**MRC scientist wins 2009 Nobel Prize for Chemistry**

Dr Venki Ramakrishnan became the MRC’s 29th Nobel Laureate in October when he won a share of the Nobel Prize for Chemistry for his research into the structure and function of the ribosome. *Network* caught up with him to find out about his impressive achievement.

“At first I thought it was someone pulling my leg,” says Venki of the phone call from Sweden telling him he had won the prestigious prize. “When I realised it was genuine it was a bit of a shock.”

Venki is a molecular biologist at the MRC Laboratory of Molecular Biology (LMB). Along with his co-prizewinners Dr Thomas A. Steitz of Yale University and Dr Ada E. Yonath of the Weizmann Institute of Science in Israel, he has established the atomic structure of the ribosome, allowing us to gain a detailed understanding of how this essential component of life works.

“Virtually everything in every cell was either made by the ribosome or made by enzymes that were themselves made by the ribosome,” explains Venki. “Proteins are essential to life in many ways. They carry out nearly all the reactions in the cell, and also regulate its development and growth. They’re involved in making structures, such as skin, carrying oxygen in our blood, sensing light in our eyes and defending us against infection. All proteins are made by following the instructions in our genes. And the ribosome is the large molecular machine that does all of this.”

But to understand the ribosome, scientists needed to have a detailed picture of what it looks like. Through many years of painstaking research, the three Nobel Prize winners worked out the atomic structure of the ribosome using a visualisation technique called X-ray crystallography to map the position of each of the hundreds of thousands of atoms that make up the ribosome.
Reflecting on the past year, we have seen more excellent progress for the MRC, and what better way to end 2009 than with our 29th Nobel Prize, and the MRC Laboratory of Molecular Biology’s 14th. I was delighted to hear about Dr Ramakrishnan’s success, and this achievement is testament to the MRC’s continued investment in the best scientists to carry out excellent science. Long may this continue.

The recent dismissal of David Nutt, the Chair of the Advisory Council on the Misuse of Drugs, was regrettable, and has left many scientists feeling anxious about what their position is when giving scientific advice. It is urgent that steps are now taken to rebuild the relationship between scientists and the Government. The MRC wholeheartedly defends academic freedom and the need for scientists to present findings based on sound research. Government policy must be based on evidence and it is crucial that scientists are able to offer unfettered advice without the fear of reprisal. I believe this principle should be the backbone of scientific engagement with government.

Of course, it is widely accepted that scientific evidence should shape – rather than dictate – government policy, and this should be recognised by scientists who serve on government committees. However scientists must be allowed to speak freely and to offer advice in an entirely unbiased way, otherwise that advice is actually counterproductive to government. I hope to see this position clarified in the near future, or we run the risk of losing the confidence and expertise of other advisers.

Sir Leszek Borysiewicz

Update from the MRC Chief Executive

Research on this arrangement of atoms in the ribosome has allowed Venki’s group not only to understand how it contributes to protein production but also to see directly how antibiotics bind to specific pockets in the ribosome structure. This could help researchers to design antibiotics to treat people infected with antibiotic-resistant strains of bacteria, for example those that cause tuberculosis.

“Many antibiotics work by blocking bacterial ribosomes, and these structures make it possible to understand how antibiotics interact with the ribosome, and how it might be possible to design new and better antibiotics,” explains Venki. “The MRC has licensing agreements with a company called Rib-X Pharmaceuticals, founded by Dr Steitz, which is doing precisely that.”

Venki was born in India and started his career as a physicist. Gaining his degree from Baroda University in Gujarat, he then moved to the USA, obtaining a PhD in physics from Ohio University in 1976. At that point he decided to switch to biology, spending two years at the University of California as a graduate student to complete the transition. He has worked on ribosomes since joining Peter Moore’s laboratory at Yale University in 1978, and he came to work at the LMB a decade ago.

Long-term MRC support has played an important role in nurturing Venki’s career, allowing him and his team to work away at the slow process of visualising the ribosome without interruption.

“I decided to move to the LMB because I had spent a sabbatical year here in the early 90s and I knew and liked the place. I moved here in 1999 because it had a well-established tradition of supporting long-term, challenging problems which may take many years to achieve results,” he says.

“Although I’ve also been generously supported by agencies such as the US National Institutes of Health...
and more recently the Wellcome Trust, it was very important to have this core of stable MRC funding and the infrastructure of the LMB to work on this problem without the fear that I’d be cut off in the middle of it owing to a lack of publications. I think this is a key reason for the successes of the LMB – and certainly it played a major role in my own,” he says.

Research done at the LMB has won nine Nobel Prizes over the years, shared between 14 LMB scientists, including Professor James Watson and Professor Francis Crick for their elucidation of the structure of DNA in 1962. The LMB’s string of successes has led to it being dubbed the ‘Nobel Prize Factory’ by the media. Joking aside, Venki cautions that no institute should be judged by its number of Nobel Laureates, because a lot of “hugely important research” has not been recognised by the prize. He cites the examples of research into the structure of muscle by Professor Hugh Huxley, the use of phage display and humanised antibodies by Professor Sir Greg Winter, Dr Michael Neubauer’s work on how antibodies mature to high affinity for their antigens, and Dr Richard Henderson’s research into bacteriorhodopsin.

“There is so much good science being done now, it is impossible to recognise all of it with this single award,” says Venki. “And the LMB is not in the business of winning Nobel Prizes – it’s in the business of working on important and challenging questions.

“First-rate work is being done here on a regular basis. When people come here and see what everyone else is doing, they just don’t feel like working on mundane problems. So these awards are a by-product of that culture, in which people here try to work on the most interesting and best science they can.”

Some weeks after the prize was announced, the frenzy of press calls, invitations and messages from well-wishers is beginning to die down, and Venki is looking forward to focusing fully on his research again. Next, he wants to understand, in structural terms, the remaining puzzles in the process of translation in bacteria: how instructions from genes are translated into the production of proteins.

“A future goal is to work on eukaryotic translation, where initiation of translation is particularly complex. This is an important area because it is regulated by the cell, and it can be hijacked by viruses or deregulated in some types of cancer. But there are many groups worldwide working on this, so there will be a lot of competition,” he adds.

