In partnership with...

METRO FREE

MRC Medical Research Council

Max Perutz Science Writing Award 2012

Shortlisted essays

www.mrc.ac.uk/Sciencesociety/Awards

More on the prize

Professor Max Perutz, who died in 2002, was a world-renowned scientist who helped to found the Medical Research Council's Laboratory of Molecular Biology in Cambridge. He encouraged young scientists to communicate their research in plain language to the public.

The Max Perutz Science Writing Award is aimed at supporting and rewarding scientists to convey the importance and excitement of their work in an accessible way.

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

Tel: 020 7636 5422
Fax: 020 7436 6179

www.mrc.ac.uk

Published October 2012

Contents

Winner

Runner-up

Highly commended

Shortlisted

Winner

Studying blindness? There's an app for that

Andrew Bastawrous

Everything is hazy; I can't even see my glasses. I keep my eyes closed; it doesn't seem to make much difference opening them. My hand feels clumsily around the bedside table, knocking my mobile phone to the floor, and eventually I come across my glasses. On they go, and I can see again. Those brief few seconds as I awake each morning serve as a continual reminder of how much I value my sight.

Many people fear losing their sight more than any other sense. I am fortunate to have perfect vision when wearing corrective glasses or contact lenses, and privileged to be in a profession (ophthalmology) where centuries of research and practice have brought us to a point where much of blindness is curable or preventable. There is no feeling like it: when the eye patch comes off someone who hasn't seen for years, witnessing their sheer wonder as they take in their surroundings and their anticipation to see faces that have become voices and places that have become memories.

Incredibly, despite 80 per cent of blindness being curable or preventable, around 285 million people in the world are visually impaired. The majority of these people live in developing countries and have no access to suitable healthcare. Africa has the greatest disparity in numbers needing treatment and specialists available to provide it. In the UK we have 3,600 ophthalmologists compared with only 86 in Kenya, where I will be moving later this year.

There are many factors that can lead to blindness, and many complexities that lead to a society unable to deal with the burden that comes with a disability. Although each individual goes blind very much alone, there are shared stories and features, the understanding of which can enable prevention or access to curative treatment. Some of the major questions include asking how many people are blind? Who are they? Where do they live? Why are they blind?

Gathering this type of information is known as epidemiological research, a method of describing the characteristics of a population. This information is then used to inform policy-makers and health workers to benefit individuals on a large scale.

Performing such a study can be a logistical nightmare, as well as extremely time consuming and expensive. My study involves the retracing and examination of 5,000 people across a district in Kenya known as Nakuru. Taking what is effectively a fully staffed eye hospital (a team of 15 people), fully equipped (with more than £100,000 worth of heavy and fragile equipment) to remote villages, many of which have no road access or electricity supply, is extremely challenging yet absolutely vital if provision to prevent needless blindness is to be put in place.

As I pondered and planned for the challenges that lay ahead, I've had the continual thought that there must be an easier way to gather this information, a way that is less expensive and resource hungry, and therefore could be used on a much wider scale. Then it dawned on me … I use my smartphone for everything nowadays, from checking train times, navigating in the car, taking and sharing photos, not to mention using it as a phone and speaking to people.

This has led me to develop a set of gadgets and applications making it possible to use a modified smartphone (I call it the 'Eye Phone') to measure someone's vision; check their refractive error (glasses prescription); take photos of the back of the eye for diseases such as diabetic retinopathy, macula degeneration and glaucoma; and check for the presence of a cataract. All the data is then stored on the phone and can be shared with specialists anywhere in the world to provide expert diagnosis and treatment plans in even the most remote locations. Individuals are locatable on an interactive Google Map, and can be retraced and contacted to arrange treatment or follow up.

It is important to check the new device works and doesn't miss people who need help. To see how accurate the new device is, I will test the phone on the same 5,000 individuals undergoing the detailed examinations that use the gold-standard, state-of-the-art hospital equipment. We will then be able to compare the two methods and see how many of the study population we would have correctly picked up as having sight loss (as well as the reasons why) and if we would have missed anyone.

At one-fiftieth of the price and with only one non-specialist needed to perform the test, the examiner can go to the patient rather than the patient waiting for someone who might never come. It could be that those in remote and resource-poor places, silently losing their sight, could be a text message away from help.

Winner

I am the drug

Ketan Shah

I am the drug and there is a sting in my tail. I have gone by many names as I have developed, but my most user-friendly is Indium-EGF. I want to show the world that I am special.

They are trying not to put too much pressure on me, but I know they are excited as they get me ready to go into a person for the first time, hopefully in 2012. They are supposed to be detached and scientific; they are not supposed to be excited. But I know they are.

I come in two parts, stuck together in a clever way. My head is called EGF, and my tail Indium-111. EGF stands for epidermal growth factor. The human body can make EGF but I was made in a test-tube. I'm their test-tube baby. Some cells – some of the tiny building blocks of the body – have what are called receptors for me: EGF receptors. These sit on the cells and are particularly sticky only for EGF. So when I'm injected into the body, rushing around in the blood, oozing into all parts of the person I'm in, my head sticks onto the cells with lots of EGF receptors.

Sometimes cells that go wrong and turn into cancer have too many EGF receptors. Cancer is definitely not user-friendly. But cancers can be checked to see if they have lots of EGF receptors. You'll see where I'm going now – I've been designed to treat people with just those cancers. I'll be no good for other people with cancer (whose cells do not have the receptors), so there's no use wasting time and money giving me to those people. I'm special because I'm personalised.

