Millennium Medal winner Professor Janet Darbyshire’s life-changing research

Dementias: why don’t we have any treatments yet?

Network can also be downloaded as a PDF at: mrc.ukri.org/network
April sees the term of Sir John Savill come to an end and the arrival of Professor Fiona Watt FRS as the new Executive Chair of the MRC, coinciding with the MRC becoming part of UK Research and Innovation (UKRI).

Fiona is also Director of the Centre for Stem Cells and Regenerative Medicine at King’s College London where she leads a team of 80 academic researchers. Internationally recognised in her field, she has expertise in the stem cells of healthy and diseased skin.

Before founding the Centre for Stem Cells and Regenerative Medicine, she helped to establish the CRUK Cambridge Research Institute and the Wellcome Trust Centre for Stem Cell Research.

Commenting on her appointment, Fiona said: “I am very excited at the prospect of helping to shape the UK biomedical research landscape at this time of extraordinary transition. The widespread recognition that academic research has an important role to play in the UK economy, a real increase in the research budget, and the opportunity for collaborative working across the different research councils offer remarkable opportunities for the MRC to pursue its mission of improving the health of people in the UK and around the world.”

To find out more about UK Research and Innovation visit: ukri.org
Medical research has a bright future

I recently completed an eventful seven and a half years as CEO of the MRC. Thanks to wonderful support from across the MRC’s extended family, much has been achieved for medical research.

Firstly, the formation of Health Data Research UK with eight other funders will enable us to undertake discovery science in humans by linking longitudinal NHS data from 65 million citizens with biomarker investigations at scale, unravelling human biology and disease mechanisms.

Secondly, the MRC has never been better articulated with industry, with the promise of speedier translation of research into patient benefit and even more impactful contributions to both the health and wealth of the UK.

Thirdly, the MRC has played a key role in re-shaping the UK ecosystem for health research and innovation to promote partnership and added value. To the formation of the Francis Crick Institute and 23 University Unit partnerships, we can add the UK Dementia Research Institute, the UK Prevention Research Partnership, the Biomedical Catalyst and many other successful new collaborations at home and overseas.

Lastly, much that we hold dear has continued to attract MRC investment – studentships, fellowships, investigator-led research grants, Nobel Prize-winning institutes, cohorts such as UK Biobank and international initiatives such as the European Molecular Biology Laboratory and the European and Developing Countries Clinical Trials Partnership. Furthermore, the MRC has responded rapidly to crises such as Ebola, Zika and antimicrobial resistance.

I have learnt much, not least that – thanks to the people who support us, especially the UK taxpayer and successive governments – the MRC continues to be seen internationally as a world-leading organisation. I look forward to my successor Professor Fiona Watt FRS guiding the MRC into the exciting interdisciplinary environment of UK Research and Innovation as our first Executive Chair. The future is bright and MRC research will continue to change lives for the better.

Sir John Savill
MRC Chief Executive, October 2010 to March 2018
A family of compounds identified in the 1940s, called actinorhodins, were originally found to have only weak antibiotic properties.

But a team from the University of Leeds has shown that one of these compounds, γ-ACT, has strong antimicrobial activity against two types of ESKAPE bacteria. These bacteria are notoriously hard to kill due to their ‘escape’ tactics against existing drugs.

Lead researcher Dr Alex O’Neill said: “The weak activity previously published for the ACT family as a whole probably explains why this group was not further evaluated, and it is intriguing to think that other potentially useful antibiotic groups are languishing in obscurity in academic journals just needing expert review using modern processes and equipment.”

Each year, the MRC spends approximately £6.5m on AMR-related research. The biggest challenge is to develop new antibiotics to fight the growing numbers of bacteria resistant to our current arsenal of drugs.

Read more: mrc.io/antibiotics-future
Millennium Medal 2017 awarded

Congratulations to Professor Janet Darbyshire, awarded the 2017 MRC Millennium Medal for making major contributions towards the MRC’s mission to improve human health through world-leading medical research.

The Millennium Medal is the MRC’s most prestigious award and is presented every two years to recognise outstanding scientists.

As a researcher focused on clinical trials and epidemiology, Janet’s studies into tuberculosis and HIV have led to improvements in prevention and treatment worldwide.