When quizzed about whether his success has changed his life, Venki is characteristically stoical in his reply. “It is too early to tell. I hope that once the distractions die down, it won’t have changed my life much. I cannot think of anything I would do differently in my research or life as a result of it.”

And what advice would he offer to a young MRC researcher at the start of their career who dreams of one day winning a Nobel Prize?

“Setting out to win a Nobel Prize is a guarantee for failure and unhappiness. My advice would be to pick a problem that you really care about. If you’re dying to know the answer to the questions you’re working on, it will make for an exciting life and you’ll wake up each day eager to come to the lab. I believe it was Francis Crick who said you can tell what you really care about by what scientific area you find yourself gossiping and talking about constantly – I think that’s a good criterion.”
Biography of Sir Richard Doll launched

Family, friends and eminent former colleagues of Sir Richard Doll joined MRC staff at the Royal Society in October to celebrate the launch of a book about his achievements. A world-renowned epidemiologist, Sir Richard carried out groundbreaking MRC-funded research in the 1950s which proved the link between smoking and cancer.

The biography, *Smoking Kills: The revolutionary life of Richard Doll*, by Conrad Keating, commemorates Sir Richard’s long and illustrious career. It charts his groundbreaking work on smoking and cancer with Austin Bradford Hill in the 1950s, his working relationship with the MRC and his time spent as Director of the MRC Statistics Unit in the 1960s.

Born in 1912, Sir Richard’s life covered much of the twentieth century and fulfilled his early ambition to be a valuable member of society. He rejected his Establishment background and joined the Communist Party as a reaction against what he saw as the “anarchy and waste” of the 1930s. He treated the blistered feet of the Jarrow Hunger Marchers and served as a medical officer at the retreat of Dunkirk.

In 1950, Sir Richard concluded in a research paper that smoking cigarettes was “a cause, and an important cause” of the rapidly increasing epidemic of lung cancer. His historic and contentious finding marked the beginning of a lifelong crusade against the big tobacco companies and premature death from smoking. His legacy to public health research is staggering. He died in 2005, aged 93.

Author Conrad Keating said of Sir Richard: “He ushered in a new era in medicine, shaped by the intellectual ascendancy of medical statistics, a revolution based substantially on his scientific contribution.”

Former legal assistant Paula Lawlor, who flew in from the USA to attend the launch event, recalled how she first met Sir Richard in 2001: “I called him at his home in Oxford one evening to ask if he’d consider testifying in California in a tobacco case for a person who had lung cancer from smoking. The trial was scheduled to start within two weeks. A week later, Richard flew to Los Angeles and stayed for a week for his deposition and trial testimony – the outcome of the trial was a verdict for the plaintiff of $3 billion.”

Sir Richard later agreed to allow 70 other tobacco cases in the US to use a video recording of his deposition when their cases went to trial.

“Every tobacco company was represented at the deposition, grilling Richard with questions for two and a half days,” explained Paula. “He was a pillar of strength – they couldn’t touch him. The result of the second trial was a verdict for the plaintiff of $28 billion. I feel very fortunate to have known and spent so much time with this incredible man.”
Sir Leszek delivers prestigious Harveian Oration

Sir Leszek Borysiewicz was invited to deliver the 2009 Harveian Oration at the Royal College of Physicians in October – an honour that has been bestowed on a leading doctor or scientist each year since 1656.

Established by 17th Century physician William Harvey, who was the first to establish that blood circulated rather than ebbing and flowing, the Oration has since been delivered by a long line of distinguished scientists. Former Harveian Orators include the epidemiologist Sir Richard Doll in 1982, and Nobel Laureate Sir Paul Nurse in 2003.

In this year’s Oration, titled Prevention is better than cure, Sir Leszek suggested that the time has come for a new perspective on preventative medicine. Although mass vaccination has saved countless lives and gives us the opportunity to eradicate major diseases, the subject continues to be deeply controversial. Sir Leszek argued that now is the time to encourage objective and reasonable debate on the risks and benefits of mass vaccination.

A new focus for scientific study to address the anxieties and motivations of those reluctant to take part in vaccination programmes is needed, he argued, one which takes into account their often conflicting needs.

“Without wider social and political support, scientific discovery can only take us so far in preventing the spread of disease,” he explained. “The importance of taking steps to ensure widespread understanding and public support is critical to any preventative measure we may seek to introduce.”

He urged his fellow doctors and scientists to remember the essential role preventative medicine has already played in the reduction of serious illness across the world. One example of this is the eradication of smallpox, a disease which at one time killed as many as every seventh child in Europe.

Drawing on his background as an expert in infectious diseases, Sir Leszek also discussed his own contribution to the scientific analysis of the Human Papillomavirus (HPV) which has led to the development of vaccines designed to prevent cervical cancer. Highlighting the challenges of delivering vaccines and other treatments in the safest way possible, Sir Leszek cited the example of the MRC’s recent DART trial of antiretroviral therapy monitoring in HIV patients in Africa (covered in the September/October issue of MRC Network).

“The key thing to remember when undertaking health interventions is that we must remain driven by the needs of populations, individuals and patients and the efforts of scientists to strive for new discoveries to improve human health through prevention and treatment,” he said.
October saw the launch of Research Councils UK’s Framework for the future – which shows how public investment in research is helping the UK to compete in the global economy.

The framework is based around three themes: a productive economy, a healthy society and a sustainable world. These areas span the range of challenges facing society and draw together world-leading interdisciplinary research across all research councils.

For example, cross-council research to promote a healthy UK society includes studies which have shown that planting larch, pine and ash trees can help remove tiny polluting particles from the air in towns and cities, reducing the impact of air pollution on life expectancy.

And research on the bluetongue virus has benefited the economy by saving £485 million through prevention of outbreaks and protecting 10,000 UK jobs.

Read more about the framework at www.rcuk.ac.uk/framework

INDUSTRY UPDATE

New MRC spin-out company launched

A new biotechnology company, Bicycle Therapeutics, has been established based on technology developed at the MRC Laboratory of Molecular Biology (LMB).

With seed funding secured from venture capital firms, the Cambridge-based company will use new technology to develop highly stable and specific small-molecule biological drugs.