So what do I do when I get there, sticking to the cancer? Remember my Indium-111 tail? Well, Indium-111 is radioactive! I told you there was a sting in my tail. Radioactivity sounds dangerous, and it is, but the trick with using radiation as a treatment (what they call radiotherapy) is to target it to the cancer while avoiding as much of the normal body as possible. Radiotherapy machines physically point radiation at the cancer, and they do it pretty accurately. I'm different because I am injected into the bloodstream, and it is the EGF that makes sure I get to the right place and I stay there. I'm special because I'm targeted.

EGF receptors are really useful because they actually pull me into the cancer cell so my radioactive sting can work. Indium-111 only destroys things very close to it, so I get it right next to the cancer cell's DNA to kill the cell. They've spent years putting me with cancer cells in test-tubes, watching me go into the cells and kill them. I can see why they are excited. I'm special because I'm deadly to cancer cells.

Another great thing about Indium-111 is that you can see it on special body scans called SPECT scans. So after I'm injected into people with cancer, SPECT scans will be done to make sure I'm in the right place. It is amazing to think that when I'm in there, sticking to the cancer, someone can actually watch me. I'm special because you can see where I am.

It seems so simple, I can hardly wait to get started. But I'm not so simple. Being radioactive, everyone has to be careful with me. That goes for the people who make me, the staff on the wards, the person I'm going into and their friends and relatives. It means a lot of planning and measuring before my first try-out, my clinical trial. I never forget that the scientists who thought of me have had to be careful ever since they put me together.

The most important thing about my first trial is not whether I work, but whether I'm safe enough to use. That may seem odd, but it doesn't matter how deadly I am to cancer if I'm deadly to everything else too.

So in I'll go, into the blood, zipping round until I stick. My radioactive tail will be glowing on the SPECT scan, more like a firefly than a bee, and I'll stick to the EGF receptors on the cancer. I'll go into the cancer cells, and attack them with my sting. I am special. I am Indium-EGF. I am the drug. And there is a sting in my tail.

Highly commended

Curing the ‘two-bucket’ disease

Sarah Caddy

One minute you’re feeling great, and the next the contents of your intestines are coming out of both ends. This is norovirus, the horrible cause of winter vomiting disease. One in twenty people in the UK suffer from the effects of this tiny virus every year. It is described as causing ‘mild gastroenteritis’ but if you have had it, you will know it is anything but mild. And aside from the individual trauma, it is a financial disaster to the UK. An estimated £100 million is spent by the NHS each year due to ward closures forced by norovirus outbreaks.

Surprisingly, norovirus is closely related to poliovirus, a virus on the brink of extinction thanks to international vaccination. So why haven’t we managed to eradicate norovirus yet? Why can’t we treat it? Is prevention ever going to be possible?

It turns out that norovirus is very elusive when trying to grow it in cells in the lab. No experiments have managed to make norovirus replicate naturally inside experimental cells. In contrast, polio was first grown in cells in a lab in 1948, allowing extensive research to be carried out. A polio vaccine was developed just four years later, and 2012 may be the last year that poliovirus exists.

So if norovirus can’t infect cells in a lab, what other options are there for research that might lead to control of the disease? The first investigations into norovirus involved a desperate bunch of volunteers, who would drink samples of filtered diarrhoea from infected people. This improved understanding of the transmission and effects of infection. In some people vomiting and diarrhea can develop within as little as 10 hours, whereas other people are surprisingly resistant to disease.

However, to be able to develop anti-norovirus drugs, we need to understand what norovirus does to individual cells in a human. Viruses cannot replicate by themselves, they have to get into cells to hijack the normal cell machinery. They then have to assemble their freshly replicated genes into a newly made protein coat, and escape out of the first cell before infecting the next. How on earth do noroviruses manage this? Studying disease in an entire human cannot even begin to tackle this question.

Norovirus research took a leap forward in 2003 when a similar virus was found to infect mice. Over 24 per cent of lab mice in Europe carry this type of norovirus, but only those with a deficient immune system get ill. Studying such mice, which get diarrhoea but interestingly don’t vomit, is giving many insights into the infection in humans. And helpfully, this kind of norovirus can infect cells in the lab. So that is what we work on. We can visualise the virus within cells using microscopes and we can manipulate specific viral genes and see what happens to infection.

We have also started to identify specific proteins in the hijacked cells that the virus needs to manipulate in order to survive and replicate. These cell proteins have the potential to become unusual drug targets.

Most drugs that treat infection by bacteria or viruses act by binding directly to the invading bug. They then block their action and with the help of the human immune system, the infection can be cured. However, resistance to anti-microbial drugs does develop. Norovirus in particular can mutate at an annoyingly fast rate. Any fortuitous mutations which stop the drug having an effect spread rapidly through a virus population. This is survival of the fittest at very high speed.

But what if drugs target key human cell proteins needed by the virus, and not the virus itself? Drug resistance takes much, much longer to develop in humans. The time from birth of a human to delivery of their own baby can be more than 50,000 times slower than the 12 hours it takes norovirus to get into cells and produce ‘offspring’. And our genes are replicated much more faithfully than those of norovirus.

This principle of developing drugs to target human cell proteins has already been applied to treating HIV – the promising new drug maraviroc binds a cell protein and blocks HIV getting into cells. Our lab aims to prove that a similar strategy can be applied to treating mouse norovirus first, and then the disease in humans.

