A PICTURE OF HEALTH

A Selection of Irish Health Research 2005

Improving health through research and information

HRB
Health Research Board

Foreword

A Picture of Health 2005 is the third in the series of publications that describe some of the latest advances in health research by Irish researchers funded by the HRB. The broad spectrum of innovative research included in this year's report reflects the increased support from the Department of Health and Children for health research and highlights government recognition of the fact that today's health research is tomorrow's health service. It also reinforces our national commitment to contribute to the global efforts to combat disease and improve equality and equity of care in our own health system.

While the social and economic impacts of effective health research can take time to manifest, a growing evidence base shows that it reaps great rewards; improved healthcare, more effective treatment, preventative approaches to health issues and greater efficiency through new technologies. Such research also contributes significantly to our national knowledge base as we move towards a knowledge-based economy and society, and raises the profile of Irish health research among the international research community.

In addition to enabling our best researchers to tackle national and international health challenges such as cancer, diabetes and heart disease, funding provided by the HRB also helps to build research capacity within the public health system by providing training for postgraduate students, and developing the research careers of health professionals and young investigators through our various fellowship schemes. The HRB greatly values the ongoing support of the public in our mission to improve health through research and information. We hope you enjoy reading *A Picture of Health 2005*.

Professor Desmond Fitzgerald
Chairman of the Health Research Board

The heart of the matter:
Cardiovascular health and disease

Population health:
Society and people

Neuroscience:
Brain matters

Diabetes:
Understanding a common condition

Cancer:
Tackling the big C

CONTENTS

Immune affairs:
The battle rages

Infections, microbes and gut feelings

Health services:
From the cradle to the grave

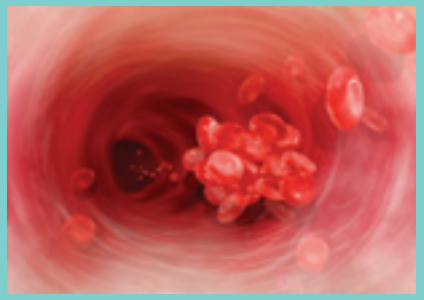
Human disease:
Confronting the causes

The heart of the matter: Cardiovascular health and disease

"Most types of cardiovascular disease are preventable."

Source: Public Health Report November 2004; HSE Midland Area.

Blood clot? The answer could be NO!

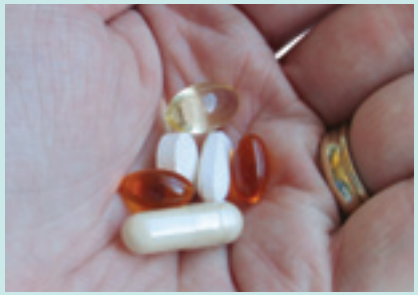


Nitric oxide can stop blood platelets sticking, scientists at the Royal College of Surgeons have discovered

Nitric oxide (chemical symbol: NO) is a small molecule that plays many roles in regulating blood flow. Consequently, it is an important target for many drugs – Viagra, for instance, targets NO as a way of improving blood flow to a certain part of the male anatomy, and angina drugs exploit NO's ability to increase blood flow, in this case to a heart struggling because of a blocked artery.

Angina can develop when a blood clot forms in an artery and blocks the flow to the heart. Scientists still don't fully understand how clots form, but it is known that small blood cells called platelets are important. Platelets normally have a silky, disc-like appearance, but when they sense damage, they dramatically change their appearance and become 'sticky', and capable of forming a clot. Dr Niamh Moran and post-doctoral researcher Sarah O'Neill, at the clinical pharmacology department of the Royal College of Surgeons in Ireland, are studying platelets in the test tube. They have discovered that there is a biochemical 'switch' that controls this change from silky to sticky. Crucially, they have also discovered that NO can trip this switch, restoring sticky platelets to their normal silky state. This is an important finding, and there has been considerable interest in the Irish study. The biochemical switch is probably not the only way that NO regulates blood flow and blood clotting, but it may explain why NO is useful in treating angina.

The dietary supplement that can unblock arteries



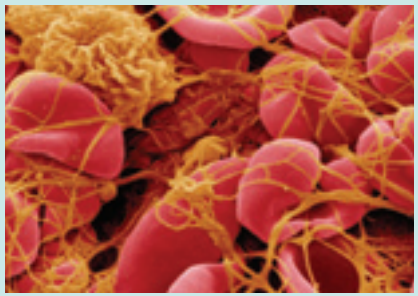
Feeding mice a supplement of conjugated linoleic acid cleared the plaques from their blocked arteries, a UCD study discovered

There are currently no drugs that can effectively clear blocked arteries. But one day a simple dietary supplement may do the trick: scientists at UCD's Conway Institute have now proven that conjugated linoleic acid (CLA), a naturally occurring fat-like substance found in red meat and dairy products, can clear the plaques from blocked arteries. This holds out tremendous promise, as atherosclerosis is the main cause of heart disease and stroke, and accounts for 50% of deaths in western societies.

There is already considerable scientific and medical interest in CLA's potential to treat cancer, diabetes and inflammation. Now, Dr Orina Belton and PhD student Sinead Toomey, have shown that, if mice with atherosclerosis take a CLA dietary supplement (equivalent to 1% of their food), the plaques in their arteries disappear. The effect happens relatively quickly – within as little as two weeks – and the UCD scientists discovered the CLA works by 'persuading' the macrophage cells that accumulate in the plaques to self-destruct.

There is however a cautionary note. CLA comes in several chemical forms, or isomers, with different atomic arrangements, the two main ones being termed 9-11 and 10-12. Each isomer seems to have different metabolic effects, and the picture is complicated by contradictory findings. With insulin sensitivity, for instance, some reports suggest CLAs can increase insulin concentrations, yet others found no effect. The UCD supplement was 80% 9-11, and so Belton attributes the positive effects they saw to this isomer. Their results suggest we might one day control atherosclerosis with a simple 'nutraceutical' dietary supplement, but in the meantime, the supplements sold in health stores are usually an unspecified mix, and people with diabetes should use them with caution or under monitoring.

Clot-busting science on a platelet



Research at UCD is revealing what happens at the molecular level when blood platelets are activated, and at the Royal College of Surgeons they can capture these changes on a movie

We don't fully understand how blood clots form, but we do know that small blood cells called platelets play a key role, and that the platelets must become activated before a clot can form. However, there is a fine line between having platelets ready to react if you're ever wounded, and inappropriate platelet activity that might produce an unwanted clot (or thrombosis) in blood vessels, which could block the blood flow to your heart or brain. People with high blood cholesterol levels are prone to developing diseased or damaged arteries that can lead to blood clot formation and so they are often prescribed 'statin' drugs to lower cholesterol levels. Patients prone to developing blood clots are often prescribed clot-busting drugs (or anti- platelet agents) that can prevent platelets from clumping together into a clot. However, these can cause bleeding complications, so the search is on for new drugs with fewer side-effects. For that, however, we need a better understanding of how clots form.

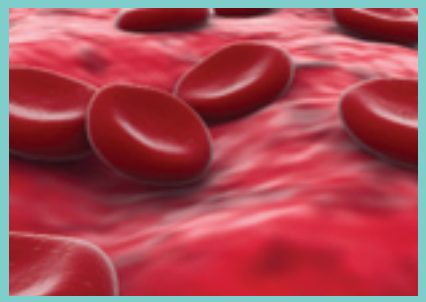
Traditionally, platelet scientists study platelet function in a test tube environment, but at the Royal College of Surgeons in Ireland, Dr Gerardene Meade and Eimear Dunne (research associate), set up a model system to study platelet function under conditions that mimic blood flowing in blood vessels. This system comprises a pump (or heart) to push fresh blood through tubing and into a chamber that mimics a damaged blood vessel surface, with a microscope and camera to image and record the flow at up to 30 frames a second. In elegant experiments they have shown that their system is a good model of the real thing, and they are now using it to study how platelets become activated.

Certain regions of a platelet receptor protein called GP1b-IX-V are known to be important in initiation of the clot forming procedure, and Meade studied a particular region and demonstrated its functional importance under conditions of blood flow. In addition, it has been shown that people often have different versions of this protein (variable regions) – something she plans to investigate further. Meanwhile, other researchers are collaborating to use this system, including scientists studying how infections can cause blood clotting, and others investigating how cancer cells spread by moving through blood vessels.

Across the city at UCD's Conway Institute, Dr Patricia Maguire (formerly of the RCSI), and PhD student Martina Foy, are studying the molecular events that happen when platelets become activated. They are interested in special regions of the cell membrane where the structure seems to be different, and these areas seem to function as meeting places – where proteins can come and go and interact with other proteins. Scientists call these putative structures 'lipid rafts' and, using new proteomic techniques to identify the molecules present, the UCD team has found over 150 proteins in the platelet lipid rafts, many of them not previously known in platelets. This suggests that platelet activation is more complex than originally thought, and by way of example, Maguire and Foy have found that one of the new lipid proteins (RGS-19), interacts with another protein (a chaperone, called 14-3-3), which can also bind with the key receptor protein, GP1b-IX-V. Maguire would now like to analyse lipid rafts in platelets from people with different blood cholesterol levels to see if some people have more rafts, or different rafts, and if this can explain why people with high cholesterol are more prone to developing dangerous blood clots.

Image caption: Scanning electron micrograph of blood corpuscles on clot

Cancer, clots and cardiovascular connections



Gene studies at UCD revealed that two genes normally associated with cancers also play a role in atherosclerosis

A blocked artery can kill. It can trigger a heart attack if it blocks blood flow to the heart, or cause a stroke by blocking blood flow to the brain. Blockages are caused by the build up of plaques, but plaques are not just fatty deposits of cholesterol: they usually become coated with a layer of smooth muscle cells, and acquire a blood supply, and thus have some similarities with tumours. Scientists recently discovered that plaques with a rich blood supply are more likely to rupture and lead to clot formation.

To explore what is happening, Dr Susan Connolly, a clinician training in cardiology, teamed up with scientists at UCD's Conway Institute for a fishing expedition…fishing, that is, to identify what genes are active in the cells around a plaque. Using DNA microarrays to reveal what's switched on at any one time, they found that some 600 genes are significantly more active in stressed smooth muscle cells than in healthy ones. Next, they identified the types of genes as they were switched on (those associated with new blood supply formation, for instance), and this spotlighted two genes of interest. They found that PTTG1 (pituitary tumour transforming gene 1), already associated with certain cancers, is activated in plaques, and especially in ruptured plaques. And that calvasculin, a gene associated with aggressive metastasising cancers, is also switched on in plaques, where it possibly mobilises the muscle cells. These intriguing connections between cancer and cardiovascular disease are another piece in the jigsaw as we piece together what happens during disease.

Calcium is not just for bones

Scientists at UCC have discovered how calcium ions act as important messengers in immune cells and in the muscle cells of blood vessels

Mention calcium and the body, and most people probably think of bones. But calcium ions (Ca^{2+}) are also important messengers in your cells, carrying in signals from outside and helping control processes such as muscle contraction. To this end, cells keep a store of calcium ions in special reservoirs and, when the ions are needed, special protein channels can be opened to release them. These all-important protein channels are called ryanodine receptors, and one type, ryanodine receptor type 1 (RyR1), is essential for controlling contractions in your skeletal muscles. Here its function is well understood, but the same protein is also found in other tissues including immune cells (the B-lymphocytes) and in the smooth muscle cells of blood vessels (vascular smooth muscle), and biologists at UCC's Department of Biochemistry are investigating its role there.

Dr John Mackrill and Prof Tommie McCarthy have discovered that when the RyR1 channels open in B-lymphocytes, the concentrations of various components inside the cell change, which they believe has implications for the immune system. In the vascular smooth muscle cells, they found that opening the channels, and releasing the calcium ions, reduces the levels of the enzymes that dismantle the blood vessel wall (specifically, the matrix or 'mortar' that holds the cells together). This, they now believe, happens because the calcium ions can switch off the genes that code for these enzymes. This may explain how blood vessels grow differently in certain diseases, information which could be useful in developing new therapies for cardiovascular problems and to stop the blood flow to growing tumours.

Are you feeling the pressure?

At DCU, scientists are discovering how high-blood pressure can alter the very structure of your blood vessels

Every heartbeat pumps blood through your vascular system, and as the blood flows through it generates mechanical forces that can profoundly affect the structure and function of the blood vessels. There is the frictional force (or shear stress) as the blood drags against the endothelial cells lining the inside of the vein or artery, and an outward pushing or stretching force (the cyclic strain) generated by each beat of the heart, which mostly affects the vascular smooth muscle cells. Over time, and especially if a person has high blood pressure or a blocked artery, these physical forces can take their toll on the blood vessels.

At DCU's Vascular Health Research Centre, scientists led by Prof Paul Cahill are investigating how the cells in blood vessels actually detect and respond to the mechanical forces involved. In one project, with PhD student David Morrow, the researchers have proven that subjecting vascular smooth muscle cells to cyclic strain makes them dysfunctional, a change that contributes to the root cause of vascular disease. They also discovered that this change regulates the expression of a family of genes, the Notch genes, which are normally active only during embryonic development of the vessel, when they are crucial to the growth of the blood vessels. The DCU study suggests that, if we could find a way to target the Notch genes in the dysfunctional cells, it might provide a new way to treat cardiovascular disease.

In a separate study, research fellow Dr Philip Cummins is investigating how the endothelial cells that line the blood vessels can detect and then respond to the mechanical forces. Several receptor proteins on the surface of the cells are probably involved, including a group called the regulatory G-proteins. Cummins has now shown that two regulatory G-proteins (Gα and G$\beta\gamma$, from the inhibitory G-protein family), play different roles in detecting the mechanical signals. These enable the cells to respond to the forces, and a better understanding of these molecular mechanisms may ultimately help us to develop new ways to diagnose, treat and manage cardiovascular disease.

Eve and ecstasy, and what they can do to you

Physiologists at the Royal College of Surgeons have discovered one of the ways in which amphetamines can affect a person's metabolism

Here's what we know. Ecstasy, or MDMA, to give the drug its scientific acronym, can seriously alter a person's metabolism, raising their core body temperature, for example, and setting their heart racing. We also know that it can mimic two neuro-chemicals, serotonin and dopamine. Now, physiologists at the Royal College of Surgeons in Ireland have discovered that ecstasy can mimic a third neurochemical, noradrenaline, and they believe this explains some of the drug's potentially lethal side-effects.

