A PICTURE OF HEALTH

A selection of Irish Health Research 2004

HRB
Health Research Board

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.

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FOREWORD

A Picture of Health 2004 illustrates the vibrant research culture within the health service, a community of 100,000 professionals. It captures, in simple summaries, the wide variety of health research supported by the Health Research Board, from 'bench' biomedical science to health services research. Stories in this edition describe Irish research into such global health issues as cancer, heart disease, arthritis, Alzheimer's disease and cystic fibrosis.

The ability to carry out world-class health research in Ireland is critical to the delivery of high quality patient care and the development of an excellent health service, which we all depend on. Improving health through research and information is the mission of the HRB. Supporting health research through a variety of grant schemes is one of the ways we can achieve that. Our grant schemes enable researchers to participate in first-rate research projects, Ireland-Northern Ireland collaborative programmes and training fellowships. They empower senior scientists, postdoctoral fellows, physicians in training, nurses, social scientists and postgraduate students to improve health, combat disease, reduce disability and enhance quality and equity of care.

The HRB greatly appreciates the ongoing support and goodwill of the public. We hope that these summaries will help you to understand more about the latest developments in health research.

Professor Desmond Fitzgerald
Chairman of the Health Research Board

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SECTION 1

In the community: population health

Population health research aims to improve the health and well-being of the entire population, focusing on the interrelated conditions and factors that influence the health of populations. By its nature, population health research is multi-disciplinary. It provides knowledge about the social, economic and biological determinants of health, while emphasising health promotion and education.

The heart of the matter

Can infections trigger heart disease? Can your social status protect you? Prof Ivan Perry, Dr John Sheehan, and research assistant Rita Hinchion (Public Health, UCC) investigate

Coronary heart disease is a major killer in Ireland. Hopefully, the more we understand what causes it, the more effective our strategies to prevent it. Already, we know that obesity, lack of exercise, smoking, and a diet high in animal fat and low in fruit and vegetables are important. However, there has been considerable debate about the relative importance of these, and some people believe that we should also include social status, and infections. In recent years, for instance, it has been suggested that some cases of coronary heart disease might be due to certain bacterial and viral infections (among them *C. pneumoniae*, *H. pylori* and cytomegalovirus). Not much is known about social status and heart disease in Ireland, but in most developed countries, wealthy people and people with a high social status are less likely to succumb.

To investigate these ideas, we collected detailed questionnaire information, carried out physical measurements and obtained blood samples from 377 men and women attending coronary care units with a severe chest pain or heart attack, and a comparison group of 380 healthy people. We found that the established risk factors, especially obesity and smoking, account for virtually all of the coronary heart disease cases in the Irish population. There was no evidence to suggest that infection with particular bacteria or viruses was involved. However, we did find that people from the lower socio-economic groups were somewhat more at risk of developing the disease. On the basis of this research we can say that the causes of heart disease are now almost completely understood. We can advise both men and women that their risk of developing a heart attack is extremely low if they avoid smoking, maintain normal body weight and take regular exercise.

Bottle or breast?

Research fellow Dr Laura Frost and Prof Ivan Perry (Public Health, UCC) assessed perceptions and practices regarding infant-feeding, with a view to improving breast-feeding rates in Ireland

Despite the known benefits of breast-feeding, only one-third of Irish mothers are breast-feeding their babies when they leave the maternity hospital. We set out to investigate why breast-feeding rates are so low, and examined the factors that influence Irish mothers in deciding whether to bottle- or breast-feed their babies. We also assessed how hospital and community support can best help Irish mothers who wish to breast-feed. We conducted 30 in-depth interviews with mothers in Cork, surveyed 400 first-time mothers both while they were pregnant and then six weeks after the birth of their child. We also surveyed the Irish media, and studied regional and national policies promoting the benefits of breast-feeding.

Significantly, we found that most women decide about infant feeding before they even become pregnant. The women we interviewed said they were influenced by their friends, and particularly the views of their own mother. They also identified the media as an important source of information. Most knew about the health benefits of breast-feeding, but this was not their primary reason for deciding. Other factors included a desire for partners to be involved, body image, and confidence about making decisions related to infant care. In our media survey, we found that the Irish media present bottle-feeding more positively and frequently than breast-feeding, and associate it more with normal living. Our results suggest that breast-feeding rates will not improve until the practice is seen as culturally ‘normal’. To be successful, then, breast-feeding campaigns should emphasise community-based interventions and involve the media, community health groups, and schools.

A happy smile!

Does correcting prominent teeth boost a child's self-esteem? A survey by Dr Donald Burden, and orthodontist and PhD student Niall McGuinness (Orthodontics, QUB) suggests yes

Prominent front teeth or 'buck teeth' can be the butt of hurtful comments, and are easily damaged in falls and sports injuries. Consequently, orthodontists spend considerable time correcting the problem: the children typically wear fixed braces ('traintracks') for 18-24 months, usually starting around age 13; occasionally teeth need to be removed. We wanted to establish how satisfied former patients are with their dental appearance on reaching adulthood, and to examine whether extractions affect facial profile – some vocal US and UK dentists suggest they make the face 'fall in'.

We examined 200 former patients, and 350 untreated young adults of the same age – they also completed a questionnaire. We found that the greatest impact on facial profile does not come from removing teeth, but from the continuing growth of the person's nose and chin, which in young men can continue into the early twenties. Reservations about flattening a person's facial profile are therefore probably unwarranted.

Orthodontists use various scales to grade dental appearance, including one category for 'aesthetics'. Reassuringly, we found that former patients had significantly more self-esteem than people who were not treated, regardless of dental appearance. Treated and untreated people were equally satisfied with their dental appearance except, intriguingly, for those who rated 'excellent' in the aesthetic category. Here, treated people were *more* satisfied with their appearance than those who had not been treated, yet who also graded excellent. Clearly, orthodontic treatment can boost a person's self-esteem, and their satisfaction with their dental appearance.