So, hope for the future? The title of this article is a little fanciful; norovirus is unlikely to become treatable by the end of a three-year PhD. But every week, more information is gathered and published by norovirus researchers across the globe. And every piece of information learnt from molecular research brings scientists a step closer to developing anti-norovirus drugs. Wouldn’t it be nice if you could avoid that norovirus outbreak in hospital, or in your office, or on your cruise, simply by taking a tablet?

Highly commended

Fighting Alzheimer's disease? Get the immune system on board

James Fuller

Imagine living with the knowledge that over the next decade your brain will be slowly destroyed by your own body. As neurons are snuffed out like candles, what will you lose next? Will it be precious memories? The ability to perform an everyday task? Perhaps a facet of your personality? Your family and friends will have to watch helpless as the person they love is slowly eroded away.

Imagine now finding out that with all of our medical expertise there is nothing we can do. Not one treatment that can slow the course of this deterioration. This is a reality for someone diagnosed with dementia.

Alzheimer's disease is the most common form of dementia with an estimated 20 million sufferers worldwide, incurring a £400 billion cost to healthcare services. These figures are already frightening, but our population is getting older and the number of people with dementia will double in 30 years. The only way to prevent this is to develop new drugs to combat this devastating condition. Current therapies work by increasing certain chemicals in the brain; allowing neurons to function but not stopping them from dying. Despite a lot of research and trials of potential drugs not one therapy has been found that can slow the rate at which neurons die.

So, what is holding us back from developing these new therapies? There are many problems but perhaps the biggest is that we do not fully understand how this disease works, and how to model the disease in the lab. This may be the reason why so many drugs have failed in clinical trials – clearly what we need are new approaches. By looking at the blood or brains of patients we can get an idea of what goes wrong in Alzheimer's disease and therefore design potential new treatments.

From these studies we now know that a protein called Aβ for an unknown reason builds up in the brain of Alzheimer's patients, forming large clumps called plaques. One idea suggests that the buildup of these plaques causes the destruction of neurons, and therefore removal of these plaques could protect the neurons from dying. As a result of this observation, therapies are being developed to break up these deposits or reduce the amount of Aβ produced.

One of the most effective and revolutionary ideas has been to "vaccinate" Alzheimer's patients against these plaques. This is a very similar process to what happens when you are vaccinated against a disease like tuberculosis (TB). The TB vaccine teaches your immune system to recognise and remember a dead version of the bacteria which causes the disease.

This means that when you encounter the real bacteria, immune cells can fight off the infection. During this process, antibodies are being produced that bind to the bacteria; the immune system is then activated to engulf and destroy the antibody-coated bacteria preventing you from getting ill.

At this point you may be wondering; what does this have to do with Alzheimer's disease?

Scientists can produce antibodies in the lab that bind to almost anything: a virus, a cancer cell or even the plaques we find in the brains of Alzheimer's patients. When an Alzheimer's patient is treated with an antibody that binds to plaques, these deposits become coated in the antibody. The subsequent immune response clears the patient's brain of these potentially dangerous plaques.

Fantastic, so we can now use these antibodies to help patients? Well not quite... while the antibody efficiently clears the plaques from the brain, the success has been tempered by side effects. To remove the antibody-coated plaques it is necessary to activate cells from the immune system and this can cause inflammation in the brain. While this inflammation is actually helpful in removing bacteria such as TB, inflammation in the brain can have severe consequences. Inflammation in Alzheimer's patients occurs around blood vessels in the brain causing damage and bleeding, potentially inducing further deterioration and memory loss. For my PhD project I am developing new antibodies to prevent these nasty side effects. By making tiny adjustments to the structure of antibodies we can control how the immune system responds to the therapy. We are hoping that these new antibodies remove the plaques without inducing further damage to the brain.

Advances in healthcare have greatly increased the length of time we live, however the quality of life we experience in our older years has not increased at the same rate. Dementia is one of science's biggest challenges and the problem will only get worse if new therapies are not found soon.

Harnessing the power of the immune system using antibodies may be one of these therapies, and this has already been an effective strategy in the treatment of bacterial infections, cancer and rheumatoid arthritis. If we could make this form of therapy safe for the treatment of Alzheimer's disease, it would be a good step forward to reduce the suffering of millions of patients worldwide.

Highly commended

The transcription factor: a key to brain repair

Ben Martynoga

Your skull contains one of the most sophisticated computing systems in the universe. Your brain can read and understand the words on this page, it can empathise with other humans, and it is even aware of its own existence. Nothing we have built or discovered comes close to this competence. Yet brilliant as your brain is, it has one fatal flaw: it is terrible at regenerating itself.

Cut your hair and it keeps on growing. Cut your skin and it rapidly heals. But once a brain disease like Alzheimer's disease sets in and starts to kill off your brain cells, the damage gets progressively worse, with devastating effects. And of course, as our families and communities live longer, age-related dementia and memory loss are ever more common.

Wouldn't it be amazing if your brain, more like your hair and skin, could go on replacing damaged or lost cells throughout your life? In my research I want to understand how the cells in the brain function with the hope of making this possible.

Scientists are already able to take cells from a mouse's brain and grow them so they go on dividing and replacing themselves forever. These cells are a type of stem cell. It's hard to know what gives stem cells their unique regenerative abilities. My work on these cells should help future doctors use stem cells to replace brain cells lost through damage or disease.

All cells contain the same set of genes. So the fundamental difference between a skin cell and a brain cell is not which genes they possess, but which genes they actually use. The process of turning specific genes on and off is achieved by tiny switches within cells which we call transcription factors.