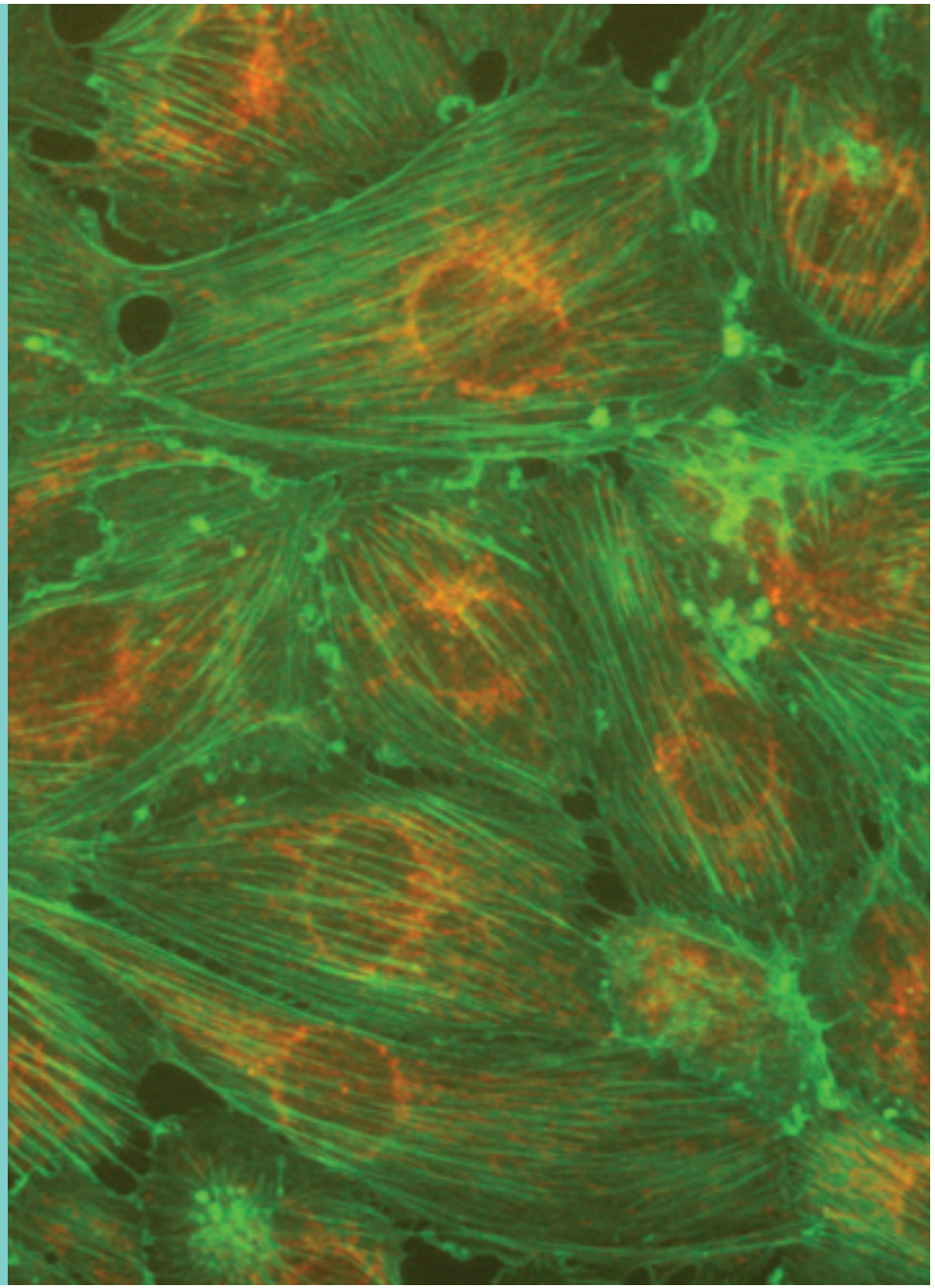
Prof Jim Docherty and Dr Sotiria Bexis are studying not just MDMA, but also three other related drugs: two amphetamine derivatives – MDEA (known in the parlance as Eve), and MDA, which is produced in the body when ecstasy is metabolised – along with cathinone (the major constituent of Khat). By analysing the effects of the four drugs on lab rats, the scientists have confirmed that all four significantly affect the animals' metabolism, altering their heart ECG patterns (ecstasy and its metabolite MDA produced the most marked change), raising their core body temperature (with MDA, again, in particular causing the animals to overheat), and increasing their blood pressure (again, MDA was worst, while MDEA had no affect on blood pressure). The scientists also discovered that MDMA can mimic the neurotransmitter noradrenaline, and interact with a noradrenaline receptor, called alpha-2, and they believe this partly explains how ecstasy can interfere with heart function and body temperature. Their research also revealed that much of the damage done by ecstasy is probably caused by the MDA produced in the body as the drug is metabolised.

An on/off signal that controls blood vessel growth

Biochemists at the Royal College of Surgeons have pieced together one of the mechanisms controlling the growth of new blood vessels

There are times when new blood vessels are a good thing – in a developing embryo, for instance, or to heal a wound. But there are also times when new blood vessels are decidedly 'a bad thing', notably when they are growing to supply a tumour, or an already inflamed region. So there is considerable scientific interest in understanding the signals that switch this growth on and off. Angiogenesis is the name scientists give to blood vessel growth, and the process happens when endothelial cells lining an existing blood vessel start to proliferate. There are probably several mechanisms controlling this, and at the Royal College of Surgeons in Ireland, Dr Aideen Long and PhD student Frances Lennon, are studying one of those mechanisms.

They have discovered that hyaluronic acid, found in the gel that surrounds and binds the endothelial cells together, can dock with a molecule called CD44 on the surface of the cells. This, they have discovered, sets off an important chain reaction – leading to production of vascular endothelial growth factor, that activates the cycloxygenase-2 enzyme, that produces prostacyclin… that ultimately triggers the endothelial cells to proliferate. This valuable information could one day lead to the development of new drugs to control the growth of blood vessels and help treat inflammation or starve cancers of their essential blood supply.



Winning entry in HRB's *Picture of Health* image competition. Image was taken by PhD student Frances Lennon in RCSI.

Image caption: Activated endothelial cells stained for actin (green) and rab5 (red). Actin forms part of the cell skeleton while rab5 is a marker of endosomes (small portions of the cell membrane which cleave and internalise to form small vesicles which carry 'cargo' into cells).

Population health: Society and people

"…social, economic and material disadvantage damage people's health."

Source: 'Disadvantage is bad for your health', Prof Cecily Kelleher (Public Health, UCD)

Disadvantage is bad for your health

A major five-year study, that is capturing a picture of the nation's health, reveals how social, economic and material disadvantage are damaging people's health

If you are well-off – if for example both your parents had a third-level education – then you are more likely to be in good health. Conversely, if you are socially, materially or economically disadvantaged – if for example your income is so low that you qualify for a medical card – then you are more likely to rate your health as poor. That's the message, in simple terms, from a major five-year study of the health status of Irish people.

Begun in 1999, and co-ordinated by Prof Cecily Kelleher from UCD's department of Public Health Medicine & Epidemiology, the project involved a large multi-disciplinary team from UCD and NUI Galway.* They analysed information from previous national health and lifestyle surveys, and undertook two sizeable new studies: first, Lifeways, a five-year study across three generations, involving children, parents and grandparents; and second, a detailed social comparison of two communities. The aim was to assess people's current health status, and to identify the social factors that affect health status and thus what needs to change if we are to improve people's health status.

The starting point for the Lifeways project was when 1,124 Irish-born pregnant women volunteered to join the study. Data on their pregnancy and labour and the birth were collected from the maternity hospitals, and the study then grew to encompass the child and the mother's partner/spouse, and the child's grandparents – in all, over 2,000 adults across three generations. These people supplied information on their health, lifestyle and nutrition, and kept records of GP and hospital visits; over 1,000 grandparents were also clinically examined at home by a nurse.

The second, complementary study was very different, in that it entailed detailed interviews and focus group discussions in two communities (one a suburban community in a large city, and the other a more rural community, and for confidentiality codenamed Ballyeast and Ballywest), along with interviews and information from various disadvantaged groups, such as Travellers, a men's social club, lone parents, a domestic violence support group, low-income women, and carers.

The research confirmed that people who are well-off enjoy better health than those who are socially, economically and materially disadvantaged. The clearest indication comes from those with a medical card, itself a direct measure of income. Education, and especially third-level education, is also important: people who have a third-level qualification are more than twice as likely to say their health is good or excellent; and a young mother is seven times more likely to enjoy good health if both her parents had a tertiary education. As might be expected, lifestyle factors such as diet/nutrition, alcohol intake and smoking are also important. Smokers, for example, are nearly three times as likely to say they suffer from poor health as non-smokers. This ties in with the information on income, as generally smokers are also less well-off than non-smokers. The same picture emerged from a comparison of the Ballyeast and Ballywest communities: disadvantage can seriously damage your health, and it involves factors as complex as self-esteem, and as basic as access to health care services.

The project team is now drafting policy recommendations aimed at improving people's health status. Meanwhile, they recommend that the Lifeways study, which is a valuable baseline and a snapshot of the country's health status, should continue until at least the children reach school-going age.

*At NUI Galway: Prof Andrew Murphy (Department of General Practice), Dr Eamon O'Shea (Economics), Dr Margaret Barry (Health Promotion) and Dr Michelle Millar (Political Science & Sociology)

How active were you today?

It's hard to design an effective questionnaire that gathers accurate data about how active people are, but scientists at DCU have now done it

We all need at least 30 minutes of moderately intense physical activity at least five times a week, and for people with conditions such as diabetes and heart disease, regular physical activity is crucial to staying healthy. To ascertain how much physical activity a patient is getting, healthcare staff use recall-type questionnaires, typically asking someone what they did in the previous week. But the results are generally inaccurate. That's because, according to Dr Catherine Woods, an exercise scientist at DCU's School of Health and Human Performance, the questionnaires ask the wrong questions, and ask them in the wrong way.

To design effective questionnaires, you need to understand how people think and how they recall events, and give them appropriate phrases and prompts in the questions. Woods and PhD student Niamh Martin employed cognitive psychology techniques to devise model questionnaires designed to make recall easy and accurate. Their questionnaires incorporate a calendar and descriptions of physical and psychological reactions to activity, all designed to help people remember what they did on a particular day. They have now designed three questionnaires tailored to specific age groups (12-17 years old, 18-55, and over-55), taking account of lifestyle, and including activities such as housework which are often overlooked by other questionnaires.

Dr Martin is now using the new questionnaires in a healthcare intervention programme for the HSE northern area, and copies of the questionnaires are available from Dr Woods at DCU.

Keep taking the tablets

One-third of people who are given drugs for high blood pressure or high cholesterol do not go beyond their first prescription, a TCD study reveals

People with high blood pressure or high cholesterol are more likely to develop coronary heart disease. So, even if they have no obvious symptoms, they are usually prescribed drugs, such as one of the statins now used to lower cholesterol. But if someone has no symptoms, they may not appreciate the need to take a drug, and if the drug has unpleasant side-effects, they may be tempted to stop taking it. To look at patterns of drug use, Dr Kathleen Bennett, a medical statistician at TCD's Centre for Health Sciences, and PhD student Nicola Fitz-Simon analysed prescription data from the General Medical Services scheme for some 11,000 people claiming prescriptions for hypertensive drugs, and 7,000 people claiming for statins.

They found that nearly one-third of people stopped their prescription after just one month of treatment – 32% of patients taking statins, and 37% of those taking hypertensive medication cashed only one prescription. Interestingly, younger and older patients were more likely to stop than those who were middle-aged. With several statins to choose from, many patients start with one type and, if they do not respond well to it or experience unpleasant side-effects, switch to another. The researchers found that two-thirds of those switching their statin therapy did so in the first two months. All of which suggests that GPs and consultants should give extra support to patients in the first few months of a therapy, to ensure that those who need to take medication keep taking the tablets.

Door to needle in 30 minutes?

Women are less likely to survive a heart attack than men, because their symptoms are not recognised in time, according to a TCD survey

Time is of the essence if you are having a heart attack, and ideally, people need to receive the essential clot-busting thrombolysis injection within 30 minutes. Yet many people have not even seen a doctor by that time, and bad as the situation is for men, it is considerably worse for women. Numerous international studies report that women are more likely to die following a heart attack than men: one US study found that women were three times more likely to die within 30 days of being hospitalised for a heart attack, than men.

To assess the Irish situation, Dr Sharon O'Donnell, a research fellow at TCD's School of Nursing, examined the pre-hospital experience and in-hospital care of Irish men and women who had a heart attack. She discovered that Irish women do not see themselves as potential heart attack victims, do not recognise the early warning signs (often brushing them off as minor ailments), and take longer to call for help. Even when they reached hospital, medical staff took longer to recognise the women's condition. Result: while the 'door to needle' time for men in Ireland is 52 minutes on average, for women it is 70 minutes, with many taking even longer. Part of the problem, O'Donnell says, is that women often have atypical symptoms, such as tiredness and nausea, and their condition is slow to develop, in contrast to the classical male symptoms of sudden, acute chest and arm pain. She believes we need a major campaign to educate women, their families and GPs, and A&E staff about the problem. Meanwhile, if you think you are having a heart attack, take an aspirin, and an ambulance straight to hospital.

Childhood cystic fibrosis – fathers also count

Health care teams should involve the fathers as well as the mothers of children with cystic fibrosis, a UCC nurse researcher recommends

Caring for a young child with cystic fibrosis can put big demands on parents. Most studies focus on the mothers' needs and perspectives, however, and the fathers' voices are rarely heard. To redress this balance, clinical nurse Claire Hayes, working with Dr Eileen Savage at UCC's School of Nursing, interviewed the fathers of young children diagnosed with cystic fibrosis.

Caring for a chronically ill child is time-consuming and, according to Hayes, one parent will often give up work, usually the mother, so that care teams may unwittingly address mothers more than fathers. The fathers interviewed said their work commitments limited the time they could spend with their child. Nevertheless, they were all involved in the day-to-day care, especially the chest physiotherapy. Hayes found that, for fathers, an important part of managing involved getting information from the medical team, searching for the latest research news on the Web, and getting practical advice from other parents in a similar situation. Those interviewed revealed that, though they might not often discuss their child's illness with others, they were often upset by it. Their social life could also be badly affected: some were reluctant to leave their child with others and consequently it was difficult for them to have a night out together.

Hayes recommends that health care teams should actively include fathers and should stress the need for parents to have a trusted other person they can leave their child with. Care teams should consider providing more information for fathers, and offer them support, though more research is needed to clarify what support structures are needed.

What to expect from a medical geneticist

Parents need more information and support when preparing for a genetic investigation, a University of Ulster study recommends

Genetic investigations are unlike any other medical appointment. Geneticists might not listen to a child's heart, for instance, but might do something unexpected such as examining the child's feet, which can seem bizarre to parents who have exhausted the usual round of medical tests. For some parents, a genetic investigation may provide an answer after months of searching, even if that answer raises concerns about guilt or blame. But other parents' hopes are dashed if genetics cannot provide an answer. Consequently, parents need to understand fully what a genetic investigation entails, and the power and limitations of genetic testing.

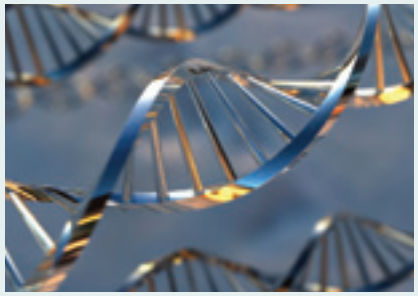
Community nurse Dr Owen Barr, a nursing researcher at the University of Ulster, interviewed 19 parents of children who were being referred for their first appointment with a medical geneticist, and he surveyed some 200 health visitors in Northern Ireland. He found that most parents welcomed the genetic investigation but were poorly informed about it, and that health visitors could not support them, because they were not aware of the referral. Dr Barr's study has already led to changes in Northern Ireland: the Belfast service produced a new information leaflet for parents, and its letter of appointment now invites any parent with questions to contact them directly. But Barr says it would also help if GPs and consultants appreciated the special nature of genetic testing, and informed health visitors of a referral, so they could also support the family.