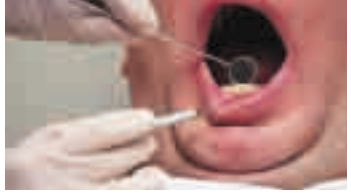
Tackling drug abuse and hepatitis infection in Irish prisons

From detailed interviews with prisoners, Dr Jean Long and Dr Shane Allwright (Public Health & Primary Care, TCD) have identified strategies that could help minimise the consequences of drug misuse in Irish prisons

Drug abuse and the associated risk of hepatitis C infection are endemic in Irish prisons. While drug users in the wider community can access programmes such as needle exchanges, the only evidence-based support in Irish prisons at the time of this study was a detoxification programme provided for a small number of clients. Clearly, something more is needed, but to succeed, any intervention must take account of prisoners' views.

We interviewed 31 men in Dublin prisons (16 injecting and 15 non-injecting drug users) to ascertain their experiences of drug use and their views about interventions.
We found that drug users in prison face additional health risks, especially increased risk of hepatitis C infection. For instance, limited availability of heroin means users often shift from smoking to injecting (this uses much less heroin), but syringes and needles are often shared with many people, and clean 'gear' is hard to come by.

Significantly, we found that prisoners see their time inside as an opportunity to tackle their addiction. They would welcome support programmes, and believe the services provided for drug users in the wider community should be extended to prisoners.
Those we interviewed saw the health benefits of syringe exchanges, but many worry that the syringes could be used as weapons, or cause accidental needlestick injuries.
Overall, we found that Irish prisoners would welcome intervention measures – creating an opportunity health professionals should not miss.



In the dentist's chair…

Prof David Coleman and PhD student Claire Tuttlebee (Dental Science, TCD) have identified a design flaw in the dentist's chair

The modern dentist's chair is actually a sophisticated medical instrument, complete with drills and other attachments, including a suction device for cleaning the patient's mouth, and a water cooling system (to counter the heat generated by the drills and other instruments). Unfortunately, the cooling lines and suction system are quickly colonised by films of bacteria, including the notorious disease-causing *Pseudomonas* family. This is a widespread problem, and a particular worry for people susceptible to infections.

We studied how 'biofilms' form in the waterline and suction systems, and how best to eradicate them. A badly contaminated water cooling system can produce tens of thousands of bacteria per ml of water, but we found these tubes are easy to disinfect: flushing them overnight just once a week with hydrogen peroxide effectively kills the biofilms, and reduces bacterial counts to a few hundred per ml, the same level seen in drinking water. The suction system is more problematic: this tubing is open to the air and receives 'nutrients' sucked from the patient's mouth, and contamination levels here can reach millions of bacteria per ml. Worse, the system is almost impossible to sterilise: disinfectant is sucked through the tube so quickly, there is almost no contact time.

Based on these findings, we are redesigning the suction system so it can be filled with disinfectant and properly disinfected. Our research has also highlighted the scale of contamination problems in modern dental chairs. We are now working with an international dental chair manufacturer to develop practical solutions to these biofilm problems.

Diabetes and obesity in Irish children

Prof John Nolan, Dr Siobhan McQuaid, and exercise physiologist Donal O'Gorman (Endocrinology, St James's Hospital, Dublin & TCD) are studying the growing epidemic of type-2 diabetes in Irish children

Ten years ago, type-2 diabetes was a disease of middle-aged and elderly people. Indeed, it was often called 'late-onset diabetes', to distinguish it from the type-1 diabetes which usually manifests early in life. Now, however, we are seeing a new phenomenon at our Dublin clinic: children and adolescents with type-2 diabetes. Unlike people with type-1, who produce no insulin and must inject the hormone to remain healthy, people with type-2 diabetes do produce insulin, but for reasons we don't yet understand, their insulin is less effective. To tackle this growing epidemic, we need to understand the mechanisms underlying the new childhood form of type-2 diabetes, and how it differs from that seen in older people.

Our studies to date in younger patients with type-2 diabetes reveal that they are much more likely to be obese (than patients with later onset diabetes), and that they have severe insulin resistance, and a more rapid loss of insulin secretion. These patients tend to have high blood pressure and traces of protein in their urine (microalbuminuria), that increase their risk of cardiovascular problems. Because obesity is so common in these young people, we also looked at eating disorder behaviour. Strikingly, 25% of them exhibit features of eating disorders: they find it hard to restrain from overeating, and are ambivalent about their eating patterns, body shape and weight. Early onset type-2 diabetes is such a new phenomenon, particularly in Europe, that we have no treatment guidelines yet. There is agreement, however, that it is a serious public health concern, and as a result of our findings we have opened a new Young Person's Diabetes Clinic.

SECTION 2

Health services: focus on healthcare

Health services research identifies and quantifies healthcare needs, and studies the provision and use of health services to meet those needs.
It is a multidisciplinary field that studies the social factors, economic systems, organisational structures and processes, health technologies, and personal behaviours that affect access to health care, the quality and cost of health care, and ultimately our health and well-being.
The research focuses on individuals, families, special needs groups, institutions, communities, and populations as a whole.

Smear test? Make it a date!

Uptake of cervical smear tests is poor. Dr Jane Walsh (Psychology, NUI Galway) investigated why more women are not attending the screening programme

Every year in Ireland, approximately 1,000 women develop cervical cancer, and 70 women die of the disease. However, provided it is caught early, the disease is treatable. The Mid-Western Health Board is now running the Irish Cervical Screening Programme (ICSP) on a pilot basis. Women aged 25-60 are invited for a smear test, but uptake to date has been poor. To investigate why, with a view to improving attendance, we surveyed women's attitudes, intentions and behaviours regarding smear tests.

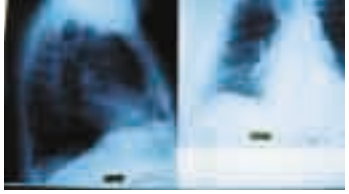
We sent questionnaires to 3,000 women in the mid-west; 1,500 also received a form asking them when and where they would attend (a planning, or 'implementation intention' form). Of the 3,000 women, just 17% attended for a smear test. However, 41% returned our questionnaire, and 77% of the 1,500 who received the planning form, completed it. Significantly, women who completed the planning form, and 'put their intention in writing', and women who had already had a smear test were the most likely to attend. The major hurdle is therefore persuading more women to have their first test. Factors here include attitudes to screening in general, the opinions of 'trusted others', such as GPs, and whether the woman was likely to regret not attending. To improve uptake, we therefore recommend: specifically targeting women who have never had a smear test, encouraging GPs to be more proactive about inviting women to be tested, and sending women a planning form with their letter of invitation.