On presenting Janet’s medal, the minister with responsibility for life sciences and industrial strategy, Rt Hon Lord Henley, said: “I was thrilled to present the Millennium Medal to Professor Janet Darbyshire, the first female recipient of this award and an inspiration to female scientists around the world. Her work has had a truly global impact and her research has been vitally important to the UK scientific community.”

Janet continues to contribute to the development of clinical trials, both in the UK and in Africa.

Read the full article: mrc.io/millennium-medal-2017

Turn to page 8 to read more about Janet’s working life.

Medical research in the spotlight

As part of the Millennium Medal award celebrations, 17 MRC-funded scientists from all stages of their careers showcased their research at an exhibition in Parliament.

50 parliamentarians and policymakers attended the event, to learn about cutting-edge research in key areas of science.

The exhibition demonstrated the importance of medical research to human health, wellbeing, innovation and economic growth, and how the MRC is driving this research forward.

Researchers shared their experiences about where they started, what they’ve achieved, and how MRC support has helped with this journey. Norman Lamb MP, Chair of the House of Commons Science and Technology Committee, spoke of the showcase as a “very excellent presentation of MRC work”.

Makis Tsioras, PhD student at the UK Dementia Research Institute (UK DRI) at the University of Edinburgh, talked to MPs about why his research is important: “Alzheimer’s disease is affecting over 45 million people worldwide and it is posing a massive socioeconomic and financial issue. We’re making very big steps by being part of the UK Dementia Research Institute which allows collaborative working.”

After talking with researchers at the event, MP Daniel Zeichner commented: “It’s important to fund research because if we’re going to get breakthroughs in the future to tackle some of the challenges we know are out there, it’s only going to be done through a properly resourced research base.”

To hear about the research of more MRC scientists visit our Youtube channel: mrc.io/research-showcase
Obituary: John Sulston (1942-2018)

Sir John Sulston, Nobel Laureate and pioneering scientist on techniques for mapping of genomes, died on Tuesday 6 March after a short illness.

Instrumental in determining the first genome of an animal, the nematode worm *C. elegans*, John led the UK team of the International Human Genome Project. He was a much admired and influential researcher at the MRC Laboratory of Molecular Medicine (LMB) and beyond.

John studied Natural Sciences at the University of Cambridge and completed a PhD on the chemical synthesis of DNA. After postdoc research at the Salk Institute, California, he joined Sydney Brenner’s group at the LMB in 1969. In Sydney’s group, John began his meticulous studies into the biology and genetics of the nematode worm, for which he would win the Nobel Prize for Physiology or Medicine in 2002, jointly with Sydney and Bob Horvitz.

With its short lifespan, transparent body and just 959 cells, the worm was the ideal specimen. John developed a way of studying every cell division in the nematode worm and mapped out the cell death process; disrupted cell death is at the root of many cancers. With colleagues, he determined the worm’s full DNA sequence, published in 1998.

John set up and directed the Wellcome Trust Sanger Centre (later Institute) in Cambridge from 1992 to 2000. There, he led the UK component of the International Human Genome Project which completed the first draft of the human genome in 2000. Making this material publicly accessible was essential to maximise the use of the data worldwide and John became a passionate defender of publicly accessible science.

Knighted in 2001, he was made a Companion of Honour in June 2017. He was a Fellow of the Royal Society, a member of the European Molecular Biology Organisation and won the Royal Society Darwin Medal.

Read more about his work on our MRC Insight blog: mrc.io/worm-cell-drawings
New director for the MRC Laboratory of Molecular Biology

Dr Jan Löwe is the new Director of the MRC Laboratory of Molecular Biology (LMB), having taken over from Professor Sir Hugh Pelham on 1 April 2018. As Director, Jan will manage a multimillion pound budget and lead over 700 researchers and staff.

Jan was the joint head of the Structural Studies Division and Deputy Director of the LMB, before his promotion following a competitive international search.

Speaking of his appointment, Jan said: “Being given such an important job makes me feel both excited and humbled. I will aim to preserve and develop LMB’s very special culture and people, so that new ideas keep the LMB at the forefront of molecular biology, where it belongs.”

Read more: mrc.io/new-LMB-director

Alzheimer’s researchers win prestigious Brain Prize

Four neuroscientists, including three supported by MRC funding, have won the 2018 Brain Prize for advancing understanding into the genetic and molecular mechanisms behind Alzheimer’s disease.