Just as putting the correct combination of words into a Google search query delivers the result you are looking for, putting the correct combination of transcription factors into a cell activates the genes needed for that cell to work properly.

By experimenting with lots of different transcription factors I have identified a small number that act together to stimulate brain stem cells to multiply.

So how might this knowledge actually help us to treat anyone? There are two main possibilities. The first is using the transcription factors to control the activity of existing brain cells. Although they are very rare our brains do contain some stem cells that are able to multiply themselves and make new brain cells, but as we get older they fall dormant. By understanding the combination of transcription factors unique to multiplying stem cells we have the potential to activate dormant brain cells when and where they are needed.

The second possibility is even more remarkable. We can use these same transcription factors to totally transform one type of cell into a completely different type. For example, scientists have already succeeded in converting skin cells into brain cells. This has radical implications. Theoretically it should be possible to take a sample from a patient's skin and create new brain cells on demand. Since these cells come from the patient themselves, they are more likely to become properly integrated and less likely to be rejected.

However, at this stage more knowledge is still required before these techniques reach clinical trials. In the first technique, we still need to learn how to control which dormant cells become activated, and perhaps even more importantly, how to stop them. Unless we can do this there is a risk that brain tumours would develop. This is also a risk of the second technique, which also comes with the added complication that it is very difficult to be sure that exactly the correct type of brain cell has been created before they are actually transplanted.

Your brain is undoubtedly the most complicated organ in your body. This is what gives it its extraordinary power. However it is also what makes it so enormously difficult to treat. We can't currently predict when these techniques will be ready for use, but the work that I am doing, with colleagues all around the world, is undoubtedly key to making brain repair a reality.

Eliza and the Great Spaghetti Monster

Rodrigo Braga

The human brain is the most complex object in the known universe. With it we have built entire civilisations and harnessed the power of nature. Yet despite their amazing complexity, all brains begin life as a tiny bundle of cells that divide, migrate and miraculously wire themselves up into the thinking machines that make us who we are. The fact that it happens at all is almost as astounding as the finished product itself, but it doesn't always work out as Mother Nature intended.

Tucked up in her crib at the Neonatal Imaging Centre of Hammersmith Hospital, newborn baby Eliza is sleeping through another magnetic resonance imaging (MRI) scan. Around her head, the scanner machinery wails and screams with high-pitched ululations, but she sleeps peacefully, ears protected by tiny muffs. Eliza was born prematurely and her doctors are making sure that her little brain is growing normally. In her short 10-week life, she has been inside the scanner more times than most of us ever will. But today is different. Today we are using a new technique called Diffusion Tensor Imaging (DTI) to help unravel the mysteries of brain development. And that is a huge task.

The human brain contains 1,000 trillion connections between 86 billion neurons (neurons are what we really mean when we say 'brain cells'). Each neuron has a long thin arm called an 'axon' that it uses to send messages to other neurons that could be on opposite ends of the brain. Connecting them all means criss-crossing the brain with axons.

To give you a sense of the resulting confusion, imagine a planet (let's call it 'Braintopia') that is packed with 10 times more people than planet Earth. Imagine that every Braintopian has to make regular long distance calls to an overbearing mother on the other side of the planet. On Earth this would be easy, but Braintopians haven't discovered mobile phones or landlines yet. Instead, all they have are those cup and string phones that children play with here on Earth. Each Braintopian carries their own paper cup, and trails along a string that stretches around the globe to mum. Simple!

It might seem absurd, but this is actually how neurons communicate, through a direct physical connection. In order that you can wriggle your toes, a daring axon made the journey from the top of your brain to the bottom of your spinal cord to pass the message on to your legs. Now if a single Braintopian trailing a string like an umbilical cord sounds ridiculous, picture the mess that a whole city-full of them would make, strings tangling through the streets like a Great Spaghetti Monster. Or worse, imagine the chaos of an entire planet-full of intercontinental strings. The resulting ball of yarn would be monolithic!

The brain has a similar connection problem, but it maintains order by packing the axons heading in the same direction together into thick fibres called 'white matter tracts'. Recent research suggests that the normal development of white matter is an important indicator that a baby's brain is healthy. If a white matter tract doesn't develop properly, the brain regions connected by that tract cannot communicate with each other. This can lead to serious physical and learning disabilities. If doctors could assess a baby's white matter early on, they could check the connections are healthy and in place, and give special attention to the infants that need it. But doing this when the brain is sealed inside a baby's head is extremely challenging. Luckily, this is where DTI comes in.

Back in Hammersmith, Eliza's scan is almost done. The DTI procedure uses the MRI scanner's powerful magnets to spin the atoms in Eliza's brain on the spot, like pirouetting ballerinas. Atoms spin frantically anyway, but when placed inside a magnet they align their spin with the direction of the magnetic field. And so the ballet begins. In this synchronised dance, each atomic twirl sends out a tiny radio signal that the scanner uses to work out where the atom is. From this, we can find atoms that are attached to water molecules and trace them as they float around Eliza's brain. The brain is 70% water, and white matter tracts act like miniature hosepipes, channelling water along them. By following the movement of water we can therefore visualise exactly where the white matter tracts lie. Using this principle we have created a white matter atlas for babies, to help doctors recognise abnormal brain development.

Eliza continues to sleep while the scanner diligently chugs away. This short 20-minute scan will produce a beautiful map of her own Braintopia without hurting her in any way. By comparing Eliza's map to our atlas, doctors can tell if her fibres are healthy, and give her the best possible start in life.