Neuroscience: Brain matters

“Cannabis causes young brain cells to self-destruct…..”

Source: ‘Why cannabis is bad for young brains’, Dr Veronica Campbell (Physiology, TCD)

The genetics of ADHD



Scientists at TCD are winning international recognition for their work on ADHD, and here we report on two studies that have identified some of the genes involved

Inattentive, distractible, impulsive, hyperactive…the main symptoms of attention deficit hyperactivity disorder (ADHD), a behavioural condition that affects 2-5% of school-aged children worldwide. Thanks to research in Ireland and elsewhere, it is now clear that a child's susceptibility to ADHD depends on many genes, as well as environmental factors. It's also now known that dopamine, a neuro-transmitter used for signalling by nerve cells in the brain, is important: block the dopamine transporter, and thus alter dopamine levels in certain regions of the brain, and you can alleviate symptoms for up to 70% of ADHD children – which is precisely how the drug methylphenidate, alias Ritalin, works.

TCD neuropsychiatric geneticist Dr Ziarih Hawi and colleagues have now confirmed that the dopamine transporter gene is associated with susceptibility to ADHD, and crucially this may determine how well a child responds to medication. The team then identified another risk gene, coding for one of the dopamine receptors, called DRD5: in a major international study across 14 countries, co-ordinated by TCD, Dr Naomi Lowe confirmed the importance of this gene in ADHD. Researchers elsewhere had shown that a second dopamine receptor, DRD4, was associated with ADHD, and Dr Hawi's team has now confirmed this and, they believe, located the problem to the gene's control region.

Intriguingly, Dr Hawi's team also discovered that the effects of these risk genes are more likely to come from the child's father than from their mother. This suggests that a mechanism known as 'imprinting' is important (some genes are marked, depending on which parent they are inherited from, to control their activity), and in this way, the father's genes become more influential in the development of ADHD than the mother's.

In addition to attention deficit and hyperactivity, people with ADHD are prone to cognitive problems, such as difficulties in thinking and planning. Two TCD psychiatrists, Prof Michael Gill and Dr Mark Bellgrove, wondered if this separate phenomenon is caused by the same genes that put people at risk of ADHD. Gill and Bellgrove found that people's ability to sustain their attention during repetitive tasks is indeed affected by several genes that code for neurotransmitters, and suggests that the genes implicated in ADHD are also responsible for the cognitive deficits, work that is helping us to understand how genes affect the development of the brain.

What is ADHD?

Attention deficit hyperactivity disorder (ADHD, or HADD) is a neurobiological disability, frequently characterised by inappropriate degrees of inattention, impulsivity and hyperactivity.

When left untreated, a child is at significant risk of developing impaired learning ability, decreased self esteem, social problems, family difficulties and potential serious long term affects.

Between 5 - 10% of Irish children are estimated to have ADHD.

Source: HADD family support group, May 2005

Time to pay attention

A study at TCD reveals that kids with ADHD have a poor sense of time, and suggests that 'time training' might improve their attention skills

Training with a metronome, and learning simple exercises to a beat, might help a child who has attention deficit hyperactivity disorder (ADHD) to improve their sense of time, and perhaps even their ability to maintain attention. That is the suggestion from a study by research psychologist Dr Celine Mullins, working at TCD with Prof Ian Robertson and Prof Michael Gill.

There are two main types of ADHD: children whose problem is inattention (the inattention subtype), and children who, in addition, are also hyperactive and impulsive (the combined subtype). Both groups seem to perceive that time runs fast, so that five minutes might feel to them more like 10. But is this because they have trouble maintaining attention, or is it something separate? Time perception is subjective and difficult to study, so Mullins devised simple computer-based tests, such as asking children to reproduce a sequence that lasted a set time, or to say which of several events happened first, and she gave these tests to children with ADHD and to other children. She found that ADHD children have poor time perception, and that this is not just because of their attention difficulties. Studies elsewhere suggest that a metronome can help children to learn simple movements (e.g. clapping and toe-tapping), and Mullins believes such time training could help ADHD children to improve their sense of time, and perhaps even win some control over their attention deficits and impulsiveness. Similarly, giving children time clues while they are engaged in a task could help them to remain focused.

Destroy a protein, create a disease

Cell biologists at UCD believe that diseases such as multiple sclerosis and Alzheimer's develop because brain cells start destroying a crucial protein

Alzheimer's disease and multiple sclerosis are very different disorders, yet they have one thing in common: both are associated with inflammation in the brain. Normally, inflammation is a good thing, part of the body's response to infection, with white blood cells moving from the blood vessels into the infected tissue where they can attack the invading micro-organism. And normally this movement is tightly controlled, since inappropriate inflammation can damage healthy tissue and cause disease. Yet this is precisely what seems to go wrong in diseases such as Alzheimer's and MS, and at UCD's Conway Institute, cell biologists are trying to understand why.

Dr Paul Moynagh and PhD student Bryan Griffin are interested in a protein called IκBβ which normally helps regulate inflammation by blocking the movement of white blood cells into tissue. They culture brain cells in the lab, and can simulate conditions in MS by exposing the cells to a signal that triggers inflammation. When this happens, they found that the IκBβ protein disappears from the brain cells for long periods. Significantly, this absence may explain how white blood cells can accumulate in the brains of people with MS. Moynagh's team has also discovered how the protein disappears: first, it is made as normal; then, in response to the inflammatory signal, it is degraded; it is then remade, but immediately modified by a process called phosphorylation, which marks it out for degradation, and then finally destroyed. The team is now looking at ways of stabilising the protein to prevent it being destroyed, work which in the long-term could be of benefit in understanding several diseases.

Interfering interferon – the cure that feels worse than the disease

Research at TCD may have identified a way to overcome some of the awful side-effects of the drug used to treat hepatitis C

Long-term hepatitis C infection can leave you needing a liver transplant, so it's important to treat the disease early. Happily, there is one drug that will cure the infection very effectively, called interferon alpha. Unhappily, it causes awful side-effects in some 70% of patients, ranging from depression, anxiety and memory loss, to manic/paranoid psychoses and even suicidal ideation. Some have likened it to "having a finger inserted in your brain", and many are tempted to stop taking the drug before their six-month course is up. Indeed, the side-effects are so severe that people on interferon alpha must undergo psychiatric assessment and monitoring. Until now, not much was known about interferon's effects on the brain. But Prof Shane O'Mara and PhD student Briana Fahey at TCD's Institute of Neuroscience, and Dr Ann-Marie O'Dwyer, a consultant psychiatrist at St James' Hospital, have now studied its effects on the brains of rats and elucidated how it affects behaviour, the brain and the brain chemistry. Interferon is actually a natural substance, produced by our immune system in response to infection; but very high doses of manufactured drug are needed to kill the hepatitis C virus.

The TCD scientists discovered that at high doses the drug reduces the brain's electrical activity, increases the levels of stress hormones, and reduces the levels of an important brain chemical, brain-derived neurotrophic factor. Rats given the drug also appeared anxious and depressive-like. Significantly, many of the side-effects disappeared if the rats were given the anti-depressant, Prozac, and the side-effects were further reduced if they were fit and allowed to exercise. O'Mara stresses that these are preliminary results, but they offer hope for the many people affected by the severe side-effects of what was once thought to be a wonder drug.

Break a protein, make a memory

What happens in your brain cells when you store a new memory is very similar to what happens when memories are erased in Alzheimer's disease, researchers at UCD have found

If we understood how new memories were stored in healthy brains, it would help us understand how memories are lost in Alzheimer's disease. So Prof Ciaran Regan and his research team at UCD's Conway Institute study what happens when they teach rats a new trick. They are particularly interested in a long protein called amyloid precursor protein (APP), which is known to play an important role in both learning and Alzheimer's disease. Indeed, the main characteristic of Alzheimer's disease is that an insoluble fragment of APP, called beta-amyloid (Aβ) accumulates in the brain, forming deposits that seem to kill the surrounding nerve cells. But what happens to APP in healthy brains?

Analysing brain samples taken from rats at two-hour intervals after they had learned to avoid a shock, revealed that one of the first steps in creating a new memory is that the APP is brought from the outer nerve cell surface inside the cell, where it is chopped into fragments. This movement helps loosen existing nerve cell connections, allowing a new pattern to emerge and so store the new memory. When the researchers blocked the protein that moves APP into the nerve cells, the rats were not able to remember their new trick. They found, too, that most of the chopping, or processing, of the APP happens in the hippocampus, the part of the brain most associated with learning and memory. Perhaps most significantly, they discovered that the enzyme that chops the APP is the same enzyme that produces the insoluble, toxic fragment seen in Alzheimer's disease. This reveals an important link between APP, learning and Alzheimer's disease.

Why cannabis is bad for young brains

In an important study with major implications, pharmacological researchers at TCD have discovered that cannabis kills nerve cells in young brains

Cannabis seems to protect adult brain cells, but actually causes young brains cells to self-destruct. That's the finding of a study at TCD's physiology department that looked at the drug's effects on brain cells and brains. This may explain how the drug can cause brain damage to an unborn foetus, and why the age at which someone starts using the drug is important.

As a drug, cannabis is potentially useful: it can kill cancer cells, for instance, by causing them to 'self-destruct', a process scientists call apoptosis; and it can protect adult brain cells from damage and degeneration. But on the downside, it can trigger psychosis or schizophrenia in some users, and cause brain damage in infants exposed to the drug while in the womb.

To understand how the drug works, pharmacologist Dr Veronica Campbell and PhD student Eric Downer study brain cells derived from young rat brains and grown in the laboratory at TCD's physiology department. They discovered that the active ingredient (tetra-hydro cannabinoid, or THC), caused the cells to self-destruct, and just as with cancer cells, it did this by binding to a protein on the cell and triggering a chain of events that culminates in apoptosis. Since this is different to THC's effects on adult cells, Campbell and Downer wondered if the age of the cells was important. So they next studied THC's effects on adult and immature rat brains, and discovered that age is crucial: THC does not kill cells in adult brains, but it does trigger apoptosis in immature brains. Campbell next wants to study how the drug affects adolescent brains, to see if this can explain the drug's damaging effects in some adolescent users. Meanwhile, she believes we need to warn women, especially teenage girls, to avoid cannabis if they might be pregnant.

Transports of delight?

Serotonin in the brain can affect our mood and behaviour, but how is it transported from cell to cell? Biochemists at TCD are investigating

Sleep, appetite, mood and pain… just some of the behaviours and neurological processes influenced by serotonin. That's quite an impact for a small molecule, but serotonin is a neurotransmitter – a signalling molecule that nerve cells in the brain use when sending a chemical message to neighbouring neurons – and disruptions to the body's serotonin system are thought to be central to many neurological disorders. So scientists worldwide are studying how serotonin is regulated and transported, work that has already led to the current generation of antidepressants, the selective serotonin re-uptake inhibitors (SSRIs) that include Prozac.

At TCD, biochemist Prof Clive Williams, Dr Jana Haase and PhD student Francesca Magnani have characterised one crucial regulator of serotonin levels, the serotonin transporter protein. This sits on the surface of neurons near junctions with other cells, and is itself thought to be tightly regulated, possibly by binding with other proteins that can increase or decrease its activity, resulting in more or less serotonin being transported in and out of the neurons, and thus regulating the amount of neurotransmitter available for signalling to neighbouring cells. Williams's team identified one such regulator, syntaxin 1A, and found that, in the laboratory at least, it prevents the serotonin transporter from functioning. They also found that syntaxin 1A does indeed bind to the transporter protein, and that both proteins occur together on the cell surface, in specialised regions called rafts. They now plan further experiments to see if these reactions also happen in real life, work that will help shed light on these important mood-modifying molecules.

Genes and autism

Genetic studies at TCD have successfully identified one gene that is associated with autism

Severe autism affects about one person in every 1,000, but milder forms are more common, affecting perhaps one in every 250. While it is still not known what causes the problem, it is now clear that autism can run in families and there is good evidence to suggest genes are involved, possibly as many as 20 genes. Among those trying to untangle this puzzle is psychiatrist Dr Louise Gallagher, who researches autism genetics at TCD. Her group has now conducted studies with 200 Irish people and over 1,000 people from other countries, and identified several genes that are associated with autism in the Irish population. One of these is located on a particular region of chromosome No 2, which researchers elsewhere also believe may be linked to autism. But what do these genes do?

Two interesting genes that the TCD group has studied are: the serotonin transporter, which codes for a protein that transports the neurotransmitter serotonin, and dopamine beta hydroxylase, which codes for an enzyme that converts another neurotransmitter, dopamine, to noradrenaline. The enzyme is particularly interesting as it may influence the severity of the disorder, and Gallagher found that children with autism have more enzyme in their blood than normal. Most recently, with PhD student Judith Conroy, the group has identified another gene associated with autism, and which is known to influence the connectivity between cells. This finding has yet to be published, but this gene may affect the ability of nerve cells in the brain to make connections, and the next step would be to investigate the gene's function further. All of which research is helping shed light on this complex and puzzling disorder.

Characteristics of Autism

Autism is characterised by severe problems in communication and behaviour and an inability to relate to people in a normal manner.

The outstanding characteristics are extreme aloneness, difficulty in relating to other people, severely impaired or no speech, insistence of the preservation of sameness, intellectual impairment in some areas - sometimes accompanied by normal or superior skills in other areas such as arithmetic, music, art or memory.

Autism occurs more frequently in males than females (approximate 4:1 ratio). There are between 1200 and 2000 children and young adults with autism in Ireland, increasing at a rate of some 100 new cases every year. Recent studies in Ireland found an incidence rate of 15 per 10,000 births.

Source: Irish Society for Autism

Diabetes: Understanding a common condition

"The daunting statistics for diabetes in Ireland are: 200,000 people in Ireland have diabetes. A further 200,000 people in Ireland have diabetes but are unaware they have it."

Source: Diabetes Federation of Ireland

Coping better with diabetes

Health psychologists at TCD have identified psychological factors that can help people to manage their diabetes

Why is it that some people with diabetes can manage their disease better than others? Is it because their disease is more stable and easier to manage? Or because they have a more positive attitude, which makes it easier for them to cope? Health psychologist Patricia White and Prof Tom O'Dowd, of TCD's department of Public Health and Primary Care, set out to investigate this, first talking to patients and their families in small focus groups, and then with a larger survey of patients attending diabetes clinics.

They looked at two types of people: those with good control of their disease, and those with poor control. A crucial factor seems to be the person's attitude and perception.

People with poor control are more likely to be distressed or angry about their diabetes, and to have trouble sticking to a diet. Their way of coping with the problem is, as it were, to avoid it, by using distracting therapies. In contrast, those with good control of their symptoms are more likely to tackle any problems that arise. Armed with this information Ms White is beginning a new study, to see if people with poor control of their disease can be helped to devise better coping strategies. Significantly, the current study also found that many patients have a poor understanding of diabetes and its long-term implications, suggesting that health professionals need to look at how and when information is presented to people.

