest in physics and describes the MRC-funded research which led to the invention of MRI – an imaging technique that has completely transformed our diagnosis of disease. The Long Road to Stockholm

Sir Peter Mansfield, the inventor of magnetic resonance imaging (MRI), has written a new book about his life and Nobel Prize-winning work called The Long Road to Stockholm.

Published by Oxford University Press, the book is part autobiography, part medical history. It tells the story of how Sir Peter’s war time childhood initially sparked his interest in physics and describes the MRC-funded research which led to the invention of MRI – an imaging technique that has completely transformed our diagnosis of disease.

Opening the Gateway to Research

A sophisticated new system which brings together information on all grants funded by the UK research councils has been launched.

The system is being developed as part of the Department for Business, Innovation and Skills’ Innovation and Research Strategy, and the initial live system will be launched at the end of 2013. The website is being updated regularly and can be found at http://gtr.rcuk.ac.uk. Feedback is welcomed, and should be directed to gateway@rcuk.ac.uk.

Celebrating collaboration

MPs and senior figures from bioscience came together at the All-Party Parliamentary Group on Medical Research Annual Dinner in the House of Commons in February, with discussion focusing on the interface between public, charity and industry funding.

The MRC has produced a booklet to accompany the event, containing highlights from Researchfish which show that almost half of all MRC-funded researchers work with charities, and a third do so with the private sector, either through collaboration, joint funding or co-authorship. You can download it from: www.mrc.ac.uk/APPG

Make all research data public

The MRC has joined many other research organisations in signing up to Sense About Science’s All Trials Registered, All Research Reported campaign to make all clinical research – both positive and negative – publicly available. Find out more at www.alltrials.net and read an opinion piece about the issues around the campaign by the James Lind Initiative’s Sir Ian Chalmers on page 22.

Measuring impact

The latest MRC Economic Impact Report was published in January, summarising the outcomes and impacts of MRC-funded research from 2008 to 2012. The information is taken from our research data–gathering system, Researchfish (formerly known as MRC eليف). This has allowed the MRC to track, for example, links with 86 companies which were established or have grown as a result of MRC research, 49 of which were established since 2000, and in total employing around 450 people. You can download a copy at: www.mrc.ac.uk/Publications/EIRF
Meet the mastermind behind monoclonal antibody therapies.

It was an elderly woman with lymphoma who changed things for Greg Winter. It was 1989 and the patient at Addenbrooke’s Hospital in Cambridge was the first person to take Campath-1H, a human antibody that had been fused with parts of a rat antibody to attack cancerous lymphocytes (white blood cells).

Greg was behind the technology that had ‘humanised’ the antibody. At the time, the therapeutic promise of antibodies derived from rodents was hampered because patients’ immune systems would attack the foreign antibodies. Though Greg didn’t know it then, his humanising technology would go on to create one of the most successful classes of drugs ever.

“Remember going to see this sweet lady who was sitting doing her knitting and talking about how she just wanted to hang on a little longer for her husband. She had been at death’s door and had started to recover,” says Greg.

“Remember thinking ‘we’ve done this’. It was a turning point, I’d only really been interested in laboratory research and I realised I had to do something with this technology — I couldn’t just walk off back to the lab.”

**An academic entrepreneur**

Greg’s technologies are involved in around 65 per cent of marketed antibody drugs today, including Humira and Humira, and antibody therapeutics had a global market valued at £25 billion in 2010. But while his science has gone on to be applied on an extraordinary scale, Greg sees himself foremost as an academic.

With a background in protein structure research, Greg had been working on the engineering of enzymes and was now interested in building new proteins. But Greg Melino, who along with Georges Kohler had discovered a way to make rodent antibodies to attack cells and proteins involved in disease, had become Head of the LMB’s Division of Protein and Nucleic Acid Chemistry and was keen for Greg to switch focus to antibodies.

Greg wondered if he could engineer entirely new proteins using an antibody scaffold. He saw that all antibodies have the same basic structure — a common scaffold onto which are attached different protein ‘loops’ that make them attack a specific structure. Perhaps he could transpose loops from one antibody to another, and thereby transfer this specificity?

Greg took the loops from a mouse antibody with a known target and transplanted them into a different antibody of known 3D structure. ‘This kind of transfer required significant resources so, in 1989, Greg set up Cambridge Antibody Technology (CAT).’