Nurses, doctors and organ donation

To identify some of the barriers to increasing organ donation, research fellow Mary Smith and Prof Hannah McGee (Health Services Research, Royal College of Surgeons in Ireland) have surveyed the views of staff working at the front line in the country's intensive care units

Identifying organ donors, determining brain death and requesting donations raise complex social, legal and ethical issues for staff and families. Donation rates here, though relatively high, dropped following the recent organ retention controversies. They have since recovered somewhat, but will have to treble over the coming decade to meet the growing need. To identify barriers to increasing organ donation, we reviewed the Irish organ donation system, and surveyed the views of intensive care unit (ICU) staff. In all, 132 doctors and 875 nurses from the country's 37 ICUs completed our questionnaire; and 12 doctors and 15 nurses were also interviewed in-depth.

We found that the more organ donation cases someone sees, the more pro-donation they are. Doctors believed they support donation as much as nurses, but nurses disagreed and, indeed, nurses are more likely to carry donor cards and to discuss donation with their families. Nurses are most confident comforting bereaved families, and believe doctors should be more pro-active in asking for donations. Both nurses and doctors believe recent controversies eroded public trust and also undermined their own professional confidence in approaching families. However, they also underestimate public support, which the latest evidence suggests is about 70%. Resources emerged as a major issue, affecting staff time, bed numbers, training, support for transplant coordinators, and places where bereaved families can have some privacy. Based on our research, we recommend: a professional forum where nurses and doctors can discuss relevant issues, a national organ procurement service, improved resources, and greater education and training for ICU staff.



Minimising X-ray doses for children

To help ensure children receive the lowest dose possible, Dr Patrick Brennan, PhD student Kate Matthews and MSc student Tracy McCrudden (School of Diagnostic Imaging, UCD), are devising reference doses for the most common childhood X-ray examinations

Several factors affect the radiation dose someone receives during an X-ray examination, such as how the image was recorded and the X-ray energy. Because it is essential that patients receive the lowest dose possible, countries are obliged to establish 'diagnostic reference levels' (DRLs), which are dose levels that would not generally be exceeded. Several countries have compiled adult DRLs, but X-ray practices vary internationally. Hence, most countries need to compile national DRLs, and our UCD team compiled values suitable for adult examinations in Ireland.

Reference doses are even more important for children, however, because children are more sensitive to radiation, as their bodies are actively growing. Yet there has been little research, here or abroad, on childhood DRLs. To redress this urgent need, we conducted a three-year study examining how children are X-rayed here, and compared this with the best international practice. We studied 4,000 X-rays, taken in 40 hospital departments, and considered factors such as the amount of radiation delivered. This allowed us to calculate provisional DRLs for seven common childhood X-ray examinations (notably chest, abdomen, and hips), across five age groups: premature babies; infants under one-year-old; and 1-5, 6-10 and 11-15 year-olds. We are still collecting data to finalise what are currently provisional DRLs, though it is unlikely the figures will change much. Once finalised, these tables should be important not just in Ireland, but as international baselines.

What's that you said?

People with severe physical impairments can use computerised devices to generate synthetic speech. Dr Martine Smith and Isobel Connolly (Clinical Speech & Language Studies, TCD) identify the social and technical problems that can arise for speaker and listener alike

Some adults with severe physical disabilities do not have sufficient muscle control to speak. Instead, they must rely on alternative means of communicating – everything from gesturing, to pointing at pictures, to using computer devices that generate synthetic speech. We interviewed 24 adults who use synthetic speech devices, to explore how they feel about their communication options, how effective they find their device, and for what kinds of situation.

Most of those we interviewed regarded their speech devices as very important for communicating, but also stressed the importance of other ways of communicating. One-third said they would like to use their device more often, but that other people often react to it badly. Almost 40% felt they did not know enough about the technology involved, few had regular contact with a speech and language therapist, and many had no one to contact in the event of a technical problem.

To tackle some of these issues, we held workshops for staff working in long-term residential facilities, to improve their understanding of communication difficulties and of the various devices. Significantly, although many of the residents have communication difficulties, over 90% of the staff had no training in this area. Our workshops helped to improve staff sensitivity to the experiences of people with communication difficulties, their skills in programming communication devices, and their confidence. In subsequent interviews, residents said their communication experiences had improved, but they also highlighted the importance of involving residents in developing such programmes.

Measuring a stroke patient's mobility

Dr. Francis Morgan (Physiotherapy, Royal College of Surgeons in Ireland) has devised a new, quick and easy scale to assess how a stroke patient is improving

Many stroke patients have difficulty performing everyday movements such as walking, and their recovery can be slow. Rehabilitation can help them to regain some, perhaps even all of their mobility, but physiotherapists need to be able to measure the improvement. Marking mobility on a scale can also boost the patient's morale and motivation, if it shows that they are making progress. Existing scales to measure mobility are mostly tedious and difficult to use, especially in a busy clinic, and can be tiring for the patient. Only one is widely used: the motor assessment scale (MAS). Developed in Australia, it checks eight types of movement, but can take over 10 minutes to complete.

We developed a new and simpler approach, specifically for stroke patients, the stroke activity scale (SAS). It asks physiotherapists to score the quality and timing of five important everyday movements: getting out of bed, sitting balance, standing up, walking, and using their arm to pick up a glass and take a drink. To test our new SAS, we compared it and the MAS by scoring the same group of patients simultaneously. The results were very similar, but our scale was three times quicker, taking only three minutes to complete. It is also simpler, and does not call for any special equipment or training, which makes it more likely to be used in a busy clinic. We are now piloting the SAS in several clinical practices.