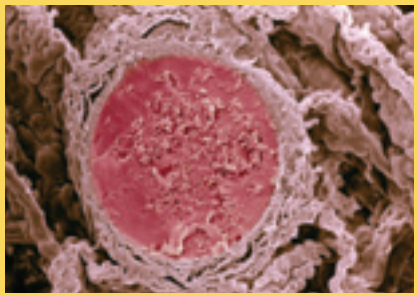
A nutrient that makes you make insulin

Biochemists at UCD have discovered that glutamine prompts your pancreas cells to make the hormone insulin

When someone develops Type II diabetes, the first thing that happens is that their body stops responding to insulin. Their muscle and fat cells, for instance, no longer respond to the hormone, and no longer take up glucose from the blood. Result: blood glucose levels rise. Then their pancreas, which normally produces insulin, starts to fail, so their insulin levels drop, and their blood sugar problems get worse. To understand why this happens, Dr Philip Newsholme and PhD student Mary Corless are studying the detailed biochemistry involved in insulin production.

Using state-of-the-art technologies which are unique in Ireland, they study pancreatic cells in the laboratory and monitor how the beta cells, which produce the insulin, respond to different nutrients. In this way they identified a key nutrient, an amino acid called glutamine, that helps the beta cells to survive. Glutamine is produced when proteins are digested, and plays an important role in various tissues. In the brain and liver, for instance, it is involved in the synthesis of neurotransmitters and urea respectively. Its role in the pancreas was not known until the UCD team discovered that it stimulates the cells there to begin insulin production, news which they have now published internationally. The next step, Dr Newsholme says, is to discover what is actually happening – how glutamine switches on the insulin gene, for instance – information which might one day lead to better treatments for diabetes.

When blood vessels are damaged



Why are people with diabetes prone to cardiovascular trouble? Pharmacologists at UCD found that an enzyme is part of the problem

Heart attack, stroke, poor circulation, even gangrene…just some of the serious cardiovascular complications that can arise for people who have Type II, or late-onset diabetes. Now, you may be wondering, how trouble with high blood sugar levels can cause such problems. The root cause, it seems, is that high blood sugar levels can increase the concentrations of certain energetic oxygen molecules circulating in the blood, and these can damage the endothelial cells that line the blood vessels.

To investigate what exactly is happening, Dr Alan Keenan and PhD student Erika Harno examined samples of blood vessels taken from a strain of laboratory rat that is prone to Type II diabetes. They found that, if the rats had diabetes, a crucial enzyme did not work properly: instead of producing nitric oxide in response to insulin, this nitric oxide synthase enzyme produced a damaging superoxide molecule. Result: damaged blood vessels. Studies elsewhere have shown that folic acid (one of the B vitamins), and certain drugs called ACE inhibitors can help counter this damage. Keenan thinks they do this by helping the enzyme to work more efficiently, and next he hopes to study how these compounds interact with insulin and with the enzyme.

The current study threw up another important finding: at higher insulin doses the mis-functioning enzyme produces even more superoxide. Yet high doses of insulin are sometimes used to treat diabetic patients who have had a heart attack. Keenan warns that their findings mean this approach should be taken with caution.

Image caption: small blood vessel in alveoli

Protecting cells from the ravages of diabetes

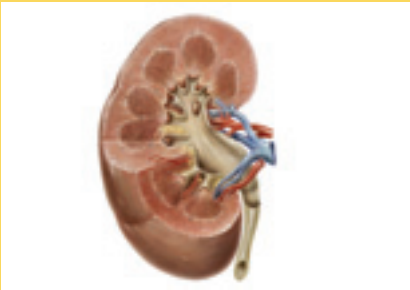
Could a simple dietary supplement protect cells from some of the damaging effects of diabetes? Two TCD biochemists think so

Taurine is a small yet fascinating molecule. A type of amino acid, it was first isolated from beef – the name comes from *taurus*, Latin for bull – but most of our tissues actually have lots of it, which suggests it does something important. Our bodies synthesise taurine, but we also get it from our diet, and large amounts are added to some dietary supplements and soft drinks. Despite the bullish name, taurine's main functions seem to be protecting our cells from damage. The molecule has fascinated Prof Keith Tipton for decades, and with PhD student Joseph Healy he recently investigated taurine's role in two very different situations: nerve death, and diabetes.

Giving a toxin called MPTP to laboratory rats will cut off the energy supply to their nerve cells, resulting in a condition similar to Parkinson's disease. But Tipton and Healy found that, if the rats are first given a taurine supplement, this protects their nerve cells from damage by the toxin. However, give the rats too much taurine and, mysteriously, the effect disappears.

To investigate taurine's role in diabetes, Tipton and Healy, collaborating with colleagues in Italy, gave laboratory rats streptozotocin, a toxin that kills the pancreatic cells which produce insulin. As a result, the rats developed insulin-dependent diabetes, when, typically, blood sugar levels rise and fat cells can no longer take up glucose. But as before, if the rats were first given taurine, their fat cells were somehow protected and continued to take up glucose as normal. Significantly, these rats did not experience the tissue starvation normally seen in diabetes, although their blood sugar levels were still high. This suggests that some diabetes patients might benefit from taking taurine along with their glucose-lowering drugs, though clinical trials would be needed to confirm this.

When your kidney becomes fibrous and fails



Cell biologists at UCD are chasing new drugs that could prevent kidney disease in diabetic patients

Of all the complications of diabetes, one of the worst is kidney failure, which leaves many patients needing dialysis or, worse, a transplant. Connective tissue and collagen start proliferating and invade the kidney, and the kidney cells' internal skeleton or scaffolding becomes disrupted. Result: diabetic nephropathy. In 1994, scientists described the proteins or 'growth factors' that drive these changes and that are somehow activated by high blood sugar levels. Now, a handful of specialist research teams worldwide study the detailed biochemistry of these growth factors, including scientists at UCD's Conway Institute. There, cell biologist Dr John Crean and Prof Catherine Godson have pieced together the steps involved for the connective transforming growth factor, alias CTGF.

Like other growth factors, CTGF has diverse functions, but in fibrotic disorders it seems to specifically drive the accumulation of connective tissue. Hence it is a possible target for treatments in diseases such as diabetic nephropathy. US company Fibrogen, which owns the rights to CTGF, already has promising results from early clinical trials with an antibody that knocks out CTGF, and the firm supplied purified CTGF to UCD. This allowed Dr Crean to discover that CTGF first binds to a particular cell surface molecule, and that this releases two biochemical signals that tell the cells to produce more fibronectin and collagen. Crean found that increased levels of CTGF are probably also responsible for disrupting the kidney cells' skeleton. These fundamental biochemical discoveries are helping the US company to refine its clinical trials, and the UCD researchers are now screening potential drug compounds that block CTGF, as an alternative to antibodies for treating fibrotic diseases.

A gremlin in the kidney works

The gremlin gene damages the kidneys of people with diabetes but, as UCD researchers have found, embryos need the same gene for their kidneys to develop properly

People with diabetes often develop kidney failure. Their kidneys can become scarred, the kidney cells may grow wildly, and the filtering channels can become blocked and eventually fail. When that happens, the person will need dialysis or, worse, a transplant. In 2000, researchers at UCD's Conway Institute discovered that a gene called gremlin was involved in this diabetic kidney disease. The more active a person's gremlin gene, the worse their kidney disease was likely to be. But what is the normal, healthy function of this gene? To investigate, Dr Vincent Dolan, a kidney consultant, teamed up with Dr Carmel Hensey, who studies how tadpoles develop.

Together, they discovered that gremlin is essential for healthy kidney development in the embryo. So essential, that it has changed little in millions of years and frog gremlin is very similar to human gremlin, even though frog kidneys are much simpler than ours. Dolan and Hensey found that if there is little or no gremlin activity (if they knocked out the gremlin gene, for instance), tadpoles develop only a rudimentary kidney at most; and with too much gremlin activity, they develop extra kidneys. Normally, the gene is switched off in adults, but in diabetic kidneys it somehow switches on again, triggering inappropriate growth that damages the tissue. The scientists hope that, if they can understand how gremlin does this, it could lead to a treatment that would prevent this damage.

What is diabetes?

Diabetes Mellitus, or just diabetes as it is more commonly known, occurs when the sugar (glucose) level in the blood is too high. This happens when the body is not burning up carbohydrates properly due to a defect in the pancreas, the gland that produces insulin. Insulin is the hormone which keeps blood sugar levels within the normal healthy range. Diabetes may be present either when no insulin is made or when insulin is made but not working properly.

There are two types of diabetes - type 1, or insulin dependent diabetes, which usually occurs before the age of 35. A person with type 1 diabetes makes no insulin and therefore needs to inject insulin to regulate blood sugar levels and remain healthy. Type 2, or non-insulin dependent diabetes usually occurs in adults after the age of 40 and is extremely common in old age. In this case, the person with diabetes makes some insulin, but this does not function properly. Usually associated with being overweight, this condition responds well to weight loss through dietary regulation. Sometimes weight loss is not enough and tablets are required to help the person's own insulin to work. This type of diabetes is also known as adult-onset or maturity-onset diabetes.

With an average of seven years between onset and diagnosis, the earlier the condition is detected the easier it will be to manage. Early detection gives the ability to protect against heart attack.

Diabetes is considered by the World Health Organisation (WHO) as a growing epidemic with present numbers of people affected by diabetes set to double over the next 10 years to 240 million worldwide.

The incidence of the disease in Irish adults is also expected to rise dramatically in the immediate future as a direct result of the growth in obesity. It is estimated that up to 75% of the risk of type 2 diabetes is caused by obesity.

The daunting statistics for Diabetes in Ireland are: 200,000 people in Ireland have diabetes. 200,000 people in Ireland have diabetes but are unaware they have it. A further 250,000 people have impaired glucose tolerance or “pre-diabetes” of which 50% will develop diabetes in the next 5 years if lifestyle changes are not made.

One of the most disturbing trends in the area of diabetes at present is the growing number of children now being diagnosed with type 2, where traditionally this was a disease of the over 50s. The reason for this is lifestyle, and in particular obesity.

Source: Diabetes Federation of Ireland

Cancer: Tackling the big C

"Thanks to new genetic techniques, scientists are discovering how certain cancer drugs work, and the information is helping to identify which patients will respond well to the drugs."

Source: 'Genes, drugs and cancers', Prof Mark Lawler and colleagues (St James's Hospital)

New screening tests for colon cancer

Two clinical research teams are developing new tests and approaches to screen for colon cancer in Ireland

If colorectal cancer can be detected early, then the prognosis is excellent, with 97% of patients surviving to the crucial five-year point. But that's a big 'If', and it all depends on having an accurate and effective screening test. The current 'gold standard' is colonoscopy, but this is invasive, time-consuming and costly. The alternative is a test for blood in the stool (the faecal occult blood test, or FOBT), which is relatively cheap and quick, but only about one-third as effective as a colonoscopy, and it misses up to 50% of cancers. Clearly, we need a better screening test, and in 2003 a German company, ScheBo, released a commercial test that looks promising. Now, gastroenterologist Prof Colm O'Morain, of the Adelaide & Meath Hospital, Tallaght, with Dr Ramona McLoughlin and PhD student Ellen Shiel, have given the German kit its first independent clinical trial.

The kit tests for the presence in stool samples of an enzyme, called M2-PK. This enzyme is closely associated with several cancers, and so its presence in stool samples would indicate the existence of colorectal cancer. The Tallaght team tested stool samples from 162 patients, of whom 97 had a normal colonoscopy, 30 had pre-cancerous growths (adenomas), and 35 had colorectal cancer. They found that the new kit performed well, detecting 97% of the cancers, and 76% of the adenomas that had been detected by colonoscopy. While this trial was relatively small, it suggests that the stool M2-PK test has great promise in screening for colorectal cancer. As an added plus, the new kit is analysed using a technique known as ELISA that is ideal for automated mass screening.

Meanwhile, at St Vincent's University Hospital in Dublin, Dr Kieran Sheahan and colleagues have validated a new screening test for familial forms of the disease. Some 5% of all colon cancers are known to be inherited, and if a hereditary form is diagnosed, then other family members who may be at risk need to be identified. But with increasingly smaller families, the traditional family history approach is difficult, so a new generation of test focuses on what happens at the DNA level.

Most familial colon cancers develop when someone lacks a working version of one of the enzymes responsible for repairing errors in DNA. Errors accumulate, notably multiple copies of short DNA sequences, called microsatellites, and the new test works by screening for certain microsatellite patterns. Sheahan found that the test successfully picks up 60% of the known familial cases (in other words, detects 3% of all colon cancers). This complements an existing antibody test that can tell which DNA repair enzymes are present or absent. Happily, people with some forms of familial colon cancer have a good prognosis – possibly because their distinctive tumours provoke a strong immune reaction which helps fight off the cancer – but intriguingly, their tumours do not respond well to the usual chemotherapeutic drugs, so an added benefit of these tests is identifying cases where other approaches should be used. This makes the antibody and new microsatellite test especially useful.

Sheahan believes that all colon cancer patients should be screened with these tests, so that other 'at risk' relatives can be identified quickly, and having validated the microsatellite test for Irish families, his team is now a reference centre for other Irish diagnosis units.

Cancer, commuting and quality of life

Regional treatment centres would make life much easier for families who currently have to bring a child to Dublin for cancer care, a UCC study finds

It's bad enough if your child is diagnosed with cancer or leukaemia, but if they have to travel long distances to Dublin for treatment, that brings added difficulties. In Ireland, primary cancer care is effectively centralised in Dublin, and 16 of the 17 regional 'shared care centres' provide only emergency care. Dr Peter Kearney, a consultant paediatrician at Cork University Hospital, wondered how this affects the families, and how other countries provide care in regions with a similar low-density population. He and child psychologist Dr Anne Gaffney and researcher Brenda Morris interviewed families and specialist nurses in Ireland, and cancer experts here and in Scotland, Wales and Bristol in southwest England.

If families cannot make the round trip to Dublin in one day, the travelling can mean major disruption, prolonged separation, sibling neglect and money worries, especially if it entails lengthy stays away from home. In the UK, the team found, these problems are largely averted by providing primary cancer care at regional level. In other words: there it's the consultants who do the travelling, not the families. This means the regional centres need additional resources and infrastructure, and expert staff, but already, Irish neonatal care is being reorganised along similar regional lines. Kearney believes that something similar is needed for cancer care, and that this would be a tremendous boon for families coping with childhood cancer.

Genes, drugs and cancers

Research at Dublin's St James's Hospital is helping to predict which patients will respond well to cancer drugs

Thanks to new genetic techniques, scientists are discovering how certain cancer drugs work, and the information is helping to identify which patients will respond well to the drugs. At the Institute of Molecular Medicine in St James's Hospital, Prof Mark Lawler, Prof Shaun McCann, Dr Eibhlin Conneally, PhD student Lorraine Tracey and postdoc Dr Kathy Gately, are investigating interferon alpha (INF-α), which is used to treat cutaneous T-cell lymphoma and chronic myeloid leukaemia (CML), and imatinib mesylate (brand-name Glivec), also used to treat CML.

Glivec is one of the new molecular medicines: designed specifically to interact with a molecule in the cancer cells, it promises to revolutionise CML treatment, which until now usually needed a bone marrow transplant. The team has developed a molecular test to monitor the progress of patients taking Glivec, and they discovered that, when a patient becomes resistant to the drug, this is often due to mutations in the gene for a kinase enzyme. This information may help improve the next generation of drugs, or identify drugs to be taken in combination with Glivec.

For the cutaneous T-cell lymphoma, which manifests as skin lesions, the researchers – in collaboration with the National Cancer Centre in Madrid – identified six genes that are altered in the cancers. This genetic signature could be the basis of a test for this disease, which can be difficult to diagnose. The team also identified a genetic signature, involving some 40 genes, for patients who respond well to INF-α treatment. If these can be narrowed down to a handful of key genes, it could form the basis of a prognostic test to predict which patients will respond to treatment.