**Spinning out**

Researchers at CAT soon established a technique for creating human antibodies in bacteria. Greg says: “Not many people really believed in antibody therapeutics — we almost ran out of money in the early 1990s. But by the mid-1990s antibody drugs were appearing on the market and things picked up.”

Greg stepped back from CAT in the mid-1990s but that didn’t stop him from co-founding Domantis in 2000, another company aiming to make drugs based on the smallest functional unit of antibodies. And in 2009, he established Bicycle Therapeutics, another spin out aiming to develop a new class of drug that behave as mni-antibodies.

CAT was sold in 2006 to AstraZeneca for £700 million and Domantis went to GlaxoSmithKline in 2000 for £230 million. The MRC has received around £190 million in income from Greg’s intellectual property.

**A fundamental question**

For Greg, lab-based discovery science is key to finding solutions to medical problems — even if the researchers don’t know it at the time.

“Sometimes it’s better to do basic research and be opportunistic. I stumbled across humanising antibodies — I was interested in something else and then realised there was a more practical dimension to it. That’s often the beauty of fundamental research.”

Excited to learn more?

**Meet the mastermind behind monoclonal antibody therapies.**

Sir Greg Winter is the co-winner of this year’s MRC Millennium Medal. Katherine Nightingale went to meet the mastermind behind monoclonal antibody therapies.
The tiny molecular reaction fuelling an economic giant

Professor Sir Philip Cohen was also awarded the MRC Millennium Medal in February to mark the enormous benefits - both to human health and the UK economy - of his pioneering work on protein phosphorylation.

Hazel Lambert visited Philip at the MRC unit he established in Dundee to find out more.

Protein phosphorylation is a reaction we can’t see, feel or hear that happens countless times in every cell of every tissue in the human body. It influences health on both a cellular and body-wide level, so it’s a crucial target for development of new therapies for common conditions like high blood pressure, diabetes and cancer.

Phosphorylation simply means addition of a phosphate molecule to a protein. This reaction helps to control the millions of proteins that pop up and down repeatedly throughout the cell. Phosphorylation can switch a protein’s function on or off, so it is interrupted in some way the proteins and cells can become a little unruly. This can in turn lead to disease. For example, a cell that can no longer follow instructions to self-destruct may grow uncontrollably into a tumour.

Three agents are involved in protein phosphorylation: a protein, a phosphate and an enzyme that enables the reaction called a protein kinase. The enzyme is either added to or removed from the protein by the kinase. Changing the shape of the protein allows it to fulfil its role in the cell. In this way, phosphates regulate the activity of cellular proteins.

At the heart of the reaction

At the MRC Protein Phosphorylation Unit (PPU) in Dundee, researchers study the impact of phosphorylation, the steps that lead towards it, the blocks that hinder it and the effect when it goes wrong. Here, lab shelves strewn with blue-lidded bottles and foil-capped tubes sit alongside powerful protein sequencing facilities that attract researchers from all over the world. Together these scientists form a multi-lingual team fluent in the complexities of molecular biology and united in their goal to unpick the links between the phosphorylation process and disease.

The unit was established in 1990 by Philip, whose vision also created the award-winning industry partnership, the Division of Signal Transduction Therapy (DSTT) in 1998 and the Scottish Institute for Cell Signalling (SCILLS) in 2008.

Towards new medicines

Understanding how, where and why protein phosphorylation works is important now and for the future development of new medicines. The DSTT collaboration is a unique and effective partnership that has this aim at its core. It allows academic researchers to collaborate with leading pharmaceutical companies to maximise translation of basic research into therapies for patients. They are working together to accelerate the development of improved drugs to treat global diseases like cancer, rheumatoid arthritis and Parkinson’s disease. These new drugs work by targeting other protein kinases or parts of a similar system based on a protein called ubiquitin.

Ubiquitin regulates how and when other proteins are recycled. It also works as a tag to direct proteins around a cell and so keep it running healthily. Scientists at both PPU and in the DSTT are keen to better understand the role of the ubiquitin system in health and in disease.

Links with industry

The DSTT is reputedly the world’s largest collaboration between the academic community and the pharmaceutical industry. The consortium is made up of six leading pharmaceutical companies: AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Janssen Pharmaceutica NV, Merck Serono and Pfizer, and fifteen research teams based at the University of Dundee. Thirteen of the teams are based within the MRC PPU and SCILLS. Together, consortium scientists tackle early-stage research in multiple areas, including cancer, arthritis, lupus, hypertension and Parkinson’s disease.