The inflamed brain: why my research matters

Hannah Buggey

Picture yourself in the shower. Now imagine that familiar feeling when the water starts to build up around your feet, and you're racing to finish washing out shampoo before water spills over the edge of the shower tray. This clogged up drain is similar to what happens during a stroke.

In your plumbing, a hairball sticks together with bits of soap and becomes lodged in the U-bend. In stroke, a clot often forms from a build-up of fatty plaques in our blood vessels – the ones we're always being told can be avoided by eating cholesterol-lowering margarine. This clot can break away and travel through your blood into your brain where the vessels have lots of twists and 'U-bends'.

When a clot gets stuck here, the areas of the brain the blood is feeding are cut off from their supply of oxygen and nutrients. In the same way that you need to act fast to stop the shower water spilling over the edge, you need to act fast after a stroke. Brain cells can't cope without oxygen, and during a stroke two million of them die every minute.

I bet you know at least one person who's had a stroke. That's because it's a huge problem: in the UK someone has a stroke every five minutes. Despite this, there's still only one medicine available. When your shower gets clogged, you pour down drain-unblocker and it breaks up the hairball. This is essentially how the stroke drug tPA works. It gets infused into your blood and travels to the blockage. Here, it dissolves the clot, restoring blood flow to the brain.

So why does my research matter? The trouble with tPA all comes back to acting fast. Doctors can only give you tPA if you get to the hospital within 4.5 hours after having a stroke.

Shockingly, only 20 per cent of patients make it in time for this window. Just like the shower flooding if you act too slowly, if you take tPA more than 4.5 hours after having a stroke you risk a vessel bursting and flooding the brain with blood. This can cause far more damage than the initial stroke.

To address this problem with tPA, scientists all over the world are trying to find better ways of treating stroke. In my research, I'm looking at anti-inflammatory drugs. You might think that this sounds strange, and that inflammation has more to do with arthritis and sprained ankles than it does with stroke. In fact, after a stroke your brain becomes really inflamed, and this can cause more damage than the initial loss of oxygen.

Think of the nasty pus you see around an infected cut or in a spot that you can't resist squeezing. This pus is made up of white blood cells, which are like the body's army for fighting infection and injury. There are loads of different types of white blood cells, and the ones I'm interested in are called neutrophils.

Normally, there aren't any neutrophils in the brain because they're kept out by a strong wall-like structure called the blood-brain barrier. After a stroke this barrier gets damaged, and over the following days more and more neutrophils get into the brain. Although neutrophils are normally important in fighting infection, in the brain they can be damaging and release substances that can break down the barrier even more. Like a domino-effect, this lets more neutrophils get in, and the damage keeps progressing.

For my research, I'm looking for ways of stopping neutrophils getting into the brain after stroke so we can limit the on-going damage. The drug I'm testing acts like a bouncer at the blood-brain barrier and stops neutrophils being able to pass through. There's lots of evidence suggesting that stopping neutrophils might help people have less brain damage and make a better recovery after stroke.

Although lots of scientists like me are trying to make better drugs to treat stroke, like with anything, the best cure is prevention. Young, fit and healthy people don't tend to have strokes. Normally, stroke patients have other things wrong with them like high blood pressure, diabetes, high cholesterol and obesity. All of these conditions cause an inflammatory response in the body, meaning there are more neutrophils and other white blood cells hanging around. If you have a stroke now, the additional inflammation caused on-top of this can cause devastating damage to the brain.

Stroke patients who also have diseases like these are more likely to die or become disabled. That's why trying to limit inflammation is important, and that's why my research matters. So if you're reading this in Metro, sitting on the bus and eating a packet of crisps, maybe consider ditching the crisps and getting off a couple of stops early. Trust me, your brain will thank you.

The road to cancer: as simple as ATG...

Holly Callaghan

Spelling mistakes – we all make them. Usually a result of carelessness, a 'g' might become a 'c', an 'a' might become a 't'. If you're writing a letter maybe you'll correct or cross out the offending word, or even scrunch up your paper, throw it away, and start again. Our cells have a remarkably similar distaste for misspellings. The genetic alphabet is made up of only four letters: A, T, G and C. Cells must diligently copy their DNA, all six billion letters of it, in a precise order so that they can replicate. Some cells, such as skin cells, replicate every half hour, while others, for example brain cells, divide once then never again. Think for a moment about your colon. The surface of this impressive 7.5 metre long digestive organ completely renews every four days – that's a lot of dividing cells!

Of course, no cell is perfect, and mistakes happen. The enzyme in charge of copying your DNA might copy the wrong letter, or environmental agents like UV light might alter a letter, which can be replicated when the cell divides. But, much like the auto-correction function on your computer, controls are in place to stop these mistakes becoming incorporated into the finished product. DNA repair mechanisms recognise faults and fix them – most of the time. If a mistake is not corrected it will be passed down to the daughter cell. That's when a simple mistake becomes a mutation.

"But what harm can one little teeny tiny change possibly do?" you might ask. Well that all depends on where it is. The majority of the time the error will occur in 'junk' DNA, or DNA which doesn't code for a gene, so the mutation will quite happily stay with you, doing nothing, for life. The trouble lies in mutations which occur within your genes. Take, for example, p53 (named because it's a protein and its molecular mass is 53 – terribly unoriginal). It's been nicknamed "the guardian of the genome", due to its role in preventing mutations. As you can imagine, if the gene which codes for p53 becomes mutated then the entire genome of that cell becomes unstable, vulnerable to further mutations.