Hepatitis C and general practice

Dr Walter Cullen and research nurse June Stanley (General Practice, UCD) found that new guidelines for GPs have improved the treatment of people with hepatitis C

Hepatitis C infection is so common among people who have used or injected drugs that the greater Dublin area is facing an epidemic. The virus can cause serious, sometimes fatal liver damage. Infected people need to be given access to appropriate medication, encouraged to lead a healthy lifestyle and to be immunised against other liver infections. Early diagnosis of hepatitis C is important, but not everyone is tested as early as they should be, perhaps because they are reluctant to attend their doctor, for instance, or because of their doctor's heavy workload.

The Dublin Area Hepatitis C Initiative, which was put in place to tackle this growing epidemic, brought together a panel of experts to review the latest medical literature and devise 'best practice' guidelines for hepatitis C care. These guidelines were then introduced on a pilot basis in over 20 practices that care for people who have used heroin; educational seminars were held for staff; and a specialist primary care nurse worked with practice staff and patients.

We looked at the impact of these initiatives after six months, and found that significantly more people were now being tested for hepatitis C, and that more infected people were being referred to specialist units. Both patients and doctors reported that the project had increased their awareness and understanding of this health problem. We recommend that all doctors be made aware of hepatitis C, and of the new practical guidelines. Additional support is needed for primary care practices, however, if we are to address the growing problem of hepatitis C in Ireland. This project was co-funded by the Irish College of General Practitioners and the Eastern Health Board.

Travellers and hospice care

The Traveller community does not avail of hospice palliative care facilities to the same degree as the settled community. Dr Regina McQuillan and researcher Onja Van Doorslaer MA (St Francis Hospice, Dublin) asked if this was because their attitude to dying differs from that of settled people

Since our hospice opened in 1995, several Travellers have used our home-care service, but only two have availed of in-patient palliative care. Is this because access is difficult for Travellers? Or because they view dying differently from settled people? Or perhaps because Travellers die younger and seldom develop cancer? Cancer statistics do not record ethnicity, hence we don't know if Travellers are less likely to die of cancer. Talking with both palliative care service providers and Traveller focus groups in the eastern region provided us with a lot of information about factors that may affect the use of palliative care services by Travellers.

These factors were wide and varied ranging from lack of information about palliative care services to a fear of the diagnosis of cancer. Some cultural differences between the Travelling and settled communities were noted, especially around the involvement of the Traveller's family in the process of dying and death, as well as attitudes towards talking about illness, cancer and death. For example, Travellers feel strongly that emotional support for the dying should come from relatives, not healthcare professionals. In general, however, there were more similarities to the settled community to be seen – a similar level of knowledge about palliative care, a similar fear of dying and the need to feel hope (particularly among Travellers), and a similar desire to care for the sick and ill at home as much as possible. Related to this, most Travellers expressed a preference to die at home or in a hospital rather than a hospice.

Most palliative care staff surveyed had not cared for a Traveller within their service. It is important then, that we examine how palliative care services can be best promoted to Travellers. We strongly recommend providing palliative care in hospitals, and in a 'setting of hope', educating palliative care providers about cultural differences, and informing Travellers about palliative care services. It would also help if ethnicity was recorded in health and cancer statistics.

Nursing and palliative care

To improve post-graduate training for nurses, research fellow Kevin Connaire and Prof Cecily Begley (School of Nursing & Midwifery, TCD) have studied the special skills needed in palliative care nursing

Specialised nursing calls for specialised skills. Theatre nurses need to be familiar with sophisticated instrumentation, for instance, while palliative care nurses need considerable inter-personal skills. As part of a training and curriculum development programme, we wanted to analyse the skills that nurses employ when caring for people who are dying. We observed nearly 300 hours of nursing practice at all six of the country's in-patient hospices, and interviewed 40 expert hospice nurses and 11 patients.

Caring for the dying is complex and challenging, as each patient has different needs. We found that one important aspect is helping patients to maintain their 'optimal functioning' as their illness progresses. Most patients, for instance, have some function that is important for them, such as still being able to feed themselves, and a skilled nurse can help them achieve this. Not surprisingly, inter-personal skills are paramount in a hospice, especially the ability simply to 'be there' for a patient. Skills such as being able to listen, being silent with the patient, and being able to touch them are essential, and can help nurses to provide the necessary psychological and spiritual comfort. Other important skills we observed were: helping patients to deal with the reality of dying, and helping bereaved families to deal with the loss and move on. Significantly, the skills we observed in the nurses were also those the patients identified as important, which confirms that Irish palliative care nurses provide a valuable service.

SECTION 3

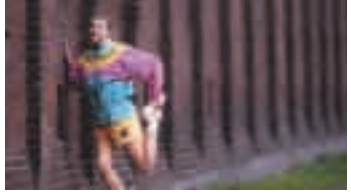
Affairs of the heart: cardio-vascular health and disease

In 2003, diseases of the circulatory system accounted for 10,984 of all deaths in Ireland or an annual rate of 2.8 per 1,000 of the population. Of these, 5,648 were due to coronary heart disease and 2,255 to cerebrovascular disease. Ireland is still above the EU average for premature deaths from cardiovascular disease. Last available figures show that Ireland has 54.63 premature deaths per 100,000 in comparison with the EU average of 52.73 premature deaths per 100,000.

Principal causes of death in Irish people in 2003
(men and women, all ages, all causes)

1	Coronary Heart Disease	20%
2	Stroke	8%
3	Other Circ Diseases	11%
4	Cancer	26%
5	Other	35%

Source: Central Statistics Office. (2004)



Hearts . . . and minds

Prof Andrew Murphy and PhD student Victoria Ngozi Ononeze (General Practice, NUI Galway) studied why many cardiac patients do not take the preventive measures needed to stop further heart problems

The good news is that treatments for heart disease are now so successful that most patients can lead a normal life. The bad news is that, consequently, the disease is no longer as feared as it once was, and many patients do not realise that they still need to make changes, especially to their lifestyle.

To explore this further, we examined the experiences of people living with a heart condition in the west of Ireland. In all, 56 people from all walks of life, and 14 medical professionals participated in the study. We questioned 26 people with heart disease about their views; and a further 30 people took part in discussion groups to test whether those views reflected the general experience. We also talked to family doctors, and doctors and nurses who look after cardiac patients in hospital.