In total, the DSTT has attracted £50m funding from the pharmaceutical industry. The partnership was renewed for the third time in July 2012 with a commitment of £74 million over four years, securing 50 jobs in Dundee until 2016 in the process.

At the time, Philip commented: “Collaborations between academia, laboratories and the pharmaceutical industry typically last a few years. Therefore to maintain and expand support for the DSTT from 1998 until at least 2016 is unprecedented and remarkable. It shows how valuable the collaboration has been for the pharmaceutical industry.”

The PPU’s success has not gone un-noticed by the Minister for Universities and Science, David Willetts, who said: “Collaboration between the life sciences industry and academia is vital for the development of new treatments and leverages significant private funding into our research base. This investment will continue the excellent work taking place at the University of Dundee on major global diseases, helping to bring benefits for patients and the economy.”

Future directions

Professor Cohen stepped down as PPU Director in 2012 and was replaced by Professor Dario Alessi, who also now leads the DSTT. Professor Alessi predicts there will be a new wave of effort to seek therapies based on the phosphorylation and ubiquitin pathways for conditions other than cancer.

He said: “This year is exciting because it’s expected to be the year that the first non-cancer application of a kinase-based drug is likely to be launched for treatment of immune disease. I think this will create a new burst of effort to generate drug discovery in diseases beyond cancer: the area that has been most productive up to now.”

“Protein phosphorylation is at the heart of virtually all chronic disorders. But side effects are less likely to be tolerated in conditions other than cancer because the treatment is long term. Our knowledge is now catching up and therapies that inhibit kinases and that have fewer side effects are within reach so we are hoping to develop ways to use them.”

Phosphorylation simply means addition of a phosphate molecule to a protein. This reaction helps to control the millions of proteins that pop up and down repeatedly throughout the cell.
LATEST DISCOVERIES

Early HIV treatment delays need for long-term therapy

A 48-week course of antiretroviral therapy (ART) taken in the early stages of HIV infection slows damage to the immune system and delays the need for long-term treatment, research coordinated by the MRC Clinical Trials Unit suggests.

The five-year SPARTAC trial involved 366 adults across eight countries, whose HIV had been diagnosed within six months of becoming infected. They either received no medication - the standard practice for early-stage infection - or ART.

It took on average of 222 weeks for those who received the early treatment to need to start long-term treatment - a delay of 65 weeks compared with those who had received no medication. These patients also had higher CD4 T cell counts, potentially protecting them from secondary infections, and lower levels of HIV in the blood for over a year after stopping the early treatment.

As well as showing that early ART has immune system benefits for patients, Professor Jonathan Weber, the chief study investigator, said as well as showing that early ART has immune system benefits for patients, Professor Jonathan Weber, the chief study investigator, said:

"When a person first contracts HIV, they are at their most infectious. But they are also often unaware that they have contracted the disease and hence are more likely to spread the infection. The sooner they can be diagnosed, the better our chances of limiting the spread of the virus."

SPARTAC was funded by the Wellcome Trust and coordinated by researchers from Imperial College London and the MRC Clinical Trials Unit, with immunology research conducted by the University of Oxford.


Bacteria’s stem cell Trojan horse

Leprosy bacteria have the amazing ability to hide inside cells of the nervous system and reprogram them to take on the properties of stem cells, researchers at the MRC Centre for Regenerative Medicine at the University of Edinburgh have discovered.

The scientists found that leprosy bacteria in mice were able to protect themselves from the immune system by hiding inside nervous system support cells, called Schwann cells. Once infection had taken hold, the bacteria were able to convert the Schwann cells to become stem cell-like and able to differentiate into any type of cell for example muscle cells. This enabled the bacteria to spread to other tissues in the body without detection by the immune system.

The finding increases our understanding of how leprosy spreads inside the body and could also help scientists improve the safety and use of lab-produced stem cells, pointing the way to new treatments to repair and replace damaged tissues.

Lead scientist Professor Anura Rambukkana said: “This is the first time that we have seen that functional adult tissue cells in mice can be reprogrammed into stem cells by natural bacterial infection, which also does not carry the risk of creating tumourous cells.

Potentially you could use the bacteria to change the flexibility of cells, turning them into stem cells. Then you could use standard antibiotics to kill the bacteria completely so that the cells could then be transplanted safely to tissue that has been damaged by degenerative disease.”