Keeping cancer at bay after surgery

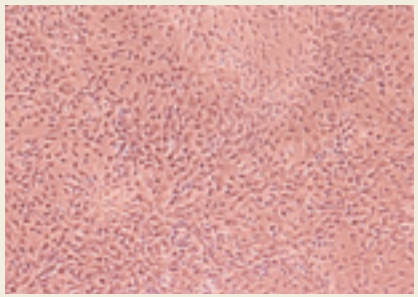
Cancer researchers at Cork University Hospital are studying why some cancers return aggressively after surgery

It is a natural and understandable reaction. Our immune system perceives surgery as a wound, and responds with lots of immune cells and molecules designed to promote healing and regrowth. The question that researchers at Cork are asking is, do these healing and growth promoting substances affect any cancer cells that might be present. It is an important question, as cancer surgeons can't always be sure they have removed every last cancer cell. Increasingly, evidence, much of it from research at UCC,* suggests that the immune response to surgery can indeed make cancer cells grow aggressively. Now, cancer surgeon Dr Calvin Coffey and colleagues at UCC's University Hospital have investigated how this might be happening.

Studying tumours taken from laboratory rats and from biopsies donated by cancer patients, they discovered that several genes are turned on in tumour cells after surgery. The genes are involved in a process called the PIC-kinase pathway, and the net effect is to make the cells grow and in such a way that they become resistant to several chemotherapy drugs. However, if the researchers treated the cancer cells with a chemical that blocks the PIC-kinase pathway, they found they could reverse the change and almost 'tame' the tumours. But the tumours still grew, albeit more slowly, suggesting they can use an alternative pathway, one Coffey hopes to identify soon. Clinical trials with patients are still some way in the future, but these latest results confirm that surgery can, perversely, stimulate the tumour it was intended to kill.

*Last year, we reported on related research from another Cork team, who discovered that tumours in lab rats are less likely to return after keyhole surgery, than after more intrusive open surgery, probably because keyhole surgery does not provoke such a strong immune response.

How cells control their self-destructive tendencies



Cell biologists at TCD have worked out how a particular protein regulates cell suicide

The cells in your body have a self-destruct mechanism. It's how they remove themselves from the scene when their job is done, or they have become old, damaged or infected. Scientists call the process apoptosis, and it's tightly regulated by a complex interplay of numerous controlling mechanisms so that it happens only when it should. Sometimes, however, the controls become faulty and cells commit suicide when they should not – if eye cells did that, for instance, you would go blind – or they don't self destruct when they should, in which case they proliferate and form tumours.

One protein that helps keep apoptosis under control is called Smac, and Dr Emma Creagh, working with Prof Seamus Martin at TCD's genetics department, has now pieced together the Smac picture. Creagh has discovered that Smac is normally kept under wraps in a special compartment in the cell and only released when the cell is fully committed to self destructing. Smac's release is normally held in check by another protein, called Bcl-2; many cancer cells have higher than normal amounts of Bcl-2, so this explains why they can no longer release their Smac and trigger self-destruction. Significantly, Creagh discovered that Smac's role is to ensure that the caspase enzymes which essentially dismantle the cell can get to work, and that Smac does this by inhibiting the proteins that normally inhibit the caspases. There is now growing interest in drugs that can mimic Smac and force cancer cells to die. Clinical trials of several are underway, and the TCD research has helped the pharmacologists to understand how the new drugs work.

Software – for a better fitting drug

Pharmaceutical chemists at TCD have designed computer tools for drug design that have already helped identify possible new drugs to fight breast cancer

Time was when drug designers relied on serendipity and 'hit and miss' screening to identify new drugs. These days they're more likely to use computers to design the perfect drug, exploiting powerful software, DNA sequence information, and 3D pictures of what a particular target protein looks like, combined with detailed chemical data about how the existing drugs work, to produce improved designs which can then be tested in the lab.

At TCD, pharmaceutical chemist Dr Mary Meegan wants to design new drugs for breast cancer, perhaps more effective or with fewer side-effects or cheaper to manufacture than the current drug, tamoxifen. Tamoxifen acts by binding to oestrogen receptor proteins in breast cancer cells; oestrogen normally binds there, and switches the cells into proliferation mode, but when tamoxifen binds it changes the receptor's shape and prevents oestrogen from binding and the cells from proliferating.

Meegan, colleague David Lloyd and PhD student Andrew Knox use software written by their collaborator, Vladimir Sobolev of the Weizmann Institute, to assess computer models of hundreds of chemicals and how well they interact with the oestrogen receptor. They confirm the fit by testing the compounds on breast cancer cell lines in the lab. Significantly, they have devised a new and powerful scoring system to rate how each compound fits with the oestrogen receptor, something they may be able to commercialise. Already, they have successfully identified several hopeful candidates, new would-be tamoxifens, and these will shortly be tested on breast cancer cells in a follow-up study.

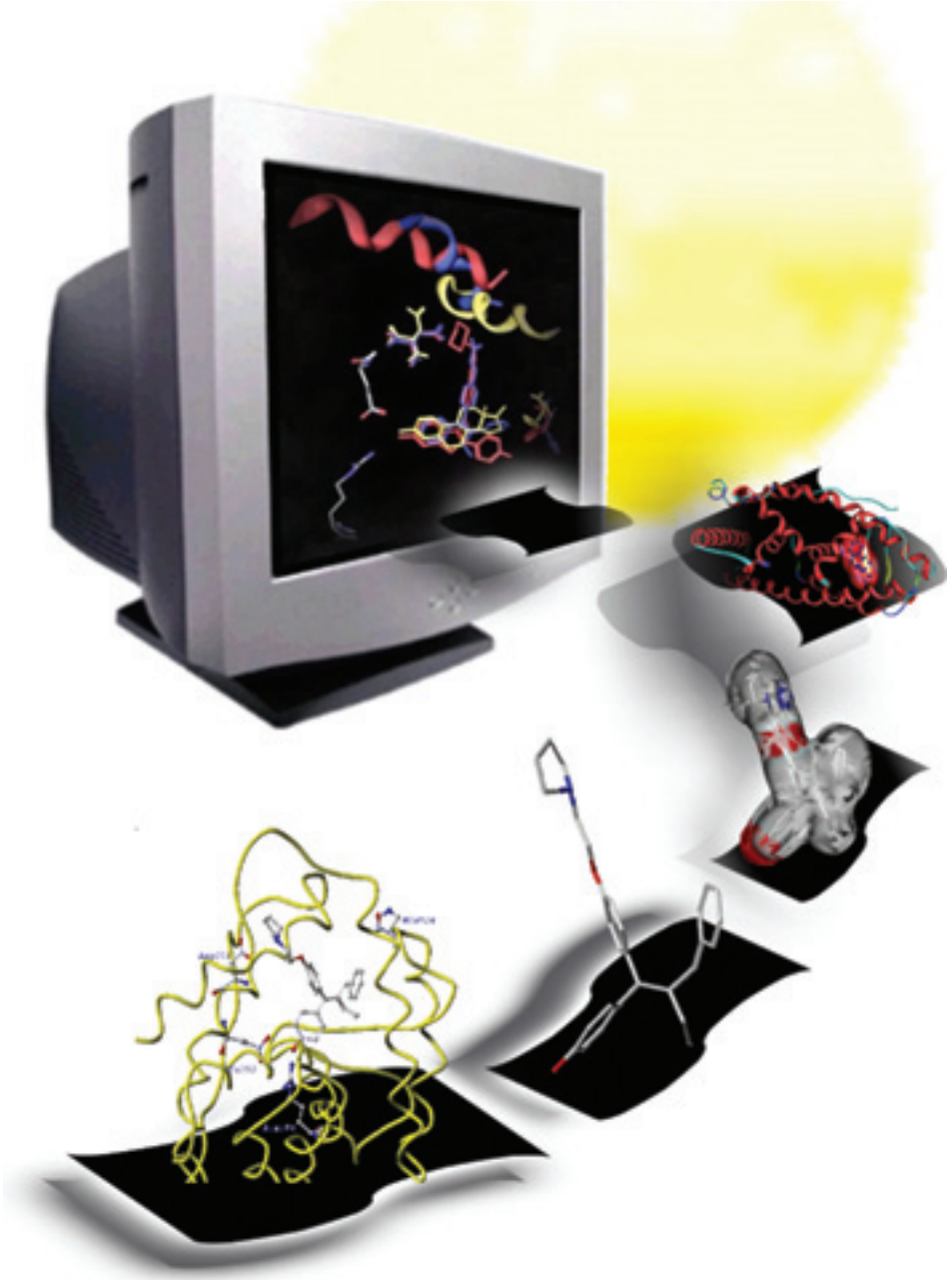


Image caption: Three crystal structures of the oestrogen receptor are shown superimposed on the computer screen. The platforms emerging from the computer represent the levels of screening from (a) cavity analysis of receptor binding site to (b) ligand complementary volume to (c) selection of ligand to (d) docked structure.

Chernobyl, radiation and thyroid cancer

Some 18% of thyroid cancers among Irish patients could be due to radiation similar to that released by the Chernobyl disaster, a TCD study suggests

The most common form of thyroid cancer is papillary thyroid cancer (PTC), so-called because the tumour is covered with nodules or papillae. Fortunately, PTC seldom kills. But that changed with the Chernobyl disaster, when a new and more lethal form of PTC became common in children there. In the 1990s, geneticists discovered that this Chernobyl form was associated with a particular rearrangement of chromosome 10: essentially, a chunk of DNA flipped over, bringing together two genes that were normally located far apart.

This change, called ret/PTC3, left one particular gene permanently switched on, driving a process (known as the MAP-kinase path), which causes thyroid cells to grow wildly. A different rearrangement, called ret/PTC1, is seen in the less aggressive, classical PTC. Dr Stephen Finn has now found the Chernobyl rearrangement in 18% of Irish papillary thyroid cancers, although the Irish cancers are not identical to those seen in Chernobyl – for example, their appearance under the microscope is slightly different.

Significantly, by irradiating cells in the laboratory, Dr Finn has discovered that the Chernobyl rearrangement is caused by gamma radiation, such as given off by caesium-137 (the main radioactive isotope released by the Chernobyl explosion); conversely, beta radiation (as given off by radioactive iodine), and X-rays can cause only the classical rearrangement. However, this is not to say that 18% of thyroid cancers here are due to Chernobyl, as more data would be needed to rule out other sources.

Dr Finn, who is part of a thyroid cancer research team led by Dr Orla Sheils at TCD's department of histopathology, also discovered that the gamma radiation acts by removing part of the protective cap at the end of chromosome 10, which may make the chromosome more sticky and more liable to rearrangement. Intriguingly, chromosome 10 is particularly vulnerable, possibly because its position in the nucleus of the cell is more exposed.

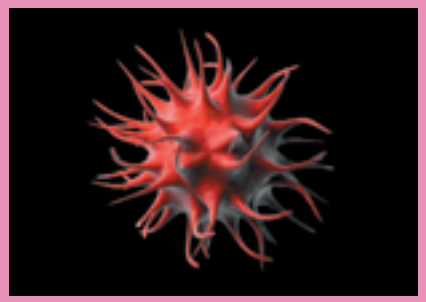
In characterising Irish thyroid cancers, Dr Finn identified a new risk gene, platelet-derived growth-factor receptor-beta (PDGFRB), the first time this gene has been associated with thyroid cancer. The gene acts in the same MAP-kinase path as ret/PTC and may account for a further 20% of Irish thyroid cancers. Finally, the TCD study identified several other genetic changes associated with thyroid cancer and they are now working with industrial partners to design better diagnostic tests. Current tests are imprecise, and surgery is often needed to confirm a diagnosis, so a better test would save many people from unnecessary surgery.

Immune affairs: The battle rages

“…a little inflammation is a good thing.”

Source: ‘Parasites, hygiene and allergy’, Dr Deirdre Campion (Veterinary science, UCD)

Viruses and you – it's an arms race!

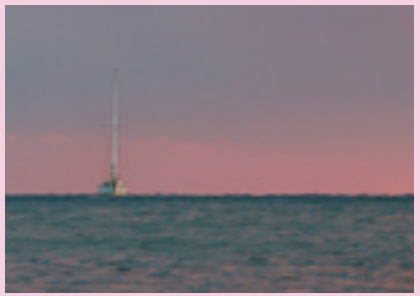


A better understanding of our immune system is coming from research under way at TCD

It's an arms race. Your body's immune system constantly works to detect and destroy viruses, and the viruses fight back by developing ways to slip past the 'radar', evade capture and even subvert the immune system to their own end. And Vaccinia, the virus that is the basis of the smallpox vaccine, is particularly good at this, because it can disable our body's alarm system. The alarm depends on molecules known as the toll-like receptors (TLRs), which normally alert your body to the presence of an invader and set the immune system to attack. But Vaccinia produces two proteins that disable the alarm, by inhibiting the biochemical pathways that are triggered by the TLRs. This allows the virus to survive inside our cells and explains why, occasionally, a Vaccinia vaccine can make some people ill.

TCD biochemists Dr Andrew Bowie and PhD student Geraldine Maloney have now studied what one of the viral proteins, known as A52R, does inside our cells, and found that it binds to two different alarm proteins, IRAK2 and TRAF6. By binding to IRAK2, they found, it turns off the processes that would normally switch on a suite of genes aimed at eliminating the virus. By binding to TRAF6, it turns on other processes that produce more interleukin-10, a protein that allows viruses to survive for longer in the body. So, not only does A52R evade the immune response by blocking TLR effects, it also subverts the TLR system for its own purposes. This TCD work has improved our understanding of how the immune system deals with viruses, and may one day help us design better vaccines.

Getting back to normal after inflammation



Shape-shifting cells are important in resolving inflammation, UCD cell biologists have discovered

Shape-shifting doesn't just happen in sci-fi movies – it can also be important in determining how cells function in the body. And cell biologists at UCD's Conway Institute have discovered it plays an important role in restoring normal function after inflammation. Inflammation is an important aspect of our body's defences, but chronic inflammation is the basis of several serious illnesses so it is important to restore normal function quickly. Prof Catherine Godson and PhD student Keira Reville are investigating one important mechanism involved: the specialised macrophage cells that clear away dead and dying cells which accumulate at inflamed sites, and how this task is controlled. The dying cells normally remove themselves from the scene by following a 'cell suicide' programme called apoptosis. These apoptotic cells have to be removed, however, before they burst and release their potentially toxic contents. Enter the macrophage, a cell that can engulf them, a process helped along by lipid or fat-like molecules called lipoxins, which are naturally produced in the body.

Prof Godson and her team have now discovered that lipoxins function by triggering changes in proteins inside macrophages causing them to change shape. This change 'primes' macrophages and enables them to engulf more dying cells – increasing their appetite, as it were. A specific protein in the macrophage, called myosin, seems to be crucial: when the researchers blocked myosin, the macrophages could no longer respond to the lipoxins: they did not change shape, and did not consume more dying cells. This finding helps us understand how inflammation is resolved, and may suggest new ways to treat chronic inflammatory conditions associated with inadequate removal of dying cells.