Bicycle’s technology involves the production of peptides (small sections of protein) which are stable enough to withstand unfolding and the action of proteases – enzymes which break down proteins. This should allow them to overcome the weaknesses seen with previous generations of peptide-based therapeutics. The technology is based on the pioneering work of its founding scientists Dr Christian Heinis and Professor Sir Gregory Winter, who previously founded Cambridge Antibody Technology and Domantis.

Bicycle’s Chief Executive Officer, John Tite, said: “We are delighted to have created this exciting new company based upon such an innovative technology and with scientific founders with such a great track record. Bicycle Therapeutics aims to develop its proprietary technology to create a pipeline of drugs which have the potential to be truly differentiated medicines.”

Dr Hugh Pelham, the Director of LMB, added: “It is very satisfying to see another new company coming from the laboratory’s research, and we will continue to work with the company to ensure that the benefits of this technology are realised as quickly as possible to improve human health.”

MRC Technology, the MRC’s sole agent for exploitation of MRC discoveries, was involved in the formal negotiations with the venture capital firms for the MRC technology licence and formation of the company.

Read more about the company at: www.bicycletherapeutics.com
Each year, a small proportion of UK infants suffer brain damage after being starved of oxygen during birth. MRC research has shown that cooling treatment during the first six hours of life could save over 100 babies a year from this fate.

Birth asphyxia occurs when a baby’s brain and other vital organs are starved of oxygen or blood, usually during labour or birth. In the UK around 1,400 infants each year are affected – one in every 500 full-term births. Asphyxia can be difficult to detect before a baby is born and can cause severe brain damage, cerebral palsy and even death in around half of the worst affected cases.

The MRC-funded TOBY (Total Body Hypothermia for Neonatal Encephalopathy) trial, results of which were published in October, set out to test the theory that bringing about mild hypothermia in the babies could reduce the damaging effects of oxygen deprivation. It followed 325 infants showing signs of birth asphyxia in hospitals in the UK, Hungary, Sweden, Israel and Finland. The babies were randomly assigned to receive either cooling treatments or standard intensive care. The findings showed that reducing the body temperature of the infants to 33-34°C for 72 hours followed by gradual re-warming reduced the likelihood of brain damage by 57 per cent.

These findings have been passed to the National Institute for Health and Clinical Excellence (NICE), the body which is responsible for treatment recommendations in NHS hospitals. They will be considered by NICE’s Interventional Procedures Advisory Committee in December, as part of the evidence base in this research area. If the committee decides to recommend cooling treatments for birth asphyxia, guidelines on the topic are likely to be published in summer 2010.

Co-chief investigator Dr Denis Azzopardi from Imperial College London says: “The study builds on a 20-year body of research but gives, for the first time, irrefutable proof that cooling can be effective in reducing brain damage after birth asphyxia. Although unfortunately it doesn’t work in every case, our study showed the proportion of babies that survived without signs of brain damage went from 28 per cent to 44 per cent with cooling treatments.”

Dr Azzopardi explains that brain injury from asphyxia is thought to occur in two phases. The first phase happens during the period when the brain is starved of oxygen or blood (or both), but the second phase of brain damage happens later on, after the baby has been resuscitated – and it’s during this phase that the cooling treatment can be effective.

“During the second phase of brain damage, which can go on for hours or days, it appears that the lack of oxygen damages the mitochondria, the powerhouses inside cells. This sets off a chain of events which causes the brain cells to go into apoptosis – programmed self-destruct mode. We think that lowering the temperature halts these processes, either by direct effect on apoptosis, by stopping the chain reaction which begins apoptosis, or by suppressing metabolism.”

Dr Azzopardi and his colleagues have received further MRC funding to begin studies in a small number of patients in January 2010. They plan to test the efficacy of xenon gas as an intervention for cooling infants.

Full TOBY trial results were published in the 1 October 2009 issue of the New England Journal of Medicine:
http://content.nejm.org
In October the MRC awarded £5 million to two projects which will bring stem cell treatments into trials in people. The first will look at age-related macular degeneration (AMD), a leading cause of blindness among the elderly, while the other will study acute myeloid leukaemia (AML), a cancer of the blood.

The projects have been funded as part of an international collaboration with the Californian Institute for Regenerative Medicine (CIRM) and will bring UK and US researchers together in a bid to speed development of stem cell treatments that can eventually be used in the clinic. The first programme to emerge from this enterprise is expected to begin first-in-man clinical trials within four years.

The AMD study will be led by Professor Pete Coffey at the UCL Institute of Ophthalmology and Professor Mark Humayun at the University of Southern California. Professor Coffey said: “The stem cell route we have proposed offers an opportunity for more successful results based on a single surgical treatment and hopefully a mechanism for preserving an individual’s eyesight.”

The AML project will be led by Professor Paresh Vyas at the University of Oxford and Professor Irving Weissman at Stanford University. Professor Vyas explained: “Many of those with acute myeloid leukaemia are over the age of 65 and not suitable candidates for aggressive chemotherapy. New treatments, targeted at the cancer stem cells that current evidence suggests propagate the disease, could eventually offer more people real options for treatment and an increased chance of survival.”

Sir Leszek Borysiewicz added: “The MRC has led the way for UK translational researchers and together with our partners at CIRM we look forward to realising the full potential of stem cell research.”
Bowel cancer drug mix may affect survival

The largest ever trial in advanced bowel cancer has shown that the anti-cancer drug cetuximab improves the survival of patients only when given alongside one of two standard combinations of chemotherapy drugs. Patients who received standard capecitabine/oxaliplatin treatment plus cetuximab showed no benefit, whereas those who received the alternative standard drug combination fluourouracil/oxaliplatin with cetuximab did show some benefit. Results from other trials of cetuximab in advanced bowel cancer patients back up this finding. The study also set out to discover whether taking breaks from standard chemotherapy could cut side-effects, reduce time on treatment and improve patients’ quality of life without impacting on their lifespan. Patients on intermittent chemotherapy had fewer side-effects but their median survival was 1.4 months shorter than patients who received continuous chemotherapy. Lead investigator Professor Tim Maughan of Cardiff University explained: “Although these results don’t give a clear indication that one treatment option is better than another, they do provide more information about the potential effect different treatment options can have. The results will help inform patient-clinician discussions and ultimately decisions on individual treatment.” The study was funded by the MRC, Cancer Research UK, the National Cancer Research Network and Merck Serono. Trial results presented at the National Cancer Research Institute annual conference, Birmingham, 6 October 2009.