Published online at www.cell.com, January 2013

Flu susceptibility gene discovered in Chinese populations

Research partly funded by the MRC suggests that Chinese people are more vulnerable to the H1N1 Swine flu form of flu because of a genetic variant which is more common in Chinese populations. The finding could help identify those at high risk of severe infection and prioritise them for treatment.

Researchers at the MRC Human Immunology Unit at Oxford University and Beijing Capital Medical University showed that inheriting the variant, called rs15252-C, increases a person’s chance of getting severe infection by six times.

The variant is found in around one in 3,000 people in Caucasian populations and was already known to be associated with more severe influenza. It is 100 times more common in Han Chinese, the predominant ethnic group in China, and the study results showed that it was present in 69 per cent of Chinese patients who had severe pandemic H1N1 influenza in 2009. The finding could help to explain why new influenza viruses often appear in China and South East Asia.

The MRC Human Immunology Unit’s Dr Tao Dong, who led the research, commented: “Understanding why some people may be more affected than others is crucial in improving our ability to manage flu epidemics and to prevent people dying from the virus. It’s vital that we continue to fund research that examines flu infection, from the smallest details of our genetic code and in the populations around the world that continue to be vulnerable to infection.”

Published online at www.nature.com/ncomms, 29 January 2013

A new way to prevent early birthdays?

MRC funded scientists have found that inflammation in the womb can switch off key genes which stop a woman from going into labour, pointing the way to the development of new treatments for preventing premature birth.

During a normal term pregnancy, the womb remains in a relatively inactive state - under the control of genes which prevent contractions - until the baby is ready to be born. In womb tissue taken from pregnant women, the research team studied the effects of a substance called tumour necrosis factor (TNF), which causes the inflammation associated with normal labour.

They discovered that inflammation was able to switch off the genes needed to keep the womb inactive and re-start contractions, even after it had been treated with a group of experimental drugs which maintain activity of the genes, called histone deacetylase inhibitors.

Lead researcher Dr Neil Chapman from the University of Sheffield Medical School explains: “While this experimental drug can stop the womb contracting, it cannot stop the inflammation associated with normal labour from switching off the genes needed to ensure the uterus does not start to contract too early. This means histone deacetylase inhibitors may not be a suitable medication to give a pregnant woman when her labour starts prematurely.”

The finding highlights a potential new role for TNF, although the scientists say more work is needed to work out how it reduces relaxation of the uterus.

Published online at www.bjc.org, January 2013
The complex and destructive nature of war has been a catalyst for some of the MRC’s greatest medical discoveries over the past century. Sarah Harrop reports.

From penicillin to ‘Iraqibacter’

Today, multi-drug resistant bacteria are one of the greatest challenges faced by the medical community. At the University of Birmingham, Professor Mark Pallen has been carrying out MRC-funded research on a type of multi-drug resistant Acinetobacter bacterial infection, which is usually found in hospitals. Military patients returning from the Middle East are particularly susceptible to the bacterium, so much so that it used to be nicknamed ‘Iraqibacter’.

“Patients who are critically ill are given lots of antibiotics, which degrades their natural balance of bacteria in the body. Acinetobacter gets into wounds and takes up a vacant niche,” Mark explains.

In 2008, Mark and colleagues published a study which proved that a particularly virulent outbreak had jumped from a military patient returning from Afghanistan to a civilian patient in an adjacent bed. The MRC has funded him to carry out more detailed work on whole genome-sequencing of Acinetobacter samples to look for tiny genetic variations – known as single nucleotide polymorphisms – that distinguish different bacterial isolates, and then use this information to piece together how the infection was transmitted from person to person, providing new insights into how multi-drug resistant infections can spread in hospitals.

Insights into trauma

The use of explosive shells for the first time on the frontline meant that surgeons began to see cases of traumatic shock – the body’s reaction to severe injury involving loss of blood. MRC researchers discovered that shattered tissues produce substances which hamper blood circulation, so they devised a blood substitute, gum acacia (derived from acacia tree sap) to restore lost blood volume. Blood transfusion was difficult to preserve and transport, so this invention helped save many lives.

Nearly a century later, Professor Janet Lord, a principal investigator at the MRC Centre for Immune Regulation in Birmingham, is also working to save the lives of those injured in conflicts. She’s studying the inflammatory response in severely injured soldiers sent home from Afghanistan, and using the findings to advance treatment of burns and trauma in the civilian population.