Awarded annually, the Brain Prize recognises scientists who have made an outstanding contribution to neuroscience.

Bart De Strooper, Director of the UK Dementia Research Institute (UK DRI), is recognised for identifying a protein called presenilin. He discovered that mutations in presenilin genes cause production of abnormal amyloid, a component of brain plaques found in Alzheimer’s disease patients.

Michel Goedert, a Programme Leader at the MRC Laboratory of Molecular Biology, is recognised for research crucial for understanding the importance of tau protein.

John Hardy, a UK DRI professor at University College London, observed mutations in the gene coding for amyloid protein in a family with early onset disease. He suggested that Alzheimer’s disease was initiated by the build-up of amyloid in the brain.

Christian Haass is the fourth awardee, based at the Ludwig-Maximilians-University of Munich and at the German Center for Neurodegenerative Disorders.

The chairman of the Lundbeck Foundation Brain Prize selection committee, Professor Anders Björklund, commented: “These four outstanding European scientists have been rewarded for their fundamental discoveries unravelling molecular and genetic causes of the disease that have provided a basis for the current attempts to diagnose, treat and possibly even prevent neurodegenerative brain diseases.”

Read more: mrc.io/brain-prize-2018
Professor Janet Darbyshire was awarded the MRC Millennium Medal for the instrumental role she played in the development of treatments for tuberculosis and HIV. Here Janet tells us about her early memories of medicine, giraffes in Africa and the changes she’s seen her research make to people’s lives.

I was interested in public health at the very beginning. My father was a public health inspector, and worked very closely with the medical officer of health. He used to take me to the pathology lab with him, and although I mostly remember the dreadful smell, it did spark my interest in medicine.

It’s serendipity that I specialised in respiratory medicine. I applied for a job at the Whittington Hospital in London and was allocated to jobs in chest medicine and neurology. I didn’t want to do geriatrics or paediatrics, and I discovered that respiratory medicine was really interesting. So I went on to train in this area at the Royal Brompton Hospital.

Then, after that, some more serendipity. I decided I’d try and move into a research job and the MRC Tuberculosis and Chest Diseases Unit, directed by Professor Wallace Fox, happened to be located at Brompton Hospital and a vacancy arose just at the right time.

The person who made me a proper epidemiologist was Geoffrey Rose who was a wonderful epidemiologist. I’d been working at the MRC unit doing trials and epidemiological studies for over 10 years when it closed on Wallace Fox’s retirement. Geoffrey suggested I do a Master’s degree in epidemiology because, although I knew my stuff thanks to Wallace, I really didn’t have strong theoretical underpinning.

The first clinical study I was involved in was a survey in 1974, looking at tuberculosis in Kenya and the impact of treatment. After that I became involved in some of the short course chemotherapy trials. One of the first ones I was responsible for was called Study X. The trial was stopped very early because we had tried to shorten the treatment to four months, and it wasn’t long enough. A lot of patients didn’t do well and we learned that with the drugs available 6 months was the minimum for effective tuberculosis treatment.

Career in brief:
• Qualified in medicine at The University of Manchester in 1970
• MSc in Epidemiology from the London School of Hygiene and Tropical Medicine 1990
• Became head of the MRC HIV Clinical Trials Centre in London in 1989
• In 1998 established, and became director of, the MRC Clinical Trials Unit (CTU)
• Awarded an OBE in 1996 and a CBE in 2010 for services to clinical sciences
I was lucky because when I started working in Africa there was already a well-established collaboration with what was the East African Medical Research Council. There were staff based in Kenya, Tanzania, Uganda and Zambia. I used to go and visit all the clinical sites with the local people.

In the early days, the hospitals and trials there were running very well. As time went on and the East African community broke up it became more difficult. I think the biggest problem was having sufficient funds to keep things going in the district hospitals. The first request I would often have is, “Can we have some more money for petrol?”. It was the practical side of running the trials on a day-to-day basis that was the most difficult, but the results of the trials have had an impact worldwide.

I fondly remember my experiences of working in Kenya; the smells, the colours, the most amazing view of the Great Rift Valley, the giraffes and the mountains, Kilimanjaro and Kenya. When my husband was visiting and we went to a lodge we had a family of elephants walk right in front of us. I’ll never forget how very friendly and hard working the people I worked with were.