Finding a system that controls lung inflammation

Medical researchers at the Royal College of Surgeons are investigating how our immune system switches inflammation on and off

If you have a lung infection, your immune system will react and try to protect your lungs by mounting an inflammatory response. But inflammation, while necessary to fight infection, can be harmful if it continues and so, once the infection has cleared, your body has to be able to switch the inflammation process off. At the Royal College of Surgeons in Ireland, Dr Clifford Taggart is investigating just how the immune system does this.

One of the main proteins orchestrating the inflammatory response is called nuclear factor κB (NFκB), which works by binding to DNA in the cells, and switching on genes that code for pro-inflammatory proteins. In healthy cells, NFκB is normally prevented from binding to the DNA by what are called the inhibitory κB (IκB) proteins. When inflammation is needed, these IκB are taken out of the way, by being chemically marked for destruction, and then degraded by various enzymes. The cells normally switch off the inflammation by producing anti-inflammatory proteins, including one called secretory leucoprotease inhibitor (SLPI), and Dr Taggart's research has shown that this interacts directly with DNA, thus preventing NFκB from binding and from switching on the inflammation genes. Taggart's next step is to study cells in biopsies taken from patients who have chronic lung inflammation, to see if the mechanism he observed in cells in the laboratory is what actually happens in real life, and to find out what goes wrong when chronic inflammation develops.

Parasites, hygiene and allergy

Physiologists at UCD's Veterinary College find that a little inflammation is good for your gut

They call it the hygiene hypothesis. The notion that, if our immune system is to work properly, then it must be challenged early in life. And if this doesn't happen, the immune system may respond inappropriately later in life, leaving us prone to allergies and problems such as inflammatory bowel disease. As the intestine is exposed to large numbers of foreign bodies and pathogens it ought to be an important site for immune system training.
To investigate events there, gastro-physiologists Dr Deirdre Campion and Prof Alan Baird, and PhD student Ms Leah O'Brien, study the effects of infection with a parasite that causes mild inflammation of the gut wall.

The team discovered that a little inflammation is a good thing. It makes the body produce more immune cells and nerve cells. During infection, these induce the gut to secrete more water, resulting in diarrhoea, which helps flush out the parasites. There is a long-term benefit too: even after the parasite infection has cleared, the gut wall remains primed, and ready to respond to any subsequent exposure to parasites, bacteria or viruses. In effect, the first mild infection makes your body more resistant to later infections. However, a severe parasite infection seems to make the immune system hypersensitive, resulting in chronic inflammation and diarrhoea that can persist for long after the original infection has cleared. The results suggest that training is important. The team's next project is to look at ways of exploiting this to prevent Salmonella infections in hens, where it poses a health hazard if people eat contaminated chickens or eggs.

How an infection can trigger an asthma attack

At NUI Maynooth, cell scientists have pieced together a biochemical chain reaction that starts with an infection and ends with asthma

Thanks to the sequencing of the human genome, scientists have identified several genes associated with asthma. But what do these genes actually do? Scientists at NUI Maynooth's Institute of Immunology, led by Dr Bernard Mahon, are focusing on one such gene, which codes for a protein called CCL28 that is involved in signalling between cells. They have now pieced together much of the CCL28 story and can even explain how a chest infection might trigger an asthma attack.

First, they cloned the gene, then made CCL28 protein, and devised two ways to measure how much CCL28 is present in cells and secretions. Thus equipped, they discovered that CCL28 is normally present at low levels in the cells lining the airways and that, in mice, CCL28 levels rise dramatically during an asthma attack. Significantly they also discovered that CCL28's role is to physically mobilise certain immune cells, the TH2 cells, which orchestrate the inflammation associated with asthma. Perhaps most interestingly, they discovered that the presence of another signalling molecule, IL-1β, will cause CCL28 levels to rise, and IL-1β itself is already known to rise when there is a bacterial infection. So Dr Mahon suggests that, first, an infection triggers higher IL-1β, which raises CCL28 levels, which mobilises TH2 cells, which result in inflammation. To test his hypothesis, he next wants to see if CCL28 levels vary in asthma patients with the severity of the disease, and if drug treatments work by lowering CCL28 levels. All part of trying to understand a major disease that is on the increase.

The white blood cell that can restrict your breathing

Research at the Royal College of Surgeons is shedding light on the mechanisms that trigger asthma attacks

They are having asthma attacks in the labs at the Royal College of Surgeons in Dublin. Happily, these are small-scale attacks, that take place in a dish when nerve cells come in contact with a type of white blood cell called an eosinophil. Eosinophils are produced by the immune system when it perceives a threat; they are also involved in allergic responses, and are found in tissues at the site of allergies. Usually only a few eosinophils are found – typically about 10 for every million other cells. So the big question is: What are they doing?

At the RCSI, respiratory consultant Dr Richard Costello and research fellow Dr Marie Therese Walsh discovered that eosinophils actually irritate nerve cells. In particular, that they stimulate the nerves to produce more of the chemical signal which tells muscle cells to contract. Net result: muscle cells will contract more than they should, just as in an asthma attack, when a person's airways contract. The RCSI team has now discovered the detailed molecular steps that happen when eosinophils and nerve cells interact in the laboratory, and in a new HRB-funded project, will now see if these same things happen in real life in people with asthma. By improving our understanding of asthma, this work might one day lead to better ways of treating the problem.

Liver stem cells – and their many career options

Cell biologists at St Vincent's University Hospital in Dublin have uncovered an important role played by stem cells in the liver

Stem cells aren't just for embryos – these powerful cells, which can mature into specialised cell types, are also found in many adult organs. The best-known adult ones are in the bone marrow, where they give rise to new blood and immune cells. There are stem cells in the liver, too, and researchers in Birmingham have recently confirmed that these can give rise to new liver cells, thus explaining how the liver can regenerate following damage and disease. But the liver is also home to certain immune cells, notably theso-called 'natural killer cells' that have potent anti-cancer and anti-virus powers. An important question in understanding liver function and the immune system, is where do these cells come from?

At St Vincent's University Hospital, Dr Lucy Golden-Mason studies samples donated by patients having liver biopsies, and she has just shown that the immune cells in the liver are generated locally, and from liver stem cells. The Dublin and Birmingham researchers are now collaborating to see if there are two types of liver stem cells – one for immune cells, and one for liver cells – or if, as they currently suspect, there is just one, which is directed into one or other of the 'career options' by factors in the liver. Ultimately, by understanding what prompts stem cells to mature and specialise, we may one day be able to push the stem cells down targeted career paths – into liver cells, to help repair damaged tissue, or into immune cells to fight cancer and infection.

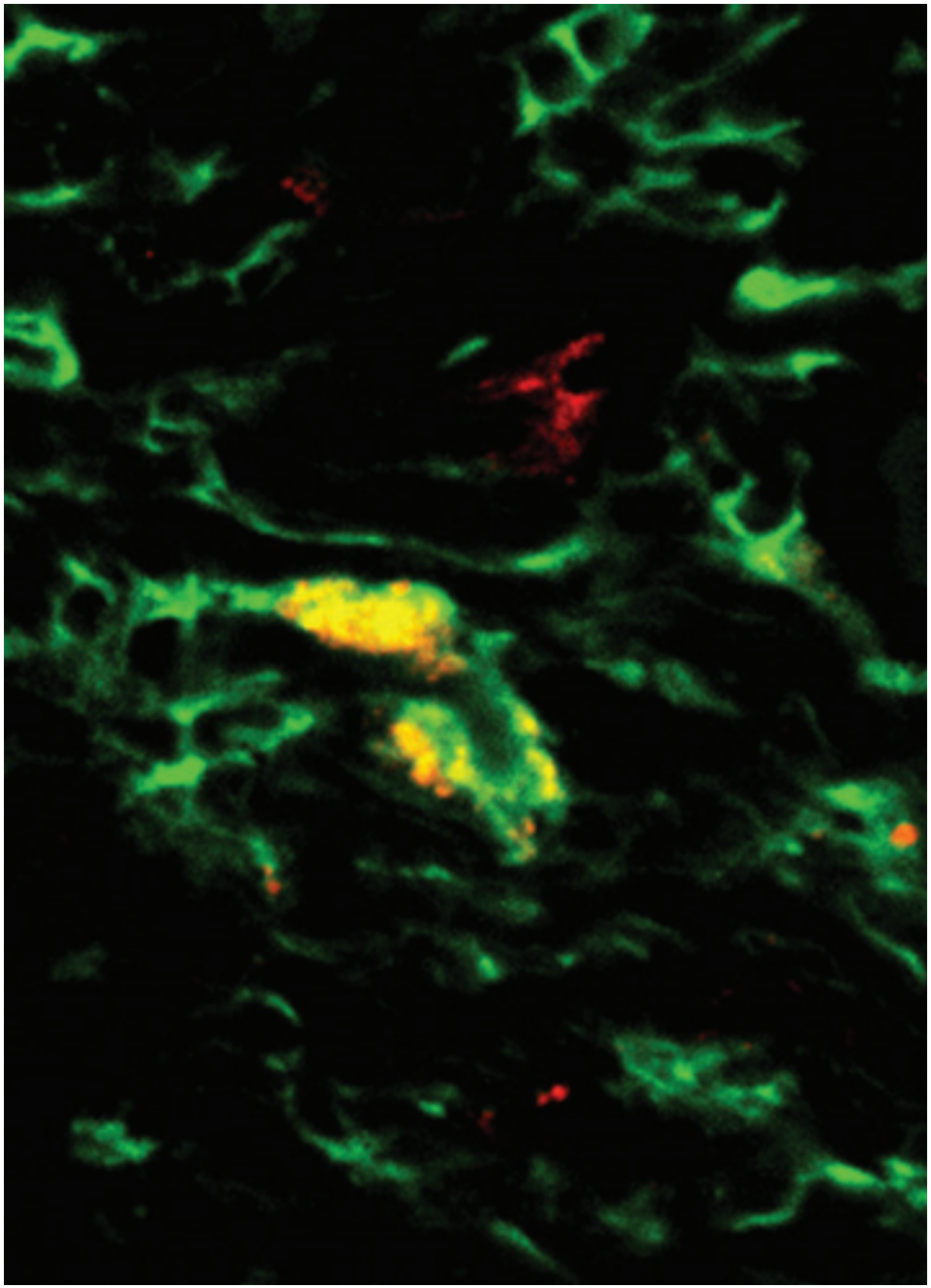
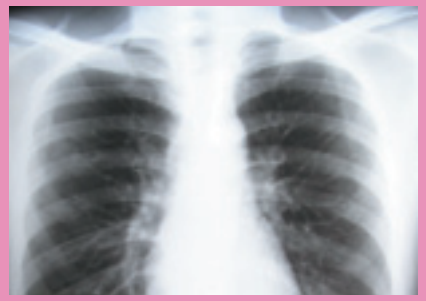


Image caption: Liver stem cells (yellow) positive for both CD45 (green) and CD34 (red)

The waste product that can do some good?



Increased CO_2 levels seem to reduce inflammation, which could benefit some patients. But UCD scientists wonder is there a downside to this simple technique?

People who are gravely ill run the risk of lung damage. This happens if their immune system responds to their condition by flooding their lungs with white blood cells, causing dangerous inflammation. The search is on for ways to prevent this, and tantalising results from previous research have shown that if white blood cells in the laboratory were treated with CO_2, the cells lost their appetite for the fight. Could it be that simply increasing the CO_2 levels in a patient's body would prevent lung damage in patients on life-support machines?

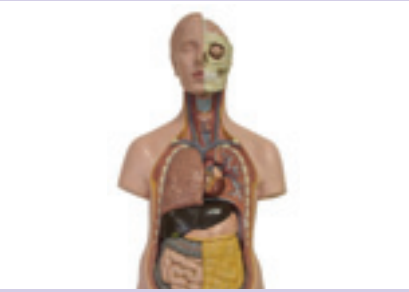
At UCD's department of physiology, Dr Donall O'Croinin and colleagues are exploring the CO_2 effect further. They are looking at what happens in animals, and asking, Is there a downside? After all, if increased CO_2 levels dampen down the immune cells, shouldn't this make the system less able to fight infection? Sure enough, O'Croinin found that rats are more likely to develop damaging lung infections if they are given CO_2. It is, O'Croinin says, the two sides of the same CO_2 coin: the very change that makes the system less likely to cause inflammation, also makes it less likely to fight off infection. So, simple CO_2 treatment will not be the perfect therapy, but it may yet prove useful in certain conditions.

Infections, microbes and gut feelings

"Over the past decade, scientists at UCC have isolated and patented two new strains of probiotic bacteria….. the bacteria might be useful in alleviating the chronic symptoms of inflammatory bowel disease."

Source: 'Probiotics and gut reactions', Prof Fergus Shanahan and colleagues (Microbiology, UCC)

Probiotics and gut reactions



Two new probiotic strains, discovered and patented at UCC, have potent anti-inflammatory and immune-boosting effects that may help alleviate inflammatory bowel disease

Over the past decade, scientists at UCC have isolated and patented two new strains of probiotic bacteria, selected from a long-list of several thousand possibles. Most other probiotics are, surprising though it may seem, isolated from faecal sources, but the Cork two are unique in that they were isolated from healthy gut samples – the rationale being that faecal bacteria could be mere passive passengers through the gut, but that anything that can live happily in our intestine is likely to be on friendly terms with our immune system, and therefore likely to have interesting probiotic effects. Now, in two related projects, scientists in Cork have pieced together how their bacteria work. The results are promising, and suggest the bacteria might be useful in alleviating the chronic symptoms of inflammatory bowel disease.

First, immunologists Prof Fergus Shanahan and Dr Liam O'Mahony, with PhD student Padraig O'Regan, working with lab mice, have proven that the two Cork probiotic strains reduce the immune system's production of inflammatory molecules, while stimulating production of anti-inflammatory molecules, and that they can do this whether taken orally or injected under the skin. This is doubly interesting: it proves the bacteria directly affect the immune system, and that their beneficial effects do not come simply because they out-compete 'bad' bacteria in the gut; also, it suggests that chronically ill people could benefit from injections of high doses of the probiotic bacteria, or active components extracted from them.

The same team also looked at the bacteria's effects on the epithelial cells which line the gut wall. They found that when the cells come in contact with disease-causing Salmonella bacteria, they switch a battery of genes associated with immune defences, but the probiotic bacteria had no effect at all, clear evidence that the gut cells can tolerate these bacteria. The next step is to identify the molecules on the bacteria responsible for the beneficial immune reactions.

In a related project at Cork University Hospital, surgeons Eamon Kavanagh, and Prof Liam Kirwan, with Dr O'Mahony, and PhD student David Shilling, studied how the dendritic cells of the immune system react to bacteria in the gut. Dendritic cells take suspect bacteria and present them to the immune system for assessment and, thanks to samples donated by patients undergoing surgery at the hospital, the team can study dendritic cells from lymph nodes in the gut, the very engine room of inflammatory bowel disease. Shilling first devised a new technique to purify dendritic cells to 95% purity, significantly better than the 50% achieved with previous techniques. This allowed them to discover that, if dendritic cells from the gut are presented with probiotic bacteria, they will stimulate a positive immune response that protects the bowel from inflammation. This promising finding suggests probiotics might one day help to calm inflammatory bowel disease and possibly reduce patient need to use steroids and anti-inflammatory drugs.

The key to infant meningitis?