Our study revealed that many people with heart trouble lead a reasonably normal life. They are aware that heart disease can happen to anyone, and they realise that much heart disease can be attributed to lifestyle. Most people take their prescribed medication, but many people do not make the necessary lifestyle changes (notably relating to diet, smoking and exercise), wrongly believing that the drugs and surgical intervention have taken care of the problem. There is therefore a need for improved patient education. We also recommend that medical professionals, while encouraging people to have a positive outlook, need to balance this by ensuring their patients realise that heart disease is a serious, life-long illness.

Feeling the pressure?

Prof Paul Cahill and PhD student Catherine Sweeney (Vascular Health Research Centre, DCU) are studying how blood vessels respond to raised blood pressure

Every heartbeat pumps blood through your blood vessels. The mechanical force of the blood flowing past prompts the endothelial cells that line the blood vessel to secrete molecular signals. These signals control the smooth muscle cells in the blood vessel walls: certain cells may respond by changing their behaviour, for instance, moving location, growing, or dying. The smooth muscle cells stretch and relax the blood vessel, and usually several types are present – some are compliant and likely to die if there is a problem, others are liable to proliferate and cause trouble – and signals from the endothelial cells control in part the balance between them.

We study how this cell population changes its behaviour during disease, and in particular when blood pressure is raised. In cardiovascular disease we know, for example, that blood vessels become stiffer in patients with high-blood pressure, and become blocked in arterosclerosis. But what is happening at the cellular level?
To explore this, we use an artificial blood vessel created in the laboratory from a hollow fibre. We grow endothelial cells on the inside, and smooth muscle cells on the outside, and a pump (our ‘heart’) pushes blood serum through the vessel to mimic real life. We discovered that, when we increase the ‘blood pressure’ in our system, distinct vascular smooth muscle cells commit suicide (a process called apoptosis). This is independent of the endothelial cells, and occurs when a specific enzyme (MAP kinase) is activated. We think this apoptosis helps the blood vessel to cope with the strain by remaining flexible and hopefully our work may one day reveal new ways of treating cardiovascular disease.

Cartoon showing red blood cells

Immunostaining of RhoA in the media layer of the pulmonary artery of a rat

How lung disease can lead to heart failure

The body responds to lung disease by cutting blood flow to the damaged areas; but unfortunately this raises blood pressure in the lung and strains the heart. Prof Paul McLoughlin and postdoctoral scientist Dr Jean-Marc Hyvelin (Physiology, UCD) believe they have identified what controls this response

If your lungs falter or fail, you are in big trouble – trouble getting oxygen into your blood system, and trouble getting rid of waste carbon dioxide. The body responds to this by cutting blood flow to the damaged lung tissue and diverting it to undamaged regions. This ensures that blood passing through the lungs is still stripped of all CO^2, and fully replenished with oxygen. However, this increases blood pressure in the lung and can eventually strain the heart, often leading to heart failure. This problem is extremely difficult to treat, as available drugs often have unacceptable side effects.

A better understanding of what is happening might allow us to develop better treatments. To that end, we study muscle cells in the blood vessels of rat lungs, and investigate what triggers these cells to contract (i.e. narrowing the vessel and reducing blood flow), and to relax (i.e. opening the vessel and allowing blood to flow).

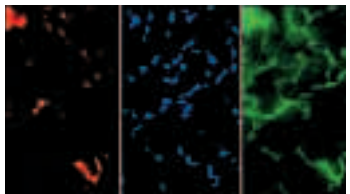
One mechanism controlling the muscle cells, involving calcium, was already known. We examined a second pathway, involving a small signaling molecule, Rho-A. When this pathway was blocked with a chemical inhibitor, the muscle cells lining the blood vessels relaxed, increasing blood flow to the lung and lowering blood pressure. Both pathways are present in all organs, but Rho-A predominates in lungs, whereas calcium is more important in the other organs. We are now studying Rho-A further, to see if blocking this pathway can ease blood flow in damaged lungs without affecting the other organs, and to investigate possible side effects of interfering with this pathway.

Muscles change with the flick of a switch

Some medical treatments use electricity to stimulate muscles. Prof Kay Ohlendieck and PhD student Clare O'Reilly (Biology, NUI Maynooth) are studying the effect of this

One relatively new way of treating damaged heart muscle, is to wrap part of the patient's back muscle around the failing heart, then wire it up to an electrical pacemaker. This ensures that the new muscle complex twitches at the same slow pace as normal heart muscle. If this 'dynamic cardiomyoplasty' is successful, what was once a fast-twitching skeletal muscle will change its behaviour, and transform its fibres into the slower-contracting fibres typical of heart muscle. An important issue, however, relates to the type of electrical stimulation that should be applied. Opinion differs as to whether you should give continuous electrical stimulation or a period of stimulation followed by a period of rest. This could be crucial, as one of our collaborators has shown that if you get the protocol wrong the muscle will degenerate.

We are investigating the biochemistry that happens when you change the frequency of electro-stimulation of a muscle. We implant electrodes into muscles, then stimulate the muscles for 3-70 days at a low frequency (about 2 Hz, similar to that of heart muscle), and then examine the muscle cells. We found that if the stimulation is followed by rest, the muscle fibres revert to their original behaviour. Continuous stimulation, however, produces long-term changes in the molecular make-up of specific receptors at the nerve-muscle cell junctions. We believe these changes allow the muscle to adapt to its new role. This information should help teams to devise appropriate protocols for electro-stimulation therapies for heart patients, people with damaged nerves and patients in a coma.



Immunofluorescence labelling of the neuromuscular junction

SECTION 4

The ageing brain: memory and Alzheimer's

What is Alzheimer's disease?

Alzheimer's disease is a progressive neurological condition characterised by the build up of proteins in the brain called 'plaques' and 'tangles'. These proteins gradually damage and eventually destroy the nerve cells. This can make it more and more difficult to remember, reason, and use language. The person may become disorientated and have increasing difficulty with simple daily tasks such as using the phone, making meals or managing money.