When I first got involved in HIV research in the late ’80s it was an almost universally fatal disease. Now people with HIV can have a near normal lifespan provided they remember to take the drugs and are able to manage the side-effects.

It’s often not one clinical trial that makes a huge difference. It’s more that each trial added to our understanding of HIV and improved treatment. The first HIV trial we did with a single drug was disappointing, because it showed that giving one drug very early didn’t improve survival. But it did show that giving one drug led to resistance, like in tuberculosis. We went on to find that two drugs were better than one, and three drugs better than two, and that’s the way that the therapy has moved on.

Once the cost of drugs to treat HIV had come down we set up a rather different trial, the DART trial (Development of Anti-Retroviral Therapy in Africa), with a tremendous international collaboration between the UK, Uganda and Zimbabwe, two beautiful African countries that I had not visited before.

Seeing the change my research has made to people’s lives is fantastic.
We wanted to know if treatment for HIV could be safely given without the expensive laboratory tests that were routine in the UK. DART demonstrated that HIV treatment could be given safely and successfully without routine tests, which meant for the same budget it could be delivered to more people and closer to their homes through local clinics.

Seeing the change my research has made to people’s lives is fantastic. When I first used to go to Uganda, during the HIV epidemic, we’d drive into Kampala from the airport and everyone was making coffins at the side of the road. When I went back some years later, they’d gone back to making furniture. The hospitals used to be completely full of patients with HIV/AIDS, but now things are very, very different.

I have been very inspired by those people, who continued to work under amazingly difficult circumstances in Africa, at the peak of the HIV epidemic, looking after very sick patients. They inspired me by their ability to say, “Yes, we’ll do research to improve future health, as well as treat our patients”. Their capacity is amazing and the results of their efforts have helped millions.

As told to Petra Kiviniemi

Watch a documentary about DART and other MRC-run trials at: http://www.picturinghealth.org/research-films/

MRC Festival of Medical Research
14-24 June 2018

Visit MRC events at our institutes, centres and units
Find out more at mrc.ukri.org/mrcfestival

#MRCFestival • mrc.ukri.org/festival
Dementias Platform UK Data Portal

Dementias Platform UK (DPUK) has created a new Data Portal – an online secure platform – that can be accessed by researchers anywhere in the world to run analyses on datasets from multiple cohort studies.

It is now possible for researchers to access rich data at scale in a single location, to further global understanding of the causes, symptoms and treatments for dementia.

The Data Portal contains records for over 572,000 participants, including brain scans, genetic data, clinical records and cognitive test data.

The DPUK Discovery Awards are designed to encourage and promote research within the portal. Award winners will be announced at the DPUK conference on 23 April 2018.

Explore the Data Portal: https://portal.dementiasplatform.uk/

Transforming health through data science

Health Data Research UK (HDR UK), the UK’s new health and biomedical data science research institute, has awarded £30m of funding to six sites across the UK (listed below) to address challenging healthcare issues through use of data science.

This is the first phase of investment to establish HDR UK, a multi-partner investment led by the MRC.

**Cambridge**
Wellcome Sanger Institute  
European Bioinformatics Institute  
University of Cambridge

**London**
University College London  
Imperial College London  
King’s College London  
Queen Mary University of London  
The London School of Hygiene & Tropical Medicine

**Midlands**
University of Birmingham  
University of Leicester  
University of Nottingham  
University of Warwick  
University Hospitals Birmingham  
NHS Foundation Trust

**Oxford**
University of Oxford

**Scotland**
University of Edinburgh  
University of Aberdeen  
University of Dundee  
University of Glasgow  
University of St Andrews  
University of Strathclyde

**Wales/Northern Ireland**
Swansea University  
Queen’s University Belfast

For further information, please visit www.hdruk.ac.uk
Bacteria could be the secret to controlling mosquito-borne viruses

Bacteria which can block the transmission of Zika and dengue viruses in their mosquito hosts show promise for a new way of controlling viral disease.

Scientists from the MRC Centre for Virus Research at the University of Glasgow examined virus transmission from Aedes aegypti mosquitoes infected with different strains of Wolbachia bacteria. These mosquitoes are carriers of viral diseases known for their devastating effects on people living in tropical regions.