“When you’re exposed to acute trauma – for example burns, blasts or multiple amputations – there’s an immediate inflammation response, but also an anti-inflammation response,” she explains. “Inflammation is useful because it protects against infections and stimulates wound-healing. But if it doesn’t get turned off at the right time by the anti-inflammatory response, you can’t heal properly. We’re trying to understand what controls that yin and yang balance, and what dictates whether or not a patient makes a good recovery.”

She adds: “How well you recover from a burn is age-related: the older you are the less likely you are to recover. We think that’s to do with immune system changes that occur with age, in particular having fewer cells which promote inflammation and reduced functioning of cells that fight infections such as neutrophils and natural killer (NK) cells.

So we’re taking measurements from young patients flown in from Afghanistan and comparing them with elderly burns and trauma patients. It may be that if we can restore the pro- and anti-inflammatory balance and improve function of these cells we can improve patient outcomes.”

The great war: infections and ingenuity

When the First World War broke out in 1914, the MRC was barely a year old, but it reacted quickly to focus research on the national war effort. Gangrene, caused by bacteria which thrive in oxygen-free conditions such as soil, was a particular problem for men fighting in the muddy trenches of France and Belgium during WW1. This horrifying condition causes living tissue to decay and die and was responsible for many limb amputations and deaths in soldiers whose wounds had become infected. But by the eve of Armistice Day in 1918, MRC researchers had managed to work out a cheap way to produce large quantities of an antiseptic from sea water. ‘Dakin’s Solution’ reduced secondary infections in repatriated soldiers to almost zero.

Desperate times also fuelled ingenuity. Ships bringing home the wounded had poor sanitary conditions, but antiseptics were in short supply. With MRC funding, British chemist Dr Henry Drysdale Dakin managed to work out a cheap way to mass-produce the drug. By the time of the Normandy landings in 1944, penicillin was readily available to all servicemen who needed it. With MRC funding, British chemist Dr Henry Drysdale Dakin managed to work out a cheap way to mass-produce the drug. By the time of the Normandy landings in 1944, penicillin was readily available to all servicemen who needed it.

Development of penicillin

Penicillin - the first broad-spectrum antibiotic - was discovered by chance in 1928 when Penicillum mould contaminated his culture dishes and killed the bacteria growing there. But it wasn’t until 1940 that MRC-funded scientists Lord Howard Florey and Sir Ernst Chain managed to work out a way to scale up production of the compound to make it a viable antibiotic drug.

Realising the urgent need for penicillin to treat infections in wounded soldiers during the Second World War (WW2), the pair turned their department at Oxford University into a penicillin factory and carried out clinical trials at the city’s Radcliffe Infirmary. The results helped persuade drug manufacturers in the US to mass-produce the drug. By the time the Normandy landings in 1944, penicillin was readily available to all servicemen who needed it.

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Health and rationing

Maintaining the health both of soldiers and those supporting them with the war effort was of critical importance during WW2, and the MRC was called upon to make recommendations to the War Cabinet about nutrition that directly influenced the UK’s food policy. In 1937, MRC scientists Dr Elsie Widdowson and Dr Robert McCance bravely experimented on themselves to test out the efficacy of proposed ration diets in the event of another world war. Over three months, they pushed their bodies to the limit, for example by climbing fells in the Lake District, to test the physical impact on their health of limited food supplies. Both were fit and well at the end of the fells in the Lake District, to test the physical impact on their health of limited food supplies. Both were fit and well at the end of the experiment and the results were secretly passed to the War Cabinet, which was reassured that rationing in the general population would be safe.

The pair went on to make many lasting contributions to nutrition research; their book on the constituents of commonly eaten foods is now a key part of many IVF programmes. The research discovered – in the early 1960s – how to store biological material at low temperature, pioneering techniques for the freezing of sperm, eggs and embryos which are still in use today. It also led to the development of the UK’s first test for screening pregnant women to find out whether they carry genes which cause inherited diseases such as cystic fibrosis and muscular dystrophy.

In 1946 study of the impact of poor wartime diet on those in Nazi-occupied territories, and carried out MRC-funded self-experimentation to test the safety of food rationing ahead of the outbreak of WW2. A huge body of influential nutrition research followed, including the important work of Elsie Widdowson at the University of Oxford.