Male fertility problems linked to maternal stress

Exposure to excess stress hormones in the womb combined with chemicals commonly found in the environment might increase the chance of boys being born with reproductive defects, research suggests. Scientists at the MRC Human Reproductive Sciences Unit and the University of Edinburgh looked at the effects of dibutyl phthalate, a chemical found in glues, paints and plastics, on fetal development in rats. Treatment of pregnant rats with dibutyl phthalate had some effects on their fetus’ reproductive development. These effects were markedly increased when the rats were also exposed to glucocorticoids – hormones produced in response to stress – although fetal development was unaffected by glucocorticoids alone. Birth defects seen in the rats included cryptorchidism, in which the testes fail to descend, and hypospadias, a mis-alignment of the urinary tract – both of which are on the rise in the human population. MRC Clinician Scientist Dr Mandy Drake, who led the research, said: “In most studies reproductive disorders are seen only with abnormally high levels of chemicals, which most humans aren’t exposed to. Our study suggests that additional exposure to stress, which is a part of everyday life, may increase the risk of these disorders and could mean that lower levels of chemicals can cause adverse effects.”

Published online ahead of print in Endocrinology, October 2009.
New insights into cancer drug resistance

A gene which helps to determine whether cancer cells will respond to anti-cancer drugs has been identified by MRC researchers. Professor Ashok Venkitaraman and colleagues from the MRC Cancer Cell Unit in Cambridge looked at the effects of drugs such as taxol, which work by blocking the rapid division of cancer cells. Some cancer cells are resistant to these effects and continue to divide, but it’s not understood how this resistance occurs. Using a technique called RNA interference, the research team tested the effects of over 500 genes on drug-treated cancer cells. They identified a gene encoding the protein UBE2S, which they believe is essential for cell division in drug-treated cells. Although UBE2S was not essential for cell division under normal conditions, once treated with taxol and similar drugs, the cells were unable to divide if UBE2S levels were reduced. Hence the amount of the protein present in cells may determine whether they’re able to overcome the effects of drugs which stop cell division. Professor Venkitaraman said: “This discovery not only reveals a new mechanism that controls cell division, but also may help us to use taxol and related drugs more effectively by selecting the patients who are most likely to benefit.”

Published online ahead of print in *Nature Cell Biology*, 11 October 2009: www.nature.com/ncb

Two new genetic links to Alzheimer’s found

Two genetic variants which appear to increase the risk of developing Alzheimer’s disease have been identified by scientists. A major international study analysed the genes of over 16,000 people over two years – the largest ever genome-wide association study (GWAS) of Alzheimer’s disease carried out to date. By comparing variations between the genes of Alzheimer’s patients and healthy volunteers on a mass scale, the researchers discovered the susceptibility genes *CLU* and *PICALM*. When these results were put together with another GWAS carried out in France, a third susceptibility gene, *CR1*, was also identified. Previously only one gene, *APOE4*, had been clearly identified as a potential genetic risk factor. Lead author of the study, Professor Julie Williams of the MRC Centre for Neuropsychiatric Genetics and Genomics in Cardiff, said: “This research is changing our understanding of what might cause the common form of Alzheimer’s disease and could provide valuable new leads in the race to find treatments. If we can combat the detrimental effects of these genes, we estimate it could reduce the chances of people developing Alzheimer’s by almost 20 per cent.” The study was supported by several funders including the MRC, the Wellcome Trust, the Welsh Assembly Government and the Alzheimer’s Research Trust.

Set in the heart of the leafy campus of the University of Sussex, near Brighton, is a modern red brick building housing the MRC Genome Damage and Stability Centre (GDSC). Here, scientists are hard at work unravelling the nuts and bolts of how our cells repair potentially deadly breaks in DNA, and why this crucial process goes wrong in some people – leading to an increased risk of cancer.

A descendent of the MRC Cell Mutation Unit, which closed in 2001, the GDSC was one of the MRC’s first university-based research centres to be established. It was designed to build on the work of the MRC Cell Mutation Unit by broadening its research base, and over its first eight years, the centre has gone from strength to strength. Today it has fifteen research groups with scientists from different disciplines working together under the same roof on mutual research interests. Training is high on the centre’s agenda, and it has been successful in attracting seven research fellows, including several funded by the MRC. Plans are now afoot to expand the centre beyond the current building by setting up labs in the nearby biology building of the University of Sussex.

The centre is directed by Professor Tony Carr, a former Cell Mutation Unit scientist. He explains the rationale behind the centre’s work: “Our aim is to understand how cells, and also whole organisms, respond to genome damage, and what the consequences are if these responses are lost – in terms of cancer and other aspects of human disease.”

Our genomes are arguably our most precious possessions. They are made up of long molecules of DNA that contain the genetic blueprint that tells every part of our body how to function. But the DNA in our cells is continually being damaged – our skin cells are harmed by sunlight, our intestinal cells are assaulted by carcinogens in food, and all of our cells are damaged simply by existing at body temperature.

Fortunately, our cells contain sophisticated mechanisms for repairing this damage and thereby protecting our genomes – and it’s these protective processes that are the focus of the GDSC’s work. Research carried out at the centre includes studies on the protein molecules that repair DNA inside cells, on the genes that are altered or mutated in cancer cells, and also investigations into cancer-prone people to identify other useful targets in the fight against cancer.

**Diagnosing rare genetic diseases**

Part of the centre’s research involves studying several genetic diseases in which one of these DNA repair systems is faulty. This can result in the affected individuals having very high incidences of cancer: more than 1,000 times higher than in the general population.

One example is a disorder xeroderma pigmentosa, which results from the inability of cells to repair a type of DNA damage called thymidine dimers, which are caused by
sunlight. As a result, these patients usually develop skin tumours from everyday exposure to sunlight.