Out of four strains of Wolbachia tested, the ‘wAu’ strain was found to show the greatest potential for blocking transmission of dengue and Zika virus. After feeding on blood infected with dengue or Zika virus, the mosquitoes containing wAu had less viral RNA within their tissues than mosquitoes infected with other strains, indicating lower virus transmission.

Lead researcher Professor Steve Sinkins said: “Our results with the wAu strain showed by far the most effective transmission blocking for all the viruses we tested, and it provides an exciting new option to explore for disease control programmes.”

How incurable mitochondrial diseases strike previously unaffected families

Researchers from the MRC Mitochondrial Biology Unit at the University of Cambridge have shown how children can inherit a severe – potentially fatal – mitochondrial disease from a healthy mother.

As powerhouses of cells, mitochondria produce energy and have their own separate DNA. They are inherited from a person’s mother via the egg. Mitochondrial diseases, often caused by mutations in mitochondrial DNA, are rare but can cause severe conditions including Leigh syndrome – a progressive brain disorder.

The researchers isolated human female embryonic germ cells, that ultimately become eggs in women, and tested their mitochondrial DNA. They found mitochondrial DNA mutations in the developing egg cells of all 12 human embryos studied. This suggests that healthy humans have low levels of mutations, but this can change within one generation.

Sexual reproduction normally keeps mutations in check. In mitochondrial DNA, a ‘genetic bottleneck’ helps to ‘clean’ mutations as developing egg cells containing mutated mitochondria are eliminated. But the process is not perfect therefore defective mitochondria could remain, explaining how genetic disease can appear without a family history.

Published online at: journals.plos.org/plospathogens, 25 January, 2018.

Published online at: www.nature.com/ncb, 15 January 2018.
Scientists create mini-kidneys from human stem cells

University of Manchester scientists have produced human kidney-like tissue in mice, advancing progress toward using stem cells to repair damaged kidneys.

They generated primitive kidney cells from human embryonic stem cells, grown in lab dishes with nutrients and molecules to promote kidney development.

Three months after being injected under the skin of mice, the cells formed glomeruli – a functional part of the kidney – with a blood supply and mini tubes. By adding a fluorescent tag to the urine-like substance produced when kidneys filter blood, the team saw this substance in some of the tubes, suggesting part-functional mini-kidneys. However more work is needed to scale up and use the technology to repair diseased kidneys.

Professor Adrian Woolf, one of the lead authors, said: “Worldwide, two million people are being treated with dialysis or transplantation for kidney failure, and sadly another two million die each year, unable to access these treatments. So we are tremendously excited by this discovery – we feel it is a big research milestone which may one day help patients.”

Published online at: www.cell.com/stem-cell-reports, 8 February 2018.

Insight into heavy periods could pave way towards new treatment

Scientists have uncovered a cause of heavy menstrual bleeding offering hope for a new treatment for women living with the condition – one that avoids taking hormones, which can cause side-effects.

Up to 30 per cent of pre-menopausal women deal with heavy menstrual bleeding. This can lead to severe anaemia – a lack of red blood cells to carry oxygen around the body – abdominal pain, fatigue and work absence.

Researchers from the MRC Centre for Reproductive Health (CRH) at the University of Edinburgh studied the womb lining; shed during menstruation, the remaining surface must heal to limit blood loss.

They found that lowered levels of oxygen stimulated production of HIF-1 protein, driving repair of the womb lining. Tests on mice using a drug to boost HIF-1 levels led to improved tissue repair and reduced blood loss.

Study lead, Dr Jackie Maybin, Clinical Lecturer in Obstetrics and Gynaecology at the MRC CRH, said: “Excitingly, increasing levels of the HIF-1 protein in mice shows real promise as a novel, non-hormonal medical treatment.”

Published online at: www.nature.com, 23 January 2018.
In the early 1900s, a German neurologist called Alois Alzheimer became obsessed with studying an asylum patient in her 50s, who had started to show unusual behavioural changes. After her death he examined her brain and discovered structures known as amyloid plaques and neurofibrillary tangles – the hallmarks of what became known as Alzheimer’s disease. So why, when we’ve known about the disease for so long, are there still no treatments?