It will usually take about six mutations in important genes like p53 for a normal cell to become cancerous. This doesn't seem like a lot, but in reality it is very difficult for a healthy cell to become malignant. The majority of the time, one or two mutations will cause the cell to self-destruct – sacrificing itself for the health of the organism.

The amazing self-renewal capability of the colon is rigorously controlled by special proteins working together in a function known as Wnt (pronounced 'wint') signalling. The importance of Wnt signalling is emphasised by the fact that the majority of colon cancers contain mutations affecting this process. These mutations keep Wnt signalling switched 'on', sending endless signals for colon cells to grow and divide. Mutations in Wnt signalling may go unnoticed for many years, existing as non-cancerous growths, or polyps. It is only when further mutations accumulate that these small growths become dangerous.

In an average late-stage colon cancer there will be about 75 mutated genes. The majority of these will be inconsequential – mutations that have been picked up by the cell on its journey to cancer but don't actually contribute towards cancer. These are known as "passenger" mutations. I am interested in identifying "driver" mutations – mutations that directly contribute towards the development of cancer.

The aim of my PhD is to scour the genome of colon cancer looking for mutations. I am concentrating on one gene in particular, a receptor which is known to work alongside the Wnt signalling pathway and encourage the growth of colon cells. I've already found a few mutations in this gene in colon cancer samples, and I'm working to figure out what these mutations do and how they contribute to cancer.

How does all of this help in the fight against cancer? If we understand what genetic changes occur in cancer then we can identify new drug targets. For example, a mutation may activate a protein, resulting in it constantly switching on genes that encourage a cell to grow and divide. If this mutation exists in a cell that already contains a background of other mutations, for example in genes that control the self-sacrifice of damaged cells, then the cancerous cell will not self-destruct, but will flourish uncontrollably. If we can create drugs that will inhibit the activated protein then we can slow down the growth of the cancerous cells, or even kill the cancer cells all together.

If I can help identify a drug target that might help treat colon cancer then all this spell checking will be worth it...

Cell city

Nicola Hodson

I'm sitting in Cambridge on a Monday morning observing the relentless chaos of commuter traffic. Cargo-bearing vehicles zip in, out and around the city, efficiently delivering goods to their required locations. All this hustle and bustle is essential to the integrity of such a busy city, without it everything would grind to a halt. I pull my chair back from the microscope in wonder, for what lies before me is not actually a city, but a single human cell.

My research focuses on how vehicles transport cargo into, out of and around a cell. A cell, just like a city, needs particular things to keep going. In a city, food needs to be delivered to supermarkets or to families who have ordered their groceries online. Likewise, a cell needs to bring nutrients inside and just like the supermarkets and the online shoppers, it can select exactly what it wants delivering and when.

When the cell requires a particular substance from its environment, for example iron, it can send chauffeurs up to its surface; we call these 'receptors'. These wait around patiently until their specific cargo drifts by. Once the receptors have collected their cargo, something fascinating happens. The cell surface at the location of the receptor begins to bend inwards, further and further, until it completely detaches, forming a bubble-shaped, cargo-containing vehicle. This vehicle is coated in an intriguing protein called 'clathrin' which is stiff and helps the vehicle to maintain its spherical shape whilst giving it the appearance of a tiny football.

Once inside the cell, these clathrin-coated vehicles need to deliver their cargo to the correct location. Considering how many different things a cell needs, a complex and highly developed infrastructure is required to organise it all. Consequently each cargo enters the cell stamped with a unique 'sorting signal', which is not dissimilar to a postcode that you would write on a letter or a parcel. This allows cargo within the cell to be sorted in a way akin to what occurs at a Royal Mail sorting office and distributed to exactly where it is needed via an efficient team of delivery proteins.

There are a whole host of different proteins involved in the cargo-sorting process from those that help the cell surface to bend inwards, to 'motor proteins' that give vehicles the power to zip around the cell to far-flung locations. My research focuses on identifying new proteins involved in this infrastructure to allow us to further understand how this complex cellular city functions. The reason behind this is because if the sorting network doesn't work, disaster quickly ensues. It only takes one protein, even one with a seemingly small role, to acquire a mutation and our cargo doesn't get where it needs to go. Imagine if the supermarkets or petrol stations stopped receiving deliveries, the city would soon be in chaos.

To identify these new proteins, I'm taking a systematic approach. I remove proteins from the cell, one by one, and look for cargo not arriving where it should. Much of the time when I get rid of a particular protein, nothing happens but sometimes all the cargo and receptors get stuck on the surface of the cell and I know I've destroyed something that's involved in the delivery process, like a postman or a taxi company. Then I can put the defective cells under the microscope and start investigating the function of this mysterious protein more thoroughly to find out exactly what it is and what role it plays.

Studying such a fundamental cellular process allows us to slowly, piece by piece, build up a picture of the cell's interior. Nothing illustrates the importance of the cell's trafficking infrastructure more than the fact that loss of many of the key proteins results in death before birth. Consequently, the more we learn, the more we can apply the knowledge to understanding human diseases.

A multitude of viruses and bacteria hijack the cell's transport system in order to invade and cause disease, including the flu-causing influenza virus and the AIDS-causing human immunodeficiency virus. Not only this but defective cargo trafficking in neurons, the cells of the nervous system, has been linked with learning disabilities. Therefore if we understand more about which proteins are involved in the trafficking process, we can learn how to effectively defend our cellular city.