How do bacteria reach the brain and cause meningitis? Microbiologists at TCD have discovered that reactions in a baby's gut play a key role

Bacterial meningitis is a sporadic but potentially deadly infection that develops when bacteria infect the membrane, or meninges, that surrounds the brain. Children and infants are most at risk, and in newborn babies the main cause is the common gut bacterium, *Escherichia coli.* Some scientists think that the *E. coli* start by sticking to the epithelial cells lining the gut, then somehow burrow through, reaching the blood stream which then fast-tracks the bacteria to the brain. TCD microbiologists Dr Stephen Smith and PhD student Robert Fagan are investigating this, by studying how the bacteria stick to the gut cells.

The outer surface of *E. coli* bacteria is covered with a variety of adhesin molecules, and Smith and Fagan discovered that several of these can stick to human gut cells. What is more, when they produced *E. coli* with no adhesins, and tested these in the laboratory, the mutant bacteria could not stick to, or burrow through, human gut cells. Clearly, adhesins are crucial, and it seems that each adhesin has a particular shape that engages with a matching molecule on the surface of the human cell, just as a key fits a lock. Smith and Fagan discovered that one of their keys, which they called Hek, attaches directly to a complex proteoglycan molecule on human gut cells. To confirm this, they engineered gut cells in the laboratory that cannot produce proteoglycan and, sure enough, the *E. coli* could not attach and attack them. Detailed information such as this may one day help scientists to design new antibiotics.

How to avoid cancer of the oesophagus

Smoking and being overweight makes some people more prone to developing oesophageal cancer, a national cancer study reveals

Eat more fruit and less fat, lose weight and stop smoking. It's good advice for all of us, but especially for people with a condition known as Barrett's oesophagus. In this disease, thought to be caused by acid reflux from the stomach, the lining of the oesophagus changes, becoming more rough and resembling the intestine. And people with Barrett's oesophagus who are overweight and who smoke, are more at risk of developing a nasty cancer of the oesophagus called adenocarcinoma. That's the finding from an all-Ireland study of nearly 750 people, one-third of whom were healthy, one-third had Barrett's oesophagus, and one-third adenocarcinoma. The incidence of adenocarcinoma has doubled in 10 years, and it now accounts for half of oesophageal cancers in Western societies. This is worrying, because the survival rate is low: at most 12% of patients survive to five years. People with Barrett's oesophagus are 20 times more at risk, although it must be stressed that most people with Barrett's oesophagus do not develop cancer.

Using data collected from patients around Ireland, Dr Harry Comber and Ms Siobhan Reynolds, of the National Cancer Registry, Cork, in collaboration with the Northern Ireland Cancer Registry, found that the people most likely to develop adenocarcinoma are those with Barrett's oesophagus who are also overweight and smoke. These patients should therefore be encouraged to lose weight and stop smoking. While there is much debate about whether people with Barrett's oesophagus should have regular endoscopy examinations, the results of this study suggest it would be particularly useful for overweight patients.

How mimics can turn your body against you

If a bug starts to mimic the cells in your stomach you could end up with stomach cancer, microbiologists at NUI Galway have discovered

Bacteria are wonderful mimics. To evade the clutches of your immune system many have evolved surface molecules similar or even identical to structures normally found on the surface of your own cells, which often fools the immune system into not recognising the invader. But if the infection continues for a long time, the immune system may eventually wise up and produce antibodies against the bacteria. Unfortunately, these antibodies will also recognise the original structures the mimics were copying. The result is an autoimmune disease, when the body's immune system turns against itself.

Now, researchers at NUI Galway, led by Dr Anthony Moran, have discovered that this happens with some strains of *Helicobacter pylori*. This common bacterium causes peptic ulcers and an inflammation of the stomach lining called gastritis. In severe cases, the acid-secreting cells in the stomach are destroyed (a condition called atrophy), which can be a prelude to stomach cancer. Moran and colleagues have discovered that the *H. pylori* strains associated with atrophy carry molecules identical to the Lewis antigens normally found on the stomach's acid-producing cells. Significantly, they found that antibodies produced against these bacteria will also recognise the acid-producing cells, confirming that a major cause of the atrophy is probably the immune system turning against the stomach cells and starting to destroy them. The researchers hope to develop a quick test to determine if someone has been infected with one of the problem *H. pylori* strains. Unfortunately, once the auto-immune reaction has begun, there is currently no way to stop it, so affected people need to be monitored for any early signs of stomach cancer.

Filming bugs – and why they're so resilient

Research at UCC into how bacterial communities function, could one day lead to new antibiotics

Pseudomonas aeruginosa is a bacterium that makes films. Not motion pictures, but densely populated colonies that grow as a coating or 'biofilm' on suitable surfaces, everything from plastic tubing to the lining of the lung. *P. aeruginosa* is also a major worry for health services. Among other things, it causes chronic and potentially deadly lung infections in people who have cystic fibrosis. Its biofilms have a mucus-like coating that protects the bacteria from disinfectants and from a person's immune system, and this is partly what makes an infection so difficult to treat. But biofilms are also actively organised: the bacteria can sense the presence of their neighbours, and secrete signal molecules to orchestrate the colony and make it more virulent. So researchers now study how biofilms behave, hoping to spot chinks in their armour.

Within a biofilm, the bugs need iron to survive, but this element is difficult to obtain from the environment, so the bacteria have evolved complex mechanisms for iron uptake involving, among other things, TonB proteins. At UCC's BIOMERIT research centre, microbiologists Prof Fergal O'Gara and Dr Abdelhamid Abbas have discovered a new role for TonB: they found that it is also involved in the signalling that helps the bugs become virulent. TonB is active, regardless of how much iron is present, and it helps to co-ordinate biofilm formation and to make the bacteria resistant to heat and other stresses. This is a new and central role for TonB, and understanding it could one day lead to improved treatments for *P. aeruginosa* infection.

Filming bacteria – what makes them stick?

Microbiologists at the Royal College of Surgeons in Ireland are studying a gene that helps some infectious bacteria stick to surfaces

You probably have some staphylococcal bacteria on your hands. Both *Staphylococcus aureus* and *S. epidermidis* are common in the environment (the latter occurs on the skin, for instance) and both can form biofilm communities on surfaces. If this happens inside your body, e.g. in the lung, or on a medical device such as an intravenous tube, it can cause a troublesome infection that is difficult to treat, especially if it is the notorious methicillin resistant *Staphylococcus aureus*, alias MRSA.

But what turns an everyday bug into a resilient biofilm? Clinical microbiologist Dr Fidelma Fitzpatrick, working with Dr James O'Gara and Prof Hilary Humphreys at the Royal College of Surgeons in Ireland, studied one suspect gene: the intra-cellular adhesin (*ica*) gene, which controls production of the sticky mucus that protects a biofilm and helps it stick to silicone, the main constituent of medical tubes and shunts. Analysing samples collected from intensive care patients, Fitzpatrick found that the two staphylococcal species have different biofilm mechanisms. In general, *S. epidermidis* needs *ica* to form a biofilm, although, a few bacteria lacking the gene could still form a biofilm. *S. aureus*, however, can form biofilms whether or not they have the *ica* gene, suggesting that, for them, there are other genes that also control this behaviour. Significantly, the biofilm communities of MRSA and methicillin sensitive *S. aureus* (MSSA), react differently to environmental factors such as salt concentration, and a new HRB-funded project is studying these differences. The ultimate aim of the research is to devise new and effective ways of diagnosing and treating these important biofilm infections.

What is MRSA?

MRSA stands for Methicillin-Resistant Staphylococcus aureus. MRSA is a subgroup of Staph aureus that is resistant to a range of antibiotics, including penicillin antibiotics. MRSA first appeared in 1961 soon after the introduction of the antibiotic methicillin (an antibiotic that is no longer in use). Since then MRSA has spread widely in many countries and has been particularly associated with hospitals and other healthcare facilities.

Who is most at risk of getting an MRSA infection?

In general MRSA infections tend to occur in older hospital patients and those with the most severe underlying illnesses. The following are considered to be important risk factors for invasive MRSA infection:

- Age (older age groups are more prone)
- Gender (males are twice-more at risk than females)
- Prolonged hospital stay
- Patients in intensive care, surgical and burns units
- Patients with diabetes and other chronic conditions
- Patients treated with broad-spectrum antibiotics

What is the best way to control the spread of MRSA?

The most important infection control measure and the easiest way to help prevent MRSA from spreading within the hospital (and by extension in the community) is to foster strict adherence to hand-washing policies and other hygienic practices for all staff and visitors.

How common is Staph aureus/ MRSA infection in Ireland?

The proportion of Staph aureus isolates that were MRSA for the first nine months of 2004 was approximately 42.4%. However, MRSA is a global concern and not just an Irish problem. In Europe, apart from Ireland, the highest rates (proportions) of MRSA bacteraemia are observed in countries such as Belgium (29.5%), France (28.9%), Greece (44.7%), Italy (37.6%), Portugal (45.5%) and the UK (43.1%). The lowest rates (proportions) are observed in Estonia, Scandinavia and the Netherlands (all <5%).

Source: The National Disease Surveillance Centre

Health services: From the cradle to the grave

"The health research system is the brains of the health system: it is a tool to organise, understand, operate and improve it."

Source: World Report on Knowledge for Better Health, WHO 2004

Cultural diversity and maternity services

Interpreters and anti-racism training are among the changes needed if maternity hospitals are to serve Ireland's new ethnic communities, a major UCD study recommends

Cultural diversity poses new challenges for the health services, with over 100 ethnic communities now settling in Ireland. This diversity can pose particular challenges for the maternity services. UCD public health expert Dr Anna Clarke and PhD student Suzi Lyons surveyed and compared the experiences of 1,000 women, half from ethnic minorities, and half Irish women chosen to match the ethnic women for age and other factors, and they interviewed health professionals at Dublin's three public maternity hospitals.

They found few differences between the Irish and ethnic minority women, although the latter were less likely to smoke, drink alcohol or take illegal drugs. But their study did reveal some problems relating to the maternity services: ethnic minority women often presented at the hospital late in their pregnancy and thus had fewer antenatal visits, for instance; they were also less likely to have had the rubella vaccine and more likely to be anaemic, possibly reflecting health services in their home country. Language difficulties were also a problem, both for the women and for hospital staff.

Clarke and Lyons recommend a review of antenatal and maternity services, and suggest a number of practical measures that might be implemented relatively quickly. Health boards could employ link-workers from the ethnic minorities who could act, independent of the hospitals, as advocates and interpreters for the women. Staff at the maternity hospitals should also receive cultural competency and anti-racism training, while the antenatal care should be tailored to the individual needs of the women attending the clinics.

How to divide the health funding pie

It would be fairer to allocate health funding according to needs, say analysts at TCD

Deciding how much money health authorities should receive is an important but difficult task. Usually, they receive more or less what they got the previous year, plus a little extra for inflation. But that might not reflect the needs of their constituency: rural areas need more money for geriatric care, for instance, than towns with a younger population. So, increasingly countries are switching to a 'needs based' allocation of funds. Sweden already does this, and Britain to a lesser extent. Health system analyst Dr Rosalyn O'Loughlin, working with Dr Alan Kelly at TCD, asked whether needs-based funding was doable and desirable here.

Such a switch ideally calls for a national database with a unique number for each person which would allow their health needs to be tracked and predicted (and indeed PPS numbers are now being allocated to infants at birth), plus a geographic identifier such as a postcode. This type of database does not yet exist here, so O'Loughlin tested her ideas on estimated data and found that, had she been in charge of funding, the Eastern, Southern and Midwestern health boards would have received less money (down 4.4%, 0.6% and 0.4% respectively), and the five other health boards more, with 1.8% more for the Western health board. The readjustments seem small, but the sums involved are substantial. Interestingly, the results confirms a widely held view that the eastern region is over-funded and the west under-funded.

O'Loughlin and Kelly have presented their ideas to the new Health Services Executive, and believe their system could be implemented within 5-10 years. And fairer health funding would be a positive incentive to introduce individual ID numbers and postcodes.

A rational way to plan health services

People living in border counties should have access to hospitals across the border, a TCD study of health facilities recommends

How far would you travel for a GP? What about specialist cancer care? Public health researchers at TCD have been analysing how far people currently travel to access health care, using data from across the country. Not surprisingly, they found that in general, the more specialised the care, and the less widely available the service, the more people are prepared to travel and the longer their journey. The research team of three – Dr Alan Kelly and PhD student Conor Teljeur and researcher Imanol Montoya – then wrote software to plan the optimum locations for health care facilities, taking into account existing services.

Overall, they found that existing facilities are reasonably well located – for instance, while counties Carlow, Longford and Leitrim have no hospital, residents there are no worse off on average than those living in other similar regions. That said, people living in Leitrim, north Cavan, Donegal and Monaghan would have quicker hospital access if they could use facilities across the border. The converse holds true for residents in adjacent NI counties and the researchers recommend abolishing this 'health care border'. The team also considered the optimum locations for new primary health care centres, the 'one-stop shops' intended to replace between one-third and two-thirds of GP surgeries. Co Kildare currently has 35 GP surgeries, and the researchers found that these are well-placed to serve the population. Their analysis recommends 33 primary health care centres for the county, a drop of just two, and in essentially the same locations as the existing surgeries. Having proved their system with this case study, the team believes it is a valuable practical tool that should be used when planning changes to the health services.

The new face of after-hours GP care

Out-of-hours co-operatives and locally-based defibrillators can help in providing emergency medical care, a UCD survey reveals*

Gone are the days when a GP could single-handedly offer after-hours care round the clock, and the trend now is towards co-operatives that share the burden. They first began in 1998, and today 11 co-ops across the country provide cover for over 1,000 GPs (about 40% of the total), and offer care to some 1.5 million people. The co-ops run what are effectively medical call centres, staffed by triage nurses and GPs who can deal with many queries over the phone.

To analyse how this change in care is operating, UCD's Professor of General Practice, Dr Gerard Bury and colleagues surveyed all 11 co-ops, with a special focus on how they manage emergencies. Their survey reveals that, in one recent year, the co-ops handled 340,000 calls from patients; 32% of the queries were dealt with over the phone, 56% were referred for consultation at a treatment centre, and just 12% led to a doctor making a house call. Significantly, because the co-ops see their role as preparing for emergencies that arise in normal GP care, rather than as a dedicated emergency service, they have few formal links with the ambulance services, something Bury is studying in a follow-up survey.

The project also analysed the availability and use of community-based portable defibrillators, such as the County Wicklow scheme, where community groups were given defibrillators and the local ambulance service has a contact list for volunteers on-call. This meant that in one recent emergency, a volunteer reached the victim within three minutes, and 20 minutes before the ambulance arrived. However, the UCD survey could not trace most of the portable defibrillators sold here, and recommends a registration system to improve access to the devices.

*This study was co-funded by the Pre-Hospital Emergency Care Council

I spy with my X-ray image

An Irish study of hospitals in four countries found that X-ray image quality varies significantly, and recommends continuous training for staff and the publication of a set of reference images

X-ray images are used to diagnose injuries and illness, and so image quality must be high, with good contrast and resolution, and showing all the necessary anatomical detail. A radiologist needs to be able to see clearly not just the hip joint, for instance, but also the bony patterns within it. There are, however, few practical guidelines for image quality, and most recent emphasis has been on minimising the X-ray dose the patient receives. While this is important, it is also vital that image quality does not suffer as a result.