Tony says: “Using the cells of these patients we can sequence the genes to find out which ones are defective, and look at the cells to try and understand the mechanisms behind DNA repair and what happens when it goes wrong.”

Although the centre’s work is at the fundamental end of research rather than clinical, its findings have helped to identify the genetic defects in several DNA repair disorders, and the centre now offers a national diagnosis service for rare conditions such as trichothiodystrophy, Seckel Syndrome and Cockayne’s Syndrome.

By discovering the nature of the defects in people with these disorders, the scientists are able not only to help diagnose and potentially ameliorate these conditions, but also to gain general insights into how cancers can arise and develop – speeding progress towards cures.

Tony says: “Virtually all cancers are the result of an accumulation of defects in multiple genes, which is thought to occur in part because they’re either unable to repair DNA damage, unable to detect it, or unable to kill the cells through apoptosis when damage is present. This means the damaged cells continue to divide and defects accumulate and tumours can be formed.”

**Immune system impacts**

Professor Penny Jeggo’s group focuses on how a particular type of damage to DNA called double-strand breaks are repaired or dealt with by the cell. Double-strand breaks can be fatal if they are not accurately or efficiently repaired, and mis-repair of these breaks is also a step in the development of cancer. Damage to cells by radiation is a key cause of double-strand breaks.

But some double-strand DNA breaks are made deliberately by the cell during the development of an organism’s immune repertoire. In order to recognise an antigen in the environment, the body needs to create a broad diversity of genetically distinct cells while maintaining the overall stability of their genomes. To do this, the cells use a process called VDJ recombination to make double-strand breaks and then repair the breaks deliberately erroneous way.

With a dual interest in double-strand breaks caused by radiation and the immune problems resulting from faulty VDJ recombination, a few years ago Penny’s group decided to examine some archived cells from a 14-year old leukaemia patient who had over-responded to radiotherapy and died.

“We discovered that he had been lacking one of the proteins in the repair pathway for double-strand breaks. So we set up links with Great Ormond Street Hospital and Newcastle General Hospital, the two major centres in the UK which deal with childhood immune deficiency disorders. Now they send us samples from patients to check for this disorder. The defect makes them immunodeficient and radiosensitive,” says Penny.

“As a side benefit of our studies we’ve been able to optimise treatments for these patients. For example, immunodeficient patients are sometimes given bone marrow transplantations. Before the transplant operation they are treated with conditioning chemicals which cause DNA double-strand breaks to suppress their immune systems. While these patients benefit from bone marrow transplants because they are immunodeficient, it’s important that the particular group of patients we have identified aren’t given these chemicals, because it would be fatal for them.”

More recently, Penny and a colleague from the GDCS, Mark O’Driscoll, have been using human population genetics to identify double-strand DNA repair pathway defects which result in a hereditary disorder called Seckel Syndrome. Children born with this disorder have abnormally small heads, and delayed brain development. The particular sub-set of Seckel Syndrome patients that Mark and Penny are researching are found most commonly in remote regions of the world where there
is less mixing of populations and a higher occurrence of marriages between close family relatives. As a result, these couples have more genes in common and their offspring are more likely to inherit two copies of a faulty gene.

By studying tissue collected from these patients around the world, Penny and Mark have so far identified two previously unknown defects in genes encoding double-strand DNA break repair pathways. They hope that studying what goes wrong in these patients might give further important insights into how these proteins work and also why it is mainly the brains of these children which are affected by the defective genes.

**Repair of single strand DNA breaks**

While Penny’s work concentrates on what happens when both strands of the DNA double helix are broken and repaired, Professor Keith Caldecott’s research group focuses on how breaks to single strands of DNA are fixed. These single-strand breaks are very common in our cells – more than 20,000 occur in every cell of our bodies each day and are normally very efficiently repaired. However, Keith’s research has shown that brain cells are particularly sensitive to genetic defects in components of single-strand break repairs.

“The types of disease we are looking at are those where people become progressively ataxic – that is, they lose the ability to control movement, mainly through degeneration of the cerebellum in the brain. These people can be physiologically normal until their teens or sometimes twenties and early thirties, but as they get older they lose neurological function. We think that this is because cells are continually under attack from oxidative stress as we age, but it’s not known why only brain cells are affected by this process in these patients while the rest of their cells are able to repair the damage.”

Keith and his group recently identified a new human gene associated with DNA strand break repair which might eventually help to solve this riddle.

**Commercial applications**

Keith’s group’s research has also led to the development of anti-cancer drug candidates which work by inhibiting specific components of a single-strand DNA break repair. In collaboration with the MRC’s technology transfer company, MRC Technology, candidates are being screened for efficacy and specificity. Should any show promise, it’s hoped they will be licensed to pharmaceutical companies for further development as stand-alone anti-cancer agents or as agents to improve the effectiveness of existing therapies.

Keith explains: “There’s some evidence that if you inhibit components of single-strand break repair you can target particular types of tumour. As these compounds we’re testing are likely to be relatively non-toxic to normal cells, we hope that we would be able to treat patients by using the compounds to kill cancer cells of a specific genotype without affecting the surrounding healthy tissue.”

**A bright future**

When asked how he sees the centre progressing in future, Tony is upbeat: “Our strength is our very high quality basic science, and we want to keep that as our main thrust. We are moving towards making our own mouse models of single point mutations; single amino acid changes in a gene that will allow us to study how specific changes impact on the finer interactions of proteins within DNA repair pathways.

“The centre will be investing in medical imaging and microscopy over the coming years so that we can expand the scope of our research. While our focus will remain very much on basic science, we’re also developing closer links with the new medical school at the University of Sussex so that if we discover something which might have a direct clinical research application we can inform the work that they are doing.”
This intricate image of an embryonic mouse head captured by the MRC’s Dr Tim Mohun has won a Special Award in the Wellcome Trust Image Awards 2009.

It depicts a 14.5-day-old mouse embryo, and was made using a new technique called high-resolution episcopic microscopy (HREM). At this stage of development the embryo’s eyelids have not yet formed, but the pores of future whiskers can be made out.

The image is one of 19 winning biomedical, photographic and illustrative images which were chosen by a panel of judges for their power to captivate and provoke curiosity.