Futuristic findings: tissue regeneration and artificial vision

War continues to shape and inform medical research, particularly in the fields of surgery and regenerative medicine. For those whose sight could still be saved by surgery, it is critical to intervene before the process of scarring begins, explains Rob: “Scarring is an absolute disaster for eye surgery because it changes the shape of the tissue. But if you can get something to regenerate instead, you don’t get scarring.”

Working with molecular neuroscientist Professor Ann Logan from the University of Birmingham, Rob and his research team are carrying out research on a substance derived from amniotic membranes expelled by women during childbirth which has anti-inflammatory and anti-scarring properties. They’re using the substance to encourage damaged optic nerve and retina tissue to regenerate into new tissue rather than forming scar tissue.

“I now supervise an MRC-funded PhD student who has found some of the main pathways that will allow the regeneration of damaged optic nerves. We’ve discovered a very simple way of ‘tricking’ cells into growing by reprogramming how their DNA is expressed to make it promote certain pathways. So actually by stimulating the regeneration of the nerves it prevents scarring. If we can get it to work in people, that would be a holy grail – we could make blind people see again.”

War is, unfortunately, always likely to be a part of human existence, but medicine will continue to learn lessons from it to benefit health, as it has throughout the bloody conflicts of the last 100 years.

Professor Lord, Professor Pallen and Wing Commander Scott are all part of the NHR Surgical Reconstruction and Microbiology Research Centre in Birmingham. The centre was called upon to make recommendations to the War Cabinet about the constituents of commonly eaten foods is now a key part of many IVF programmes. The research discovered – in the early 1960s – how to store biological material at low temperature, pioneering techniques for the freezing of sperm, eggs and embryos which are still in use today. It also led to the development of the UK’s first test for screening pregnant women to find out whether they carry genes which cause inherited diseases such as cystic fibrosis and muscular dystrophy.

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War continues to shape and inform medical research, particularly in the fields of surgery and regenerative medicine. For those whose sight could still be saved by surgery, it is critical to intervene before the process of scarring begins, explains Rob: “Scarring is an absolute disaster for eye surgery because it changes the shape of the tissue. But if you can get something to regenerate instead, you don’t get scarring.”

Working with molecular neuroscientist Professor Ann Logan from the University of Birmingham, Rob and his research team are carrying out research on a substance derived from amniotic membranes expelled by women during childbirth which has anti-inflammatory and anti-scarring properties. They’re using the substance to encourage damaged optic nerve and retina tissue to regenerate into new tissue rather than forming scar tissue.

“I now supervise an MRC-funded PhD student who has found some of the main pathways that will allow the regeneration of damaged optic nerves. We’ve discovered a very simple way of ‘tricking’ cells into growing by reprogramming how their DNA is expressed to make it promote certain pathways. So actually by stimulating the regeneration of the nerves it prevents scarring. If we can get it to work in people, that would be a holy grail – we could make blind people see again.”

War is, unfortunately, always likely to be a part of human existence, but medicine will continue to learn lessons from it to benefit health, as it has throughout the bloody conflicts of the last 100 years.

Professor Lord, Professor Pallen and Wing Commander Scott are all part of the NHR Surgical Reconstruction and Microbiology Research Centre in Birmingham.

Audrey Smith: discovery of cryobiology

Known as the ‘mother of cryobiology’, Audrey Smith of the MRC National Institute for Medical Research discovered, in the early 1960s, how to store biological material at low temperature, pioneering techniques for the freezing of sperm, blood, bone marrow, organs and many other tissues. Freezing of sperm, eggs and embryos is now a key part of many IVF programmes.

Elsie Widdowson: nutrition expert

Elsie Widdowson became highly respected for her 1946 study of the impact of poor wartime diet on those in Nazi-occupied territories, and carried out MRC-funded self-experimentation to test the safety of food rationing ahead of the outbreak of WW2. A huge body of influential nutrition research followed, including the important work of Elsie Widdowson at the University of Oxford.

Mary Lyon: discovery of X-inactivation

While studying the effects of radiation on DNA in the early 1960s, Dr Mary Lyon discovered that one of two copies of the X-chromosome in women can be inactivated. This explained the absence of symptoms in female carriers of inherited diseases associated with this chromosome such as Duchenne Muscular Dystrophy and colour blindness, which affect mainly men. The MRC’s world-renowned centre for mouse genetics at Harwell was named the Mary Lyon Centre in recognition of her important contributions to research in mammalian genetics.