Today, more than 35,000 people in Ireland have dementia, of which Alzheimer's disease is the most common form. The risk of developing Alzheimer's disease increases with age with its prevalence rising from approximately 1% in people under 65 years old to more than 25% for those over 80 years. Although rare and more commonly associated with older age, Alzheimer's Disease can also occur in people in their 40s and 50s. It is not yet known how to prevent or cure the condition, but there are treatments available now that can help manage the symptoms.

Source: The Alzheimer Society of Ireland

What have I forgotten?

To learn why our memories fail as we get older, Prof Marina Lynch and PhD student Frank Maher (Physiology, TCD) are investigating how brain cells change with age

We can continue to learn and remember things throughout our life, thanks in part to a protein called brain-derived neurotrophic factor (BDNF), which helps protect our brain cells. Several studies suggest that the amount of BDNF in our brain falls as we get older, however, and scientists think this may explain why elderly people have trouble remembering. We set out to investigate this, by studying a form of brain cell activity called long-term potentiation (LTP) in the hippocampus region of rat brains. We chose LTP because it is believed to be similar to what happens during learning and remembering, and the hippocampus region because it is known to be an important brain structure for memory.

We found that the hippocampus of older rats actually had *more* BDNF, suggesting that BDNF levels are not the problem. Then we realised that the cells were not signaling as much as they normally would in the presence of BDNF. It seems older rat brain cells lose the ability to respond to the protein, because, we discovered, they have fewer BDNF receptors. It is possible that the brain cells can sense this change, and try to compensate by pumping out yet more BDNF, but to no avail. We also found that the older rat brains had more of an immune molecule called interleukin-1 beta. This causes inflammation and puts brain cells under stress. Putting these findings together, we now believe that older brains function less well because of the combined effect of this interleukin-1 beta stress, and the reduction in the BDNF-induced cell signaling.

What causes Alzheimer's disease?

Dr Veronica Campbell and PhD student Marie Fogarty (Physiology, TCD) are studying how a protein associated with Alzheimer's disease can kill nerve cells in the brain

Alzheimer's is a devastating neuro-degenerative condition, and people stricken by it lose their ability to learn and remember. One hallmark of the disease is deposits of beta-amyloid – a small, insoluble protein that accumulates in areas of the brain associated with learning and memory. Scientists think beta-amyloid is actively involved in the disease, and that it prompts nerve cells in the brain to commit suicide (by following a pathway of programmed cell death called apoptosis).

We have known for some time that nerve cells exposed to beta-amyloid do indeed die, but no one yet knows how. So to investigate this, we study what happens when beta-amyloid is added to laboratory cultures of neurons, and we use several biochemical and molecular approaches to follow what happens inside the nerve cells as they react. So far, we have identified three components that are involved – a calcium-regulated enzyme (calpain); certain 'stress-activated' proteins (SAPKs); and a 'tumour suppressor' protein (p53) – and we found that the levels of these three components increase as the cells prepare to die. This information will help us to understand the effect beta-amyloid has on nerve cells in the brain, and may ultimately help us to develop new treatments for Alzheimer's disease.

You must remember amyloid beta

A rogue form of amyloid beta is important in Alzheimer's disease. Prof Michael Rowan and PhD student Francesco Amico (Pharmacology, TCD) can minimise the amount of rogue protein that accumulates, which should prove useful in developing treatments for this distressing disease

If we remember things, it is because the nerve cells in our brain can still form long-lasting connections with each other. In Alzheimer's disease, where patients lose the ability to remember, one of the earliest changes in the brain is probably when these nerve cell connections weaken. Scientists know that a natural protein, called amyloid beta (also called beta-amyloid), plays a key role in this process. It seems that in Alzheimer's patients the protein accumulates and forms clusters, either because their brain produces too much of the protein or the protein is not removed quickly enough. Either way, these rogue clusters can have a toxic effect on brain cells.

We set out to find some way of controlling amyloid beta production, so that these clusters do not form, while still allowing brain cells to produce enough of the protein to function normally. Our approach is to partially block, using selective inhibitors, the activity of the enzymes involved in 'cleaving' amyloid beta (secretases). We gave varying doses of these inhibitors to brain cells in the laboratory, and then tested the toxicity of the amyloid beta protein they produced. In this way we have proved that by controlling the dose of the inhibitor, we can control amyloid beta production and minimise the amount of rogue protein the cells produce. These inhibitor drugs are already in early clinical trials with Alzheimer's patients, and our study suggests that, if the dose is right, it should be possible to delay the onset of early symptoms, and help patients to hold on to their memories.

New drugs for Alzheimer's disease?

Dr Caroline Herron and PhD student Derek Costello (Physiology, UCD) discovered that two drugs, used to treat heart problems and diabetes, may help in treating Alzheimer's disease

A short peptide called beta-amyloid is found in the brains of all healthy humans. However, clumps of it form in the brain of people with Alzheimer's disease, where it is associated with nerve cell death. To learn more about beta amyloid, we study its effect on electrical activity in slices of rat brain in the laboratory. This electrical activity among nerve cells, called long-term potentiation (LTP), is a model for the mechanisms involved in learning and memory.

We have discovered that beta-amyloid triggers the activation of certain enzymes (notably one called JNK), that can initiate cell death – this may underlie its toxic effect on nerve cells in Alzheimer's disease. We also discovered that beta-amyloid depresses LTP, possibly explaining why people with Alzheimer's lose their short-term memory.

Normally, LTP is produced by a rapid flow of calcium into the nerve cells. We found that beta-amyloid increases this flow, via specific calcium channels (L-type) located in the membranes of nerve cells. If overloading the cells with calcium reduces LTP, then would blocking calcium channels restore the activity? We found that verapamil, a cardiac drug that blocks calcium channels, reverses the effect of beta-amyloid and restores LTP. Likewise, another class of drug (PPAR-gamma agonists), involved in regulating metabolism and currently prescribed for diabetes, can counter the effects of beta-amyloid and restore LTP. Verapamil and the diabetic drugs are already approved for clinical use, and our results suggest that they may also be useful in treating Alzheimer's disease. Before they could be prescribed for Alzheimer's patients, however, we would need to know more about how they work.