HREM allows for detailed and accurate three-dimensional visualisation of structurally complex tissues. Tissue samples are embedded in plastic resin and then very thin sections are taken off. As each slice is removed, the remaining block surface is imaged. Finally, the images are converted into a precise three dimensional model using computer software.

Tim, a Senior Scientist at the MRC National Institute for Medical Research, uses HREM to study intricate details of heart development in animal models, and developed the technique in collaboration with Dr Wolfgang Weninger at the University of Vienna. Studying the changing form of developing tissue is difficult, especially in mammal and bird embryos because they are relatively opaque. By using HREM, it’s possible to see remarkable detail of embryo heart structure and the technique allows ‘virtual dissection’ of the organ from any angle.

Tim explains: “The heart develops from what’s essentially a simple linear beating tube into a complicated multi-chambered organ with valves separating the chambers and controlling the flow of blood. This is a complicated change which occurs in three dimensions, therefore reconstructing accurate three dimensional models is a powerful tool in assisting our understanding of heart development.”
Dissolving curtains and growing armchairs. A giant, shimmering, interactive play mat for kids. A textile maze which represents how we think.

These are just a few of the inventive and intriguing ideas to come from the NOBELini Awards – pairings between young scientists and design students which celebrate scientific discovery.

The scheme is organised by the MRC Clinical Sciences Centre (CSC) in London and was inspired by the CSC’s 2006 Nobel Textiles project, which was exhibited at the Institute of Contemporary Arts last year. NOBELini kicked off with a ‘speed-dating’ session in May to pair up 30 scientists with 30 design students. The pairs competed for £2,000 prizes to develop design products that communicate and celebrate science across the themes of stem cells, energy and recycling, synthetic and systems biology, and imaging.

Award winners, announced on 25 September, included Ioannis Gousias and Elaine Ng for ALBERT in NeuroPlastic Land, Jay Stone and Berit Greinke for The Good, the Bad and the Negative and Ev Yemeni and Celine Marcq for Emotional Patterns: provocative projections. The entries were judged by a specialist panel of professional designers, scientists and journalists.

“Our basic concept was to use principles and ideas from brain imaging in neonates and young children to create stimuli for the brain,” explained Ioannis, a scientist at CSC. Design student Elaine added: “We designed a colourful, cheerful playground with real interactive element between the children and the fabrics.”

Inspired by the form and biology of neurones, the duo used light reflective and environment reactive plastic – or ‘flastic’ – to design a shimmering playground which moves and changes in response to wind and natural processes.

The Good, the Bad and the Negative originated from cell biologist Jay complaining about her negative experiment results to textile designer Berit over a pint in the pub. To Jay the results spelled failure because they proved her hypothesis wrong, but Berit saw negative results as a way of leading thoughts and ideas in new directions. Together they came up with ‘living textiles’ – including jackets made out of animal hair on which bacteria could be grown. Lack of bacterial growth would produce a thin jacket that could be used in summer, while successful growth would thicken the jacket into a warm winter garment.

NOBELini is the brainchild of Amanda Fisher, Director of CSC. Together with Carole Collet of the Central Saint Martins College of Art & Design, Amanda has pioneered new initiatives in bridging the arts-science divide. She says: “What we’d really like is to foster a long-term dialogue between professionals in the arts and the scientific community.

“The whole point is to celebrate discovery and engage the wider public in a dialogue between scientists and designers,” she added.

The winning entries can be seen at: www.csc.mrc.ac.uk/NewsEvents/News/Nobelini

The flastic interactive play mat for children, designed by Elaine Ng and Ioannis Gousias.
£17m boost to tackle the causes of neurodegenerative disease

UK research into neurodegenerative diseases received a significant boost in November. The MRC teamed up with the Wellcome Trust to jointly invest £16.99 million in three new research programmes on Alzheimer’s, Parkinson’s and motor neuron diseases.

The collaboration brings together multidisciplinary teams from around the UK who will aim to gain a better understanding of the causes of these diseases. Two of the scientists involved, Professor Peter St George-Hyslop and Professor John Hardy, have returned to the UK to conduct their research – a sign of the growing national momentum in this field.

Professor St George-Hyslop of the Cambridge Institute for Medical Research is leading the Alzheimer’s disease research programme. His team will use new methods from physics, biology and chemistry to work out how accumulation of amyloid beta and tau proteins in the brains of Alzheimer’s patients results in the death of brain cells. This should aid the creation of accurate and sensitive diagnostic tests and new ways to treat the disease.

The second group, led by Professor Christopher Shaw of the MRC Centre for Neurodegeneration Research in London, will study motor neuron disease and frontotemporal dementia. Recent research has shown that RNA-processing proteins are deposited in degenerating nerve cells and that rare mutations in three known genes cause a genetic form of these diseases. Using these discoveries, Professor Shaw and his colleagues will model key aspects of the human disorders, allowing them to explore fundamental disease mechanisms and identify new therapeutic targets.

The cause of Parkinson’s disease is the third programme to be funded, led by Professors Nicholas Wood, John Hardy and Anthony Schapira, at the Institute of Neurology, University College London. The collaboration will try to understand how ageing and genetic risk factors combine to cause the disease by looking at its genetics, identifying the biochemical pathways involved, and studying the biology of people at risk of the disease to understand its earliest stages.

Any questions?

The MRC’s Council is holding this year’s Open Council meeting on 15 December in Edinburgh. The meeting will be open to members of the public, industry and government representatives and provides the opportunity to quiz MRC Council members and Management Board about how the MRC’s budget has been spent over the last year and future priorities. The meeting will take place between 2pm and 4pm at the Macdonald Holyrood Hotel. Places will be limited. To register, email ellen.doughty@headoffice.mrc.ac.uk by 30 November.
Neuroscientists entertain festival-goers

Four MRC scientists could be found explaining their research in the unlikeliest of places this summer: the fields of music festivals.

Senior Scientist Dr Adrian Owen, Research Fellow Dr Jessica Grahn, and PhD students Rebecca Lawson and Aidan Horner from the MRC Cognition and Brain Sciences Unit went to the Latitude and the Secret Garden Party festivals this July with the outreach organisation Guerrilla Science.