Kay Davies: fighting muscular dystrophy

In the 1980s Dame Professor Kay Davies developed the first test for screening pregnant women to find out whether their baby was at risk of having the inherited muscle wasting disease Duchenne Muscular Dystrophy (DMD). In 1989 she made a further breakthrough when she discovered the gene which codes for utrophin, a molecule which is missing in DMD patients and which points the way to treatments for the disease. Pharmaceutical company trials of new drugs based around this discovery are underway. Kay is Director of the MRC Functional Genomics Unit in Oxford.

Uta Frith: changing the face of autism

Professor Uta Frith is a developmental psychologist who is best known for her research on autism spectrum disorders. In 1989 she published a handbook called Autism explaining the enigma, which is now used by psychiatrists worldwide. Her work on theory of mind in autism proposed the idea that people with autism have specific difficulties understanding other people’s beliefs and desires—the subject of a seminal paper published with Professor Simon Baron-Cohen. She is also well regarded for her body of work on Asperger’s syndrome and dyslexia.
MY WORK SPACE

Professor Brad Amos has spent much of his career designing and developing microscopes that are now used in laboratories across the world. He showed Sarah Harrop around the basement room he has worked in at the MRC Laboratory of Molecular Biology (LMB) for the past three decades.

Flea engraving
Two years ago I got to exhibit my new Mesolens* at the Royal Society Summer Exhibition. It was the society’s 350th anniversary and the engraving is from their first publication Robert Hooke’s Micrographia (1665), the first textbook of microscopy. I displayed Hooke’s engraving on one side and took an image of a real flea with the Mesolens on the other, and visitors could navigate within the enormously detailed image with the new lens. I enjoy public engagement immensely, especially talking to the seven-year-olds. The youngsters are just so excited. You say “what do you think fluorescence means?” and they’ll say “Oh, it’s fantastic and I’ve got a toy and it glows in the dark and I’ve got a pair of fluorescent socks!”

Malaysian beetles
The light reflected from these beetles is very interesting, optically. I bought them on a teaching trip to Malaysia. They’ve got a helical structure in their cuticle so they reflect left-handed circularly polarised light but not right-handed. So if you look at them through a circular polariser, the beetle looks black, but its reflection in a mirror is green or blue. The liquid crystal display on your computer screen uses the same kind of helical crystal optics.

Crystal
Having made the Mesolens*, I need to make some extra optics for it, and I intend to make some very large prisms out of this. I bought a gem faceting machine because I wanted to make demonstration specimens for my optics teaching, but of course I found that I could also cut gems with it and please the ladies. Last year I found a pale blue sapphire in New South Wales, which will make a nice little group of stones.

Jars and bottles
These are my stains for making microscope specimens. This corner looks like a kind of Chinese apothecary’s Aladdin’s cave. I’ve got a jar of sea cucumbers that I bought from a Chinese supermarket. The little calcareous spicules they have in their skin look like circular waffles under the microscope. I was originally trained as a zoologist and that training has proved highly useful when we started to develop the confocal microscope in 1985. I’ve been very lucky that everything in my training – and even some physical objects – have been used and continue to be used.

Flea engraving

Papier mâché head
We have a big tradition in the LMB, going back to the days of the Cavendish Laboratory, of elaborate and dramatic entertainments at Christmas. I made the head for a fight scene. At the end of the fight, one combatant’s head was ‘cut off’ and she fell on stage and the winner lifted this head up. The entire audience went “aaargh!” because it’s a reasonable likeness.

Gnat sketch
That’s something I did when I was 14 or 15 because I was already a bit of a microscope nerd at that age. I had an old brass microscope and that was one of the first things I looked at and drew.

Old scientific equipment
This scientific bric-a-brac will soon vanish. I’m constantly going back and forth to the University of Strathclyde where I work part-time with Professor Gail McConnell, who is developing the next phase of the Mesolens. I was afraid that when I retired, two years ago, a sell-by date would appear on my forehead. But Gail has inspired me to work harder than ever before and I hope to die with my boots on! We’ve obtained stunning half-gigabyte images of mouse embryos in which every cell is recorded in detail, which has provoked world-wide interest.

Model
We have to have a room full of solid models like this here at the LMB, but most of them were thrown away about 10 years ago because these days people build virtual models on computers. I retrieved this, which is a collagen molecule, because I couldn’t bear to see a bit of history go into the skip. It was probably made in the mid-1960s. Watson and Crick may well have worked on it.