To investigate whether quality varies from hospital to hospital, Dr Patrick Brennan, from UCD's School of Diagnostic Imaging, and PhD student Ebtehal Al-Qattan, analysed some 5,000 images taken in 20 hospitals across four countries – Ireland, the UK, Kuwait and Oman – the first time such a comprehensive study has been done for anatomical X-rays (previous studies focused on dental images). They devised a new scoring system that allowed them to rate image quality and to determine if loss of quality was due to the equipment used or the technique. Significantly, they concluded that equipment and techniques are not always up to standard, and that new digital imaging, while more convenient than film, does not necessarily produce better images. Brennan and Al-Qattan recommend publishing sets of reference images, so X-ray departments are reminded of what an image should be like, and running refresher training courses. The study findings have been presented internationally, and researchers and clinicians in Northern Ireland and the Irish Republic are now reviewing how best to improve their clinical practice.

Death, dying and dementia

How can we best meet the special end-of-life care needs of people with dementia? A Dublin sociological study has some practical suggestions

Palliative care is a valuable service for cancer patients and their families, and one that should be more widely available. The service grew out of cancer care, but that model won't suit all patients: people with dementia, for instance, have special needs, as by the time they require end-of-life care, their cognitive abilities are often severely limited, making it hard for staff to assess symptoms and pain levels. To explore what might be done to help dementia patients and their families, sociologist Dr Una MacConville, in association with consultants Regina McQuillan (St Francis Hospice) and Dr Mary Cosgrave (St Ita's, Portrane), interviewed bereaved family members, and professionals working in palliative and dementia care.

MacConville found that dementia services could usefully include families more in the care, especially as many families, having cared for their relative for a long time, will have a deep knowledge of the person with dementia. Also, families can find the move to institutional care and the change from being the main carer difficult. Resources emerged as a major issue, and a shortage of appropriately trained staff means dementia care institutions cannot provide the full range of end-of-life support services for patients and their families. So a first step might be a partnership scheme, as proposed in Britain, allowing palliative and dementia care professionals to share their expertise. Both dementia care staff and palliative care professionals would benefit: dementia care professionals have specialist knowledge of caring for people with dementia and palliative care professionals have specialist knowledge of end-of-life care.

Human disease: Confronting the causes

"Now is the time to make it happen where it matters, by turning scientific knowledge into effective action for people's health."

Source: World Report on Knowledge for Better Health, WHO 2004

Stopping the push of premature labour

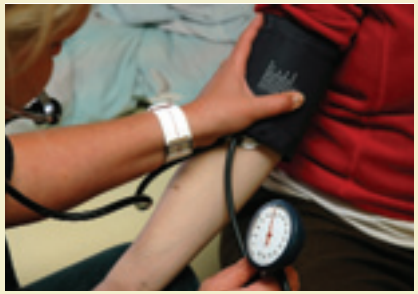
Obstetricians at NUI Galway have discovered a new drug that may be able to stop the muscle contractions of premature labour, and with fewer side-effects than the drugs currently used to treat this life-threatening problem

If a pregnant woman goes into labour before her allotted nine months, and particularly before 7-8 months, it can lead to major problems, as babies born prematurely need special care and are at risk of developing physical or intellectual handicap. Even then many premature infants do not survive, while those that do survive are often prone to long-term health problems. These premature births usually happen when, for reasons that are not yet understood, muscles in the womb start contracting before the due date. To save the pregnancy, drugs such as ritodrine have been prescribed to stop the contractions, but these can have serious side effects, notably on the blood pressure of both mother and baby and their use is now discontinued.

Now, obstetrician Prof John Morrison and PhD student Paul Hynes, at NUI Galway, have discovered a promising new drug that could have fewer side effects. In laboratory tests, the compound (currently known only as BRL 37344), is as good as, if not better than ritodrine in stopping the muscle contractions. Significantly, however, it has less effect on blood vessels, suggesting it is less likely to cause blood pressure problems.

The Galway team has discovered that the new drug acts on a protein called beta-3 adrenoreceptor, which is involved in relaxing and contracting the muscles of the womb. To date, they have tested the drug only on muscle samples and blood vessels in the laboratory, and more research is needed before BRL 37344 could proceed to clinical trials. But these initial results suggest that this could be a promising new treatment for what is currently a very serious and distressing problem.

Understanding pre-eclampsia – our constricted knowledge



Why do blood vessels sometimes constrict and malfunction in pregnancy? Obstetricians at NUI Galway are piecing together what happens

Pre-eclampsia is relatively common in pregnancy, with symptoms that include high blood pressure and swelling in the mother. Fortunately, most cases are mild, but in severe cases, the baby might be born small or must be delivered prematurely, and sometimes the problem can even threaten the mother's life. The condition develops when the blood vessels in the womb, and in the placental circulation supplying the baby, contract too much and become constricted, but it's not known what causes this. Somewhat more is known about normal high blood pressure, or hypertension, in people who are not pregnant. In particular, constricted blood vessels in such cases are associated with what biochemists refer to as the Rho A/Rho-kinase system, involving a small signalling molecule, Rho A, and an enzyme, Rho-kinase. NUI Galway obstetrician, Prof John Morrison, and Dr Anne M Friel, wondered if the same system played any role in pre-eclampsia.

They discovered that the genes for the Rho A system are actually less active in blood vessels constricted by pre-eclampsia, something they could determine by measuring the amount of mRNA the genes produced. This suggests that the constrictions in pre-eclampsia are not triggered by the same factors as in normal hypertension. The reason Rho A levels are down in pre-eclampsia, the researchers think, is because the mother's body is trying to compensate for the poor blood supply by reducing the amount of Rho A circulating, in the hope that this will relax the blood vessels and not add to the problem.

Arthritis and a two-faced hormone

An anti-inflammatory hormone that actually provokes inflammation in arthritis? Biochemists at UCD have uncovered a hormonal puzzle

If one of your joints starts to become arthritic, then the thin synovium that lines the joint changes dramatically. New blood vessels grow and the cells proliferate, so that the synovium thickens into a tumour-like growth. Hormones are thought to play a role in these changes, not least because most arthritic diseases are more common among women than men. At UCD, cell biologist Dr Evelyn Murphy and PhD student Jennifer Ralph study one hormone, corticotropin-releasing hormone (CRH), which is part of our 'fight or flight' stress response.

They built a cell culture system in their laboratory where they can monitor how cells respond to CRH.

Normally, CRH binds to receptors on the surface of cells, and this starts a chain reaction that eventually triggers the adrenal glands to produce the body's natural steroids. In this way, CRH acts as an anti-inflammatory hormone. Ordinarily, no CRH receptors are found in synovial tissue, but the UCD team discovered that the receptors are present in arthritic joints. With their cell culture system, they found that adding CRH to arthritic synovial tissue made it leaky, in a way that would allow immune cells to move into the tissue from the blood system. In other words, in an arthritic joint, CRH may actually provoke inflammation. This two-faced behaviour is not unusual, and several other molecules can act in opposite ways depending on the situation. The discovery of CRH's role in arthritic inflammation opens a new avenue to explore for an effective treatment of arthritis.

Could calcium-control drugs alleviate muscular dystrophy?

Muscle biologists at NUI Maynooth found that calcium regulation is important in muscular dystrophy, pointing the way to a possible therapy

Muscular dystrophies are crippling neuromuscular diseases, mostly caused by a defect in the gene that codes for the dystrophin protein. The gene lies on the X chromosome so, like haemophilia, this is a disease that only boys develop, and it affects about one in every 3,000 boys born in Ireland. Their muscles quickly degenerate and most will die before they reach 30, when their heart or respiratory muscles fail. Dystrophin protein sits on the muscle cell surface, connecting the inside and outside of the cell. Some forms of the disease are more severe than others, depending on whether the person has no dystrophin at all, or not enough, or a faulty type of protein. The net result in all cases, however, is inflexible muscle cells that eventually rupture, allowing calcium ions to flood in, and eventually leading to muscle degeneration.

Now, Prof Kay Ohlendieck and PhD student James Lohan have discovered other proteins that are involved. Using new proteomic techniques, they can take snapshots that show which proteins are active in a cell. Comparing snapshots for healthy and diseased muscle and heart muscle cells revealed that levels of two proteins involved in calcium ion regulation drop significantly in diseased muscle cells. For Ohlendieck, this suggests that certain drugs, already used to control calcium levels in other diseases, might help to alleviate some of muscular dystrophy's distressing and severe symptoms.

A more humane way to test toxins

A type of artificial kidney built at UCD, is shedding light on how kidney damage develops, and could be used instead of animals to test poisons*

Cell biologists at UCD's Conway Institute have made an artificial kidney by successfully growing two types of human kidney cell on filters in the laboratory. It doesn't look like a kidney, and it isn't a replacement for kidney transplants, but it is a reasonable mimic, capable of filtering and reabsorbing fluids, and already it is allowing Prof Michael Ryan and his team to investigate how drugs and toxins affect kidney cells and how kidney disease develops.

The aim is to find an alternative to animal testing – currently, millions of lab animals are killed each year in toxicity tests. Cell cultures are an attractive solution, and would also allow scientists to study how toxins cause kidney damage, but the stumbling block has been creating cell cultures that realistically mimic the human kidney.

Ryan and his colleagues believe they have now done this, and the proof comes in their studies of the immune suppressant drug, cyclosporin A, which can cause serious kidney damage. Using their artificial kidney, Ryan's team has shown that, although cyclosporin A suppresses most immune functions, it does stimulate kidney cells to produce a particular immune molecule, called transforming growth factor beta, which provokes inflammation and damages the cells. The team has also seen how certain cells in their kidney culture can transform and become diseased, and as well as shedding light on how disease develops, this confirms the value of their artificial system. The team has published its findings internationally, and hopes that their ongoing work on cyclosporin A might lead to safer immune suppressant drugs.

*Co-funded by the Hadwyn Trust for Humane Research

Live action replay – for pathologists!

Sophisticated new software from DCU can record and replay how a pathologist views a microscope slide, and is revolutionising pathology training and quality assurance

Diagnostic pathology is a complex process requiring many years of postgraduate training to achieve suitable standards of performance. Decision-making is not clear-cut and requires pathologists to weigh up several features before coming to any decision. This process of educating trainees is complicated by the fact that most training is performed via a conventional microscope, a labour intensive process that requires the expert pathologist to sit with the trainee pathologist at a double headed microscope for sustained periods of time.

All that is now changing, thanks to software developed at DCU by Dr Donal O'Shea and PhD student Dan Johnston. Their ReplaySuite program exploits the power of digital microscopy, which can capture the detail of microscopic samples at suitable resolution for diagnosis. Their system tracks where a pathologist visits as they view a digital slide, and can then replay this to others, whether trainee pathologists or for quality assurance assessment. And the beauty of the digital system means replays can be reviewed anywhere in the world.

The DCU approach is now being adopted by companies selling digital pathology slide systems, and a spin-off company at DCU, Slidepath, is marketing a range of related services. Already, a quality assurance study they have undertaken in Sweden, on the diagnosis of chronic hepatitis in liver biopsies, revealed that some people were not viewing enough of the slide, or using too low a magnification to come to an appropriate conclusion. Slidepath also plans to offer master classes with world experts, which O'Shea likens to 'pay-per-view' training courses for pathologists. So, simply by tracking where a pathologist looks, an elegant Irish idea is helping to improve the quality of medical diagnoses.

A new way to tackle psoriasis

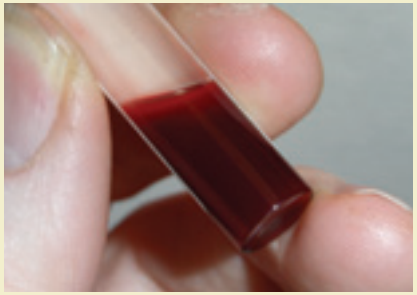
A tried and tested anti-inflammatory drug is also effective against psoriasis, a trial at St Vincent's University Hospital has found

The drug Infliximab is licensed for use in treating certain inflammatory disorders, such as rheumatoid arthritis and inflammatory bowel disease. It works by blocking a protein called TNF-α, which normally triggers the inflammation that is a feature of these diseases. But inflammation is also a feature of psoriasis – so, might Infliximab be effective against this condition too?

Psoriasis is characterised by red scaly patches on the skin, and inflamed joints. Both are associated with new blood vessels forming, a process which is regulated by various growth factors, including vascular endothelial growth factor (VEGF) and angiopoietins 1 and 2. At St Vincent's University Hospital in Dublin, dermatologist Dr Trevor Markham, working with Dr Douglas Veale, conducted a clinical trial of Infliximab with psoriasis patients, and he also investigated the drug's effects on growth factors in the laboratory.

Markham found that Infliximab was very effective against psoriasis, dramatically reducing the patients' skin and joint problems. Patients taking the drug had less of the VEFG and the angiopoietins in their blood, suggesting these growth factors are important in psoriasis. Experiments on skin cells in the laboratory confirmed that VEFG and the angiopoietins do stimulate inflammation and new blood vessel formation. On the down-side, Infliximab is time-consuming to administer (it requires a two-hour intravenous drip), and there are concerns about long-term side-effects. Yet, it was so effective it's likely to be used to treat some patients, and already, new improved derivatives are being developed to block TNF-α, and this important study proves that these drugs should be effective against psoriasis.

Ironing out the problems of haemachromatosis



Severe bloodletting, the conventional treatment for hereditary haemochromatosis, may not be as appropriate as previously thought, research at Dublin's Mater Hospital suggests

Fatigue, joint pain and, occasionally in men, impotence. These are the early symptoms of hereditary haemachromatosis, a common genetic disorder that develops if your body absorbs too much iron from the diet. The excess iron is deposited primarily in the liver and can lead to cirrhosis of the liver and, in rare circumstances, liver cancer. Early diagnosis is important and if treatment starts in time, it can restore the person's normal life expectancy, although the conventional treatment seems medieval – weekly bloodletting (phlebotomy) to remove the excess iron. Some experts now think this exacerbates the problem – because forcing the body to replace lost blood may increase the rate at which iron is absorbed from the diet. Clearly, there is much we do not understand about this disease, although recent genetic studies have helpfully identified several genes and proteins involved in iron metabolism.

At the Centre for Liver Disease in Dublin's Mater Hospital, molecular biologist Dr Eleanor Ryan and PhD student Barry Kelleher studied biopsy samples donated by haemachromatosis patients before and after phlebotomy, to see which genes and proteins are activated. They found that bloodletting does raise the levels of a key protein, DMT1, involved in absorbing iron from food in the duodenum. This suggests it might be wise to take less blood, less often. The team is now studying a protein called hepcidin, which is involved in switching iron absorption on and off, and hope to develop a test to measure blood hepcidin levels.

Health Research Board
An Bord Taighde Sláinte

Improving health through research and information

Established in 1986 (under Statutory Instrument No. 279), the Health Research Board promotes, assists and commissions and conducts medical, health, epidemiological and health services research in Ireland.

Published by:
Health Research Board
73 Lower Baggot Street
Dublin 2
Ireland
t 353 1 676 1176
f 353 1 661 2335
e hrb@hrb.ie
w www.hrb.ie

Acknowledgements
All images sourced from istockphoto.com with the exception of images on pages 3, 21, 22 and 26, which were supplied by the Wellcome Trust photographic library, and large images on pages 6 (winner of HRB image competition), 29 and 35, which were supplied by featured researchers. Science journalist, Mary Mulvihill, wrote the stories in collaboration with the featured researchers.