SECTION 5

Arthritis: understanding the causes

All research projects in this section were jointly funded by the HRB and the Arthritis Foundation of Ireland

Facts about arthritis

- Arthritis is a serious national health problem affecting nearly half a million men and women, while over 5,000 children under the age of 12 have arthritis in some form.
- One in three Irish families are affected by arthritis.
- 13% of Irish people show some signs of arthritis.
- There are over 100 types of arthritis.
- It is estimated that approximately 1% of the adult population is affected by Rheumatoid Arthritis (RA).
- RA affects women strikingly more than men, with the overall ratio about three women to one man. Also, the prevalence increases with age.

Source: The Arthritis Foundation of Ireland

A computer generated model of Mal and MyD88

Understanding rheumatoid arthritis

Prof Luke O'Neill and PhD students Eleanor Dunn and Pearl Gray (Biochemistry, TCD) are studying new ways of relieving the inflammation in arthritic joints

Rheumatoid arthritis is a chronic inflammatory disease of the joints. We still do not know what causes it, but our understanding of the disease is improving all the time, leading to better drugs to treat this painful condition. For instance, we now know that arthritic joints have very high levels of a protein called Interleukin-1 (IL-1), and several drugs that block this protein are now available. Some of these drugs are very effective at relieving inflammation in the joints, but they work only for some patients, so we are looking for new ways of turning off IL-1.

In this study we first focused on a related protein, called IL-1F5. We found this is also present at high levels in rheumatoid tissue, and analysing its structure led us to think that it might actually compete with IL-1, and block inflammation. But, when we made some IL-1F5 protein, and determined its structure by X-ray crystallography, we discovered that it was very similar to IL-1, and thus more likely to *promote* inflammation. If so, interfering with IL-1F5 might be a useful alternative way to tackle arthritis. We also studied a protein called Mal. This is an important 'on' switch for inflammation, and one of our collaborators has shown that interfering with Mal greatly reduces the inflammation in arthritis. We investigated how Mal functions, and found that it switches 'on' when it is chemically modified. So, targeting Mal might be another way to turn off the disease process.

The anatomy of rheumatoid arthritis

By exploring what happens in arthritic joints, Dr Evelyn Murphy and PhD student Alice McEvoy (Rheumatology, St Vincent's University Hospital) have identified a protein that plays a key role in the disease

Our understanding of inflammatory arthritis has recently improved, and we now have new drugs for rheumatoid arthritis. These act by blocking the signaling molecules, or cytokines, that trigger the inflammation (the cytokines are produced by the immune system, for reasons we don't yet fully understand). There are two drug types, depending on which cytokine they target: TNF, or IL-1. TNF blockers work for some patients, IL-1 blockers work for others, and some people need to take both drug types. But 30% of patients don't respond to these drugs at all – so clearly, we don't yet know all there is to know about rheumatoid arthritis.

To investigate other possible pathways, we studied a protein called NURR1. This protein is a 'nuclear transcription factor': essentially, it can move into the nucleus of the cell and bind to the DNA, where it switches some genes off and other genes on. By studying cells taken in biopsies from arthritis patients, we discovered that NURR1 plays a role in the inflammation. We found that the cytokines TNF and IL-1 can trigger cells to produce more NURR1; they can also activate the NURR1, causing it to move into the nucleus; and they can alter the protein's function. Significantly, we also found that NURR1 can cause cells to proliferate, producing the tumour-like growths often seen in arthritic joints. While more research is needed, we believe we have identified an important protein that could one day lead to new drugs for treating arthritis.

Colour artwork showing rheumatoid arthritis of finger joint

The genetics of rheumatoid arthritis

Prof Fergal O'Gara, Dr Clare Adams and PhD student Heidi Mulcahy (Microbiology, UCC) are studying genetic differences that may make some people more susceptible to rheumatoid arthritis

Rheumatoid arthritis is a crippling inflammatory disease, and a puzzling one too – we still don't know what causes it, and although we now know that some people's genetic make-up means they are more susceptible to developing the disease, the picture is not clear cut.

In the last decade research has determined that people with RA tend to have an excess of protein called tumor necrosis factor alpha (TNF-alpha). This protein plays an important role in the body's natural defence system, as part of the normal immune response. However, overproduction of TNF-alpha can lead to excessive inflammation such as that found in patients with RA.

Because of its role in the progression of RA, blocking the activity of TNF-alpha has become a key focus of new RA therapies. Indeed, TNF-alpha blocking drugs have been shown to improve health and well being in large numbers of RA patients. Nevertheless, a certain percentage of patients do not respond to anti-TNF therapy. It is thought that this may be due in part to differences in the genetic make-up of these patients in terms of TNF-alpha production.

In this study, we used molecular techniques to investigate the production of TNF-alpha and other related inflammatory immune proteins, in patients taking anti-TNF drugs. We also screened the patients for the presence or absence of variations in their TNF-alpha gene. We found that TNF-alpha levels fell only in some, and not in all patients during the treatment. In fact, TNF-alpha levels actually increased in some patients. At the outset, we had expected to find some association between a patient's response to the anti-TNF drugs and their TNF gene. However, we found there was little association between specific variations in the gene and a patient's TNF-alpha protein levels. These results illustrate the complexity of TNF expression in rheumatoid arthritis, and the non-uniform nature of the disease process.

What causes psoriatic arthritis?

Prof Oliver Fitzgerald and Dr Ursula Fearon (St Vincent's University Hospital) and PhD student Shane Curran (UCD) are studying the mechanisms involved in this puzzling autoimmune disease

Some 3% of Irish people suffer with psoriasis, a painful scaly rash that can affect the scalp, nails, knee and elbow joints. About 15% of these people also develop a frequently debilitating form of arthritis. This psoriatic arthritis is a painful, progressive inflammatory joint disease, often causing distinctive 'sausage-like' swellings of the toes and fingers. Between 15-20% of new patients attending the St Vincent's early arthritis clinic have psoriatic arthritis, making it the second most common form of defined arthritis after rheumatoid arthritis. Little is known about it, but if we are ever to develop an effective treatment, we will need to understand what causes the inflammation. Some psoriasis rashes seem to be triggered by infection (typically by streptococcal bacteria), so could infection also trigger the arthritis?