Knowing me, knowing flu

Sarah Smith

You're 100 feet below sea level, crammed onto a London tube full of commuters, all breathing in the same stale air. The tickle in your nose is becoming too hard to ignore, but where's a tissue when you need it? Aaaachhhhhhooo! Oops. You just sent 20,000 salivary droplets hurtling across the carriage. If you're infected with influenza there could be thousands of viral particles in that sneeze. If everyone in your carriage inhaled a few of these particles, the outcome could be dramatically different for each person. Why? That is where my research matters.

After a virus infects a person, the severity of the disease that develops is influenced by both the virus and human genes. A gene is a sequence of DNA nucleotides (A, T, G or C) that provides the instructions for a cell or virus to assemble a protein, the bricks and mortar of the cell. Both humans and viruses have been evolving together over time in a sort of arms race, one gaining a small advantage over the other, and then the other hurrying to catch up. This notion was inadvertently, but eloquently described by the Red Queen in Lewis Carroll's novel Alice in Wonderland, 'It takes all the running you can do, to keep in the same place. If you want to get somewhere else, you must run at least twice as fast'.

My research aims to understand the tools our body uses to fight off viral infections, and to identify how the virus makes small changes to its genes to evade the human immune system. Although influenza causes mild symptoms in most people, it can be lethal to some. It also has an enormous economic impact; the estimated financial burden of influenza epidemics in the United States alone amounts to $87.1 billion each year.

In the first few hours after an influenza infection, the sentinel cells patrolling the human body detect the invading influenza virus and release an important chemical called interferon. Release of interferon is a warning signal detected by receptors on neighbouring human cells that causes hundreds of anti-viral genes to switch on. I am studying one of these genes: IFITM3.

During a preliminary experiment, I increased the amount of IFITM3 protein in cells and the degree of infection by influenza was dramatically reduced. We then discovered that mice missing this protein became very sick when infected by influenza, whereas those with the protein recovered quickly.

My supervisor and I started to wonder whether people who became very ill after an influenza infection had any differences in their IFITM3 gene compared to the general population, possibly accounting for their severe responses. To test this idea, DNA was collected from the blood samples of 53 people who were hospitalised with a confirmed influenza infection during the 2009 pandemic. When I read the sequence of the IFITM3 gene in these patients I found that overall they were more likely than an 'average' European to have a one nucleotide change in this gene. Now, you may be wondering, how much damage can be caused by one out of 399 nucleotides being altered? Well, potentially, quite a lot.

We realised that this one change could alter the plans enough for the cell to build a shorter, trimmed protein. Think of it like a switch rail on a railway track that can be moved to determine the direction of the train: when a 'T' is substituted for a 'C' it could cause the machinery the cell uses to assemble the protein to 'derail' early, making a shorter protein.

We tested this theory back in the lab by engineering cells to make the cropped version of this protein, which we predicted would be present in these patients. We infected these engineered cells with influenza virus, alongside cells producing full-length IFITM3 protein. The results showed that 60 per cent of the cells expressing the cropped protein were infected compared to only 1 per cent of the cells expressing the full-length version. This suggests that the region of the IFITM3 protein that prevents influenza infection may have been lost in the cropped protein.

Great! So why does my research matter? Well, at the moment people are prioritised for influenza vaccinations if they are 'at-risk', such as asthmatics or the over 60s. Knowing your IFITM3 variants could also inform this kind of vaccination programme, along with other important genes we discover. Furthermore, influenza can swop and change its genes and chromosomes easily with other viruses, which allows the emergence of more virulent strains that can lead to pandemics. Ultimately, by improving our understanding of how influenza interacts with human cells we can improve not only the vaccines we design, but the treatments we provide.

Migraine: stemming the tide of pain

Greg Weir

What does migraine mean to you? Maybe it is only a mild inconvenience in your life, making a friend cancel on dinner or extra work for you as a colleague calls in sick ... again. Or perhaps it means more to you. Perhaps it means hallucinatory visions followed by hours of pain that leave you bedridden and seeking sanctuary in the darkness. For me, it means something else as well. For me it means something frustrating, something exciting and a totally absorbing challenge. I'm a PhD student researching the causes of migraine.

The first thing I must do is convince you that migraine is worthy of research. No doubt this will be an easy task when it comes to the 18% of women and 6% of men who are themselves "migraineurs." However, for those who do not suffer sporadic, intense headaches that can last several days, a hard financial fact might do the job. In the USA alone migraine costs around $14 billion annually in direct medical costs and indirectly through lost work.

Migraine is not a new disease. Hippocrates described it in 400 B.C and before him the Egyptians treated it with clay crocodiles tied to the forehead. Even earlier, humans over 10,000 years ago were compelled to immortalise the migraine menace in their cave paintings. So given how much time we've known about the condition, why are we unable to effectively treat most migraine patients? We simply don't know a lot about what is going on in the migraine brain.

There are two reasons why migraine is tricky to research. As usual, it's at least partly in the genes. However it is not as simple as one faulty gene causing migraine. In fact we think that multiple genes interact with multiple different environmental factors to induce a migraine attack. Such complexity has meant that genes associated with migraine have not been easy to pinpoint.

The pain phase of a migraine is due to activation of the trigeminal nerve, which is responsible for sensing pain from the head and face. Therefore it makes sense to study the cells which make up this nerve in the laboratory. To do this cells currently have to be taken from rats or mice. This technique has ethical considerations but also means that experiments are being performed on animal cells which may act differently to their human counterparts.