Rubbing shoulders with fire jugglers, cabaret dancers and headlining musicians such as Thom Yorke and Jarvis Cocker, they explained their latest neuroscience findings to crowds of revellers up to 100-strong.

Adrian explained how, as we age, our capacity to remember changes and how we can improve our ability to retain information. Accompanied by images of brain function from his own research and films of a monkey mastering a spatial memory task and a toddler reciting a book, he explained what happens to the brain during ageing and how neurodegenerative diseases such as Alzheimer’s affect its structure.

Jessica, who is also a classically trained cellist, outlined what functional imaging studies have revealed about the effects of music on the brain, and how musical training can change the brain’s structure and function.

Meanwhile, taking an unconventional and interactive approach, Rebecca and Aidan explained the structures and functions of the neocortex with colourful brain-shaped cakes which were then eaten and washed down with tea.

All told, several hundred festival-goers returned home unexpectedly better acquainted with the latest neuroscience findings.
Harwell lecturer asks: Is human evolution over?

The guest speaker at this year’s MRC Harwell Lecture, an annual public lecture organised by the MRC Mammalian Genetics Unit (MGU), was Professor Steve Jones of University College London. In a fascinating talk entitled *Is human evolution over?* Steve described how human evolution is grinding to a halt because of a shortage of older fathers in the West.

Speaking to a packed room of scientists, school students and members of the public, he outlined how fathers over the age of 35 are more likely to pass on mutations. He identified the weakening of natural selection and decreasing randomness of the genetic mix as other factors in our evolutionary slow-down. Steve said: “Small populations which are isolated can evolve at random as genes are accidentally lost. Worldwide, all populations are becoming connected and the opportunity for random change is dwindling. History is made in bed, but nowadays the beds are getting closer together.”

The MGU’s Nanda Rodrigues, who organised the lecture, said: “It’s a pleasure to host speakers with such high accolades and yet who are able to connect with people in the wider community.” One enthralled school student agreed, saying: “It was so cool, I don’t know where the hour went.”

The MGU also opened its doors to five members of the local Women’s Institute, who took part in a day of science in the unit’s bespoke schools laboratory. The event, which was organised by MRC Harwell’s lab manager Dr Jo Jones, saw the ladies talk to scientists about their research and learn more about the MRC’s strict animal welfare policies. They then donned lab coats to check out microscopic images of cancer cells and had a go at extracting DNA from bananas. Jo said: “They all had a fantastic time and loved being able to carry out their very own experiments. It’s definitely something we’ll be doing again in the future.”
NONOGENERIAN DENNY REFLECTS ON 65 YEARS OF TB RESEARCH

A symposium was held in September to mark 65 years of clinical research into tuberculosis (TB) carried out by Professor Denny Mitchison, former Director of the MRC Unit for Laboratory Studies of Tuberculosis, which closed in 1985.

The special meeting was timed to coincide with Denny’s 90th birthday, and hosted by the International Consortium for Trials of Chemotherapeutic Agents in Tuberculosis. Talks by scientists in the field, including Denny himself, reviewed the past, present and future of clinical research into TB.

Denny has dedicated his career to TB, authoring over 400 papers. While working as a pathologist at London’s Brompton Hospital in 1946, he designed the first clinical trials of the antibiotic streptomycin in TB patients. In the 1970s he devised a short-course drug regimen which remains the standard TB therapy to this day. Specialist laboratories in Kenya, Uganda, Tanzania, Zambia and Hong Kong also owe their existence to his efforts. He retired in 1985 but continues to be involved in developing anti-TB chemotherapy at St George’s University of London.

Commenting on Denny’s achievements, Dr Declan Mulkeen, the MRC’s Director of Research and Training, said: “Denny has made an extraordinary and impressive contribution to tuberculosis research during his time at the MRC and in his later research. We wish him congratulations on both his 90th birthday and his continuing research career.”

EMBO HONOURS MRC SCIENTISTS

Several MRC scientists join a 66-strong list of leading international life scientists elected as members of the European Molecular Biology Organization (EMBO) this year, in recognition of their proven excellence in research. EMBO membership is a lifelong honour and includes high profile researchers from all fields of molecular life sciences. The MRC scientists elected this year were: Professor Tariq Enver and Professor Roger Patient of the MRC Molecular Haematology Unit; Professor Elizabeth Fisher of the MRC Centre for Neuromuscular Diseases; Dr Anne O’Garra and Dr Stephen Smerdon of the MRC National Institute for Medical Research; Professor Stephen O’Rahilly, Director of the MRC Centre for Obesity and Related Metabolic Diseases; and Dr William Schafer of the MRC Laboratory of Molecular Biology. Several scientists with former connections to the MRC were also among the new members: Professor Jonathan Flint of the University of Oxford; Professor Ronald Hay of the University of Dundee; Professor David Porteous, Director of the University of Edinburgh Molecular Medicine Centre; and Professor Robert J White of the Beatson Institute for Cancer Research.

VIROLOGY UNIT DIRECTOR RETIRES

Professor Duncan J McGeoch, Director of the MRC Virology Unit for the last 14 years, retired in September having taken the unit through a successful partnership agreement with the University of Glasgow. Professor Chris Preston is currently Interim Director.

L-R: Professor Janet Darbyshire and Professor Andrew Nunn of the MRC Clinical Trials Unit; Professor Denny Mitchison; and former MRC colleagues Dr Eric Edwards and Dr Amina Jindani.
MRC CELL BIOLOGISTS RANKED UK’S TOP THREE

Three MRC scientists have been named the UK’s most quoted cell biology authors over the period 1996 to 2007 in an analysis published in the Lab Times. Papers by Professor Sir Philip Cohen of the MRC Protein Phosphorylation Unit (PPU) were quoted by other scientists more than any other UK cell biologist, with 20,171 citations. Professor Alan Hall, Director of the MRC Cell Biology Unit at University College London until 2007, was placed second, and another PPU scientist, Professor Dario Alessi, took third place. A paper on protein kinase inhibitors authored by Professor Cohen and his team was also named the most influential paper in Europe, gaining 2,199 citations. Professor Cohen explained: “Protein kinases have become the pharmaceutical industry’s most important class of drug target, especially in the field of cancer.”