A uniquely human organ
The human brain is a ‘black box’. It’s a very difficult organ to study. It’s the most uniquely human organ there is, very different to the brains of animals that we use as research models. We know much less about the brain and how it’s built than any other organ of the body.

Until recently, there just hasn’t been enough invested in this area of science. Now, with major initiatives like the Dementias Platform UK and the UK DRI, funding for dementia research increased. I hope that will help.

Perseverance with drug trials
We also need a change in approach from industry. Just 0.5% of compounds being developed as potential drugs for dementia have successfully reached patients, compared with an industry average of 4.1%. This is often because dementia drugs can fail to show promise in the early, preclinical testing phase. Developing a drug all the way through to market is costly. So pharma companies with an eye on their profit margin are quick to withdraw investment if a drug fails to show early results. But things are starting to pick up: since 2013, the number of Alzheimer’s drug trials has doubled.

Where are we now?
So what do we know for sure about the causes of Alzheimer’s disease? We know that, in rare cases, it is down to genetic mutations. This finding has been an important clue about what might be happening to cause the disease at the level of molecules within the brain.

We also know that there are risk factors, for example carrying a mutation on a gene called apoE, and of course ageing. But there are also other risk factors that are within our power to modify and manage. Treating hearing loss in early life has been shown to reduce the risk of getting dementia in old age. Lack of education in early life is linked with an increased risk. And then there are a few things that can be done by anybody – give up smoking, do enough exercise and keep your weight under control.

For 25 years, scientists have been working with a theory about the cause of Alzheimer’s disease called the amyloid hypothesis which lays out a linear series of events which lead to the disease. It is becoming clear that this hypothesis is far too simple.

Future focus
At the UK DRI, I want our focus to be on how the different parts of the brain respond to changes in brain chemistry that trigger the dementias. If we can improve the brain’s natural defence mechanisms, or halt destructive reactions, for instance damage to the brain caused by immune cells, that would open a whole new window on treatments.

In the next few years I expect to see great progress in the diagnosis and classification of the different dementias, and we will get much better at predicting a person’s risk of
getting them. I think we’ll also see society mobilise to cope with the risk factors that lie within our control. As a consequence, we will see the incidence of these diseases slowing – and just a one-year delay would decrease the number of people with dementia worldwide in 2050 by nine million.

For Alzheimer’s disease in particular, anti-amyloid drugs will likely become part of the preventive efforts to halt dementia. But for other dementias it will take more time. The MRC-funded discovery of the atomic structure of tau filaments – another hallmark of neurodegenerative diseases – was a major breakthrough and I am interested to see what therapies aimed at the Tau protein will bring.

My biggest hope is an approach called nucleotide therapy. It uses short molecules to ‘stick’ to, and change the activity of, messenger molecules which help make brain proteins. It might provide a breakthrough that could make the dementias treatable within just a decade. If that does not work, I think we will have around 20 years of hard work in front of us, to generate an array of drugs that can then be used according to a patient’s individual risk and disease – so-called ‘personalised medicine’.

Humanity has been able to control HIV, to make major progress in curing cancer and other diseases, and to go to the moon and beyond. So why wouldn’t we be able to find a cure for this scourge that threatens our most precious gift – this beautiful organ that makes us who we are?

In the next few years I expect to see great progress in the diagnosis and classification of the different dementias, and we will get much better at predicting a person’s risk.

Read the full article on our MRC Insight blog: mrc.io/dementia-treatments
**Network** is for anyone who has an interest in the work of the MRC, including scientists, doctors and health professionals involved in medical research, government departments and parliamentarians, and university staff and students. The aim is to provide a quick, easy-to-read summary of activities across the MRC, from research news through to funding, grant schemes and policy issues, with pointers to more in-depth information on websites and in other publications.

We are keen to receive feedback on Network and suggestions for new features from our readers. To share your views email network@headoffice.mrc.ac.uk

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Medical Research Council (Swindon office)  
2nd Floor David Phillips Building  
Polaris House  
North Star Avenue  
Swindon  
SN2 1FL

Medical Research Council (London office)  
14th Floor  
One Kemble Street  
London  
WC2B 4AN

Phone: +44 (0)1793 416200

The Medical Research Council is part of UK Research and Innovation

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