As part of my PhD I am trying to create a model that takes into account both of these considerations. The aim is to generate disease-relevant cells outside of the body which can be used for basic research and drug screening. To do this I am using Induced Pluripotent Stem Cell (iPSC) technology. The term "stem cell" is likely to prick the conscience. However unlike embryonic stem cell research, iPSCs do not utilise embryos and instead are made from adult skin samples, rendering ethical issues minimal. The premise is to take skin cells from a patient and then genetically reprogram these into stem cells capable of turning into any cell type in the body, in my case cells akin to those found in the trigeminal nerve.

This is by no means a simple task, as it has never been done before. However with success would come great opportunities. As well as being the human version of the cell type we want to study, all cells will possess the genetic background of the original patient. This means I can look for differences between cells generated from migraine patients and cells taken from people who do not suffer from migraine. From here we can hopefully address the most fundamental of questions; in what way are migraineurs' cells different, and crucially, why are they different? Such cells could also be used to screen drugs that might reverse observed differences. iPSC have significant advantages over traditional animal-based drug screening methods both in terms of relevance, due to the human origin of the cells, and ethics, as the need for animals is circumvented. All this is a large amount of blood sweat and tears away, but a goal I strive for nevertheless.

Migraine is scientifically fascinating in its complexity and the challenges this leads to when studying it. But fascinating is not enough. I want to make strides in our migraine knowledge that go beyond keeping lab folk like me fascinated, strides that drag us closer to therapeutic treatments. I might spend years with little success or my cells might, just might, help contribute in some way to drug advancement. Such a drug could be widely used or it might only help 0.01% of patients. Even in the latter scenario, that's still hundreds of thousands of people experiencing less pain in their lives. Is migraine research worth doing? I'll be heading to the lab first thing tomorrow morning ...

Something's got to give

Vicky Young

"What good is it being Marilyn Monroe? Why can't I just be an ordinary woman? A woman who can have a family ... I'd settle for just one baby. My own baby." As the quintessential sex symbol of modern time, Marilyn Monroe oozed femininity and appeared to be the ideal women, but behind closed doors she spent most of her life in chronic pain, became addicted to pain-killers, and suffered from difficulties in conceiving and at least two miscarriages.

Marilyn Monroe suffered from a disease called endometriosis, a condition where the cells that line the womb, known as the endometrium, are found on the surface of other organs within the pelvis. These endometrial cells still act like endometrium and each month they thicken and bleed, but unlike in the womb the cells can't leave the body at the end of each cycle so they just keep growing. In time these cells grow to form lesions on the organs and can interfere with organ functions and irritate nerve endings, causing chronic pelvic pain. What's more if the disease is not treated then the lesions can affect fertility and even fuse organs together.

Endometriosis is more common than you might think with up to one in 10 women suffering from the disease. Right now the only way to diagnose endometriosis is to perform pelvic keyhole surgery under general anaesthetic to look for endometriotic lesions. However this can be really traumatic for the woman and costs the NHS millions of pounds each year. Although there is no cure, the lesions can be removed during the surgery, which can help with pain, and symptoms can also be managed with pain medication and hormone treatments. But the lesions return in most women after one or two years, meaning that they need regular surgeries thoughout their lives.

My research focuses on how endometriosis originates within the pelvis. If I can find out how endometriosis develops then it could help us identify and develop a drug that can stop it. Right now most of the scientific research in endometriosis has focused on how the endometrial cells are different in women with and without the condition but what has been ignored is the pelvic lining that the endometrial cells grow on. Lining the whole of the pelvis, including the surface of all the organs inside it, is the 'peritoneal membrane'. This is a very thin layer of specialised cells that protect the organs and stop them sticking together. These are the cells that the endometrial cells stick to and grow on. My research is looking at changes within the peritoneal membrane that might make it easier for endometrial cells to stick to it and grow.

In particular I am researching a protein called transforming growth factor beta or TGF-β. This protein is important in cancer where it causes cells to multiply quickly and in the development of scars where it makes cells stickier and produces scar tissue or 'collagen'. I am trying to prove that TGF-β protein is increased in endometriosis and acts on the peritoneal membrane to make it stickier so that endometrial cells are more likely to attach to it. Once stuck the TGF-β might also cause the cells to multiply quickly and produce excess collagen creating the endometriosis lesion.

So far I have shown that TGF- protein is increased in the peritoneal membrane where endometriosis lesions are usually found. This means that TGF-β might be responsible for endometriosis developing, at least in part. I have also shown that peritoneal membrane cells become stickier when exposed to TGF-β in the lab explaining why endometrial cells stick to the peritoneal membrane. Although more research needs to be done here, it looks like TGF-β is central to this disease.

So why is my research i mportant? If I can prove that TGF-β is responsible for the development of endometriosis then we can develop drugs that target TGF-β to stop endometriosis lesions forming. These types of drugs are already being developed for the treatment of other conditions and are already showing clinical promise.

Unlike Marilyn Munroe who had to endure major pelvic surgery to treat her endometriosis, women today undergo minor keyhole surgery but that's where the differences end. The contraceptive pill and painkillers that Marilyn Munroe would have been prescribed are the same form of treatment prescribed today. The development of a new drug to treat women who suffer from endometriosis is vital to improve their quality of life and avoid the suffering that so many women experience from this disease.

www.mrc.ac.uk

In partnership with...