To read the full analysis see: www.lab-times.org

NEW DIRECTOR FOR NIMR’S WORLD INFLUENZA CENTRE

Professor John McCauley has been named the new Director of the World Influenza Centre at the MRC National Institute for Medical Research (NIMR). John joined NIMR’s Division of Virology in 2007, after several years at the Biotechnology and Biological Sciences Research Council Institute for Animal Health.

John replaces the outgoing Director, Professor Alan Hay. Alan has retired after 16 years as Director of the World Influenza Centre (also known as the World Health Organization Collaborating Centre for Reference and Research on Influenza) and 38 years in the NIMR’s Division of Virology. During his career at NIMR Alan published more than 200 research papers.

HGU STUDENT WINS EDINBURGH UNIVERSITY PRIZE

Katy Astell, a PhD student at the MRC Human Genetics Unit (HGU) in Edinburgh, has won Class Prize for the MSc Life Sciences programme. The prize is judged by the University of Edinburgh’s Life Sciences exam board, and is awarded to the top student for the year’s work across all nine Life Sciences Masters programmes at the University. Katy now works in the laboratory of Dr Andrew Jackson carrying out genetics research into hereditary neurological disorders.

COMMUNICATION AWARD FOR HNR SCIENTIST

Dr Susan Jebb, Head of Nutrition and Health Research of the MRC Collaborative Centre for Human Nutrition Research, has won the Society of Biology’s Science Communication Award for her outstanding and consistent contribution to communicating science to the public. The award, sponsored by Pfizer, includes a £1,500 prize. Susan has carried out extensive communication activities about obesity in society to a variety of audiences and her work has had significant impact and reach - especially with policy makers. She has shared knowledge of her science through writing articles for a popular magazine, giving public lectures, engaging with the media, playing a key role in government advisory committees, and giving cookery demonstrations while discussing affordable healthy eating.

MRC STUDENT BAGS PHARMACOLOGY PRIZE

Dr Sam Chamberlain, who formerly held an MRC Studentship at the University of Cambridge Behavioural and Clinical Neurosciences Institute, has been awarded the Junior Preclinical Wyeth Psychopharmacology Award for 2009 by the British Association for Psychopharmacology. He received the award for his research in healthy volunteers and in patients with impulse control disorders, which has shed light on how psychiatric medications exert beneficial effects on symptoms via actions on the brain.
**OBITUARY**

**John Eccleston**  
1943–2009

An international leader in research into small G proteins, which are involved in cell-to-cell signalling, John Eccleston was a group leader at the MRC National Institute for Medical Research (NIMR) for 25 years. He died on 30 September 2009.

John started work at NIMR in 1984, and authored nearly 100 papers during his career there. He was a group leader in the Division of Physical Biochemistry and retired earlier this year, though he remained a very active scientist until illness recently prevented him from working. One of his notable achievements includes pioneering a way of measuring how proteins bind and detach from one another using a technique called fluorescence anisotropy. These associations and disassociations of proteins are a key part of the maintenance of normal conditions inside cells and are difficult to monitor in real time in any other way. He was also renowned for his development and application of fluorescent probes.

John completed his undergraduate degree through the Royal Society of Chemistry’s Graduate Membership Education Programme at Warley Technical College and Liverpool Polytechnic. After graduating he took a technical post at Bristol University, working in a small research group, and later completing his PhD. He launched his independent scientific career in 1977 at the University of Pennsylvania, studying the enzyme mechanisms of the GTPases EF-Tu and EF-G.

Paying tribute, former NIMR colleague Dr David Trentham said: “No appreciation of John would be complete without a memory of the warmth, dry humour and friendship that he extended to all around him, and his careful and committed instruction and guidance to students at all levels.”

**OPPORTUNITIES**

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<tr>
<th>FELLOWSHIPS</th>
<th>Deadline date</th>
<th>Panel meeting</th>
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<tbody>
<tr>
<td>Career Development Award</td>
<td>29 January 2010</td>
<td>22 and 23 July 2010</td>
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<tr>
<td>Clinical Research Training Fellowship</td>
<td>22 January 2010</td>
<td>7 to 9 July 2010</td>
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<tr>
<th>BOARD</th>
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<th>Panel meeting</th>
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<tbody>
<tr>
<td>Infections and Immunity</td>
<td>27 January 2010</td>
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<tr>
<td>Molecular and Cellular Medicine</td>
<td>20 January 2010</td>
<td>30 June and 1 July 2010</td>
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<tr>
<td>Neurosciences and Mental Health</td>
<td>10 February 2010</td>
<td>21 and 22 July 2010</td>
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<tr>
<td>Population and Systems Medicine</td>
<td>3 February 2010</td>
<td>14 and 15 July 2010</td>
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Inspiring the next generation of scientists

Successful scientists often recall formative experiences at school which inspired them to take up a career in science. This summer, several MRC units hosted over 30 school pupils in their laboratories with the aim of igniting such enthusiasm for science.

The placements were organised by the Nuffield Foundation, which campaigns to create inspiring opportunities for year 12 school students (age 17 to 18) to gain experience of working in research. MRC locations which took part this year were the MRC Collaborative Centre for Human Nutrition Research, the MRC Cell Biology Unit, the MRC Mammalian Genetics Unit, the MRC Human Genetics Unit, the MRC Clinical Sciences Centre and the MRC National Institute for Medical Research (NIMR).

At NIMR, the placements were organised in the format of a summer school, which created an inclusive, collegiate atmosphere for participating students. Michael Sargent, who organised the placements, explains: “The students really engage with the ideas and technology used in their host laboratory. Supervision of novices can be demanding, but the post-docs and graduate students who generously give up their time enjoy developing their managerial skills and are delighted when their students have an interesting story to tell at the end of the placement.”

He adds: “Almost all the students go to the best universities and several former students are now working for their PhDs. The value of the experience becomes apparent later when they attribute their successes to our summer school.”

Units interested in hosting next year’s placements should make arrangements through the Nuffield Foundation regional coordinator by visiting www.nuffieldfoundation.org/go/grants/nsbsc/page_399.html