Crystal

*With funding from the MRC Next Generation Optical Microscopy call, Brad is developing the Mesolens, a sophisticated system which allows us to see a whole organism and then zoom in to see an incredible level of detail. See page 21 for more information.

Jars and bottles

Gnat sketch

Papier mâché head

Model

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Crystal
Boost for birth defect research resource

The MRC and Wellcome Trust have renewed funding for a unique research resource which collects and distributes human embryonic and fetal material to allow scientists to study human development.

Adhering to rigorous ethical and regulatory requirements, the Human Development Biology Resource (HDBR) is a tissue bank that collects donated fetal material from pregnancies which have been terminated, including pregnancies ended because of birth defects.

Most birth defects happen when an embryo inherits a fault in one or more essential genes, or when those genes are damaged by an environmental factor in pregnancy. Examples include spina bifida, heart defects and facial clefts - all of which pose serious medical problems for the child and family.

Using HDBR material, scientists are learning how critical genes and molecular signalling pathways inside cells contribute to human embryonic development and how faults in these genes may lead to birth defects. In the long term this will help develop new preventive measures that can be offered to pregnant women, for example gene therapy, stem cell transplants vital or providing nutrients like folic acid which are needed for healthy development.

The HDBR is one of a handful of tissue banks in the world which provide high quality material from embryos and early fetuses, an in-house gene expression service and a web-based resource of human gene expression data mapped onto 3D models.

The renewed funding will allow it to offer a wider range of material for research and form links with other initiatives worldwide with similar aims.

For the latest information on MRC funding opportunities, visit www.mrc.ac.uk/fundingopportunities

Case study: Ready for your close-up?

The Mesolens is a microscope being developed by the MRC Laboratory of Molecular Biology’s Brad Amos, who invented the laser-scanning confocal microscope, in collaboration with Professor Gail McConnell at the University of Strathclyde.

The Mesolens can capture the same level of detail as a confocal microscope, but on a much bigger scale.
Make all research results public

All trials registered, all results reported: a new campaign which the MRC is supporting alongside other research organisations, calls for the results of all clinical trials to be made public. Sir Iain Chalmers, Coordinator of the James Lind Initiative, says that longstanding biased under-reporting of clinical research must stop.

Successful conduct of clinical trials depends on many factors, but these studies are impossible unless patients agree to participate in them. For many patients the principal motivation for participating in clinical trials is the hope that they may receive better care, and perhaps more effective treatment. All participants in clinical trials, however, believe that their involvement will help to increase knowledge about the effects of treatments. They expect that people with health problems like theirs – and perhaps they themselves – will be able to make better informed treatment decisions in future as a result of their contributions to knowledge.

How come, then, that the research community, including research funders and regulators, have acquiesced for decades in the non-publication of around 50 per cent of all clinical trials? Can this be characterised as anything other than a gross betrayal of the trust in researchers to patients from exaggerated estimates of treatment benefits and, after years of having and disastrous excuses for inaction, it must be confronted and dealt with. Following on its influential campaign to reform the English legal laws that were being used to silence scientists, Sense about Science’s new campaign – All trials registered, all trials reported - aims to achieve just what its title calls for. Sense about Science has invited those who agree with these principles to join the tens of thousands of others who have already signed the petition.

To its great credit, the MRC was the first organisation to do so, with many years of being involved in the problem. The MRC, the MRC, is pleased to sign up to this campaign and has, as noted in the first place to which the MRC has been sign up to this campaign and has, for many years, strongly supported the position that clinical trial results must be published in a timely manner. At the end of 2012, we made both the requirement to publish, and the need for MRC-funded researchers to share data, even more explicit: “Results of MRC-funded clinical studies (whether positive or negative) must be published within a reasonable period (generally within a year of completion) following the conclusion of the study.”

As the MRC admits, it would be surprising if, in its one hundred year history, there were no unreported or unpublished skeletons in its cupboards. While monitoring future adherence to its policy, therefore, the MRC should audit the trials it has funded. An audit of the MRC-funded clinical trial publication record of studies funded by the Health Technology Assessment Programme has shown that 98 per cent of them have been reported. A similar finding from an audit of trials funded by the MRC would be very reassuring.

If action is not taken urgently by research funders and regulators, information on what was done and what was found in trials could be lost forever, leading to bad treatment decisions, unnecessary repetition of trials, and missed opportunities for good medical practice. To find out more and sign the petition, visit the AllTrials Registered. All Results Reported campaign web page at: www.alltrials.net