Certain immune cells, called T cells, are known to play a role: they are found at inflamed joints, and we recently showed that methotrexate (a drug used to treat both psoriasis and psoriatic arthritis) reduces the number of T cells in arthritic joints. Working with Prof Bob Winchester, at Columbia University, New York, we examined molecules present on T cell surfaces (T cell receptors), looking for clues about what the cells had been in contact with. However, we found little evidence that the cells were responding specifically to an infecting particle, such as a virus. This suggests psoriatic arthritis is not triggered by infection, and we may need to rethink our ideas about what causes autoimmune diseases such as psoriatic arthritis.

SECTION 6

Cancer: confronting the enemy within

What causes cancer?

It is rarely possible to find the cause of a cancer in an individual, but studies on groups of people with cancer have shown specific risk factors to be associated with specific cancers. This suggests that different types of cancer probably have different causes. These studies also indicate that cancer formation is a multi-step process, and that for most cancers the time from a cancer-causing exposure to a clinically diagnosable cancer averages about 20 years.

Among the known risk factors for cancer, tobacco stands out. Cigarette smoking is associated with lung cancers, and with a substantial proportion of cancers of the bladder, mouth and throat, stomach, pancreas and others. Diet is also a risk factor; higher cancer rates are seen in people who eat a diet high in fat and low in fresh vegetables and fruits. It is estimated that diet and tobacco together account for approximately two out of three cancers.

Family history and hormonal functions are risk factors for certain cancers (i.e. breast cancer), while occupational studies have shown certain chemicals and other substances to be carcinogenic; these include asbestos, benzene, arsenic, vinyl chloride and other industrial products. Exposure to these substances is thought to account for about 5% of all cancers.

What types of cancer are most common?

The most common type of cancer is skin (non-melanoma) followed by breast, colorectal, lung, and prostate. The largest number of cancer deaths overall tends to be from lung cancer. One in three will develop cancer by the age of 75.

Who gets cancer?

Unfortunately, almost anyone can develop cancer, even children and young adults who lead active, healthy lives. The largest number of cancers occur in the 65+ age group.

Source: The National Cancer Registry

1) Causes and underlying mechanisms

Breast cancer: disorganisation and disease

Breast cancer cells lose their ability to form organised 3D structures. Prof Finian Martin and PhD student Jillian Holwin (Pharmacology, UCD) have discovered how hydrocortisone is important in controlling the organisation of healthy breast cells

By the later stages of pregnancy, in preparation for making and delivering milk, breast cells will have become organised in three-dimensions: a branched, tree-like structure develops, made of hollow tubes that converge on the nipple; and off each tube is a small hollow sphere, where the milk components will be made. The tubes and spheres are all lined with a single layer of epithelial cells, and this 3D cell structure is essential if the mammary gland is to function properly. When breast tumours develop, however, the epithelial cells lose their ability to form such 3D assemblies, and instead form disorganised groups that can cause blockages and invade neighbouring tissue.

To get a better understanding of how breast tumours develop, we study the normal development of these breast cell assemblies. We take epithelial breast cells from mice mid-way through a pregnancy, grow them in the laboratory on a special protein scaffold, and bathe them in a suitable fluid. This allows us to mimic what normally happens, to watch the cells as they organise in three dimensions, and to study the biochemical signals that control the process. In this way, we have discovered a new molecular signalling pathway, regulated by the hormone hydrocortisone. Significantly, when we disrupt this pathway (by administering drugs, for instance), the epithelial cells no longer form a neat, normal structure. Our next step is to see if this is what happens in breast cancer and, if so, whether we can stop tumours developing by manipulating the molecular signalling pathway with new drugs.

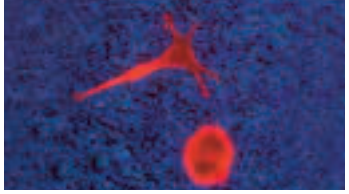
Breast cancer: the many faces of survivin

The survivin protein is found in cancer cells. Prof Martin Clynes, PhD student Rasha Linehan, and research assistant Rachel Purcell (National Cell & Tissue Culture Centre, DCU) are studying its puzzling role in breast cancer

In 1997, cancer researchers discovered a new protein, called survivin. It was found in large amounts in only two places: cancer cells, and developing embryos. Any protein that is predominantly associated with cancer is interesting, since targeting it would allow us to kill the cancer cells without also destroying healthy cells. Research quickly revealed that survivin is found in the cell body (not the nucleus) of cancer cells, that it blocks cell 'suicide' or apoptosis (thus keeping the cells alive), and that it was associated with poor patient prognosis. But, as more results came in, this picture became confused.

To clarify what survivin does, we decided to take a well-characterised cancer cell line, persuade the cells to produce more survivin, and see what happens – would the cells become more resistant to chemotherapy, for instance? So we made a DNA molecule that coded for survivin, and inserted this into cancer cells. The cells did produce the precursor to survivin (messenger RNA), but this did not translate into extra protein, suggesting that survivin is tightly regulated in cancer cells.

Frustrated in this approach, we next studied survivin in cells taken from nearly 300 different breast tumours. Intriguingly, we discovered the survivin in the cell nucleus and not, as expected, in the cell body. (Only one other study has found it in cell nuclei, and that was in stomach cancer.) Moreover, in the breast cancers, survivin was associated with both good overall patient survival and relapse-free survival. These mysterious results lead us to believe that there are several forms of the protein, probably with different functions. It now seems, too, that sometimes it is not enough to know if a protein is present, you must also know where it is in the cell.



An artistic representation of a gene chip

Skin cancer: the genetics of melanoma

Why do men generally get more aggressive skin cancers than women? Dr William Gallagher and PhD student Zoe Kelly (Pharmacology, UCD) have identified a male gene that could be to blame

Men, it seems, are more likely to develop melanoma than women are, and their melanoma is more likely to be aggressive. This is not just because men expose more of their bodies to the sun, but probably reflects some basic genetic difference. To identify this difference, we turned to gene chip technology, a new technique that is revolutionising cancer research. Gene chips are about the size of a thumbnail and can hold 500,000 DNA fragments. They allow us to probe some 40,000 genes in a cell, revealing which ones are switched on or off at any time, and providing a snapshot of gene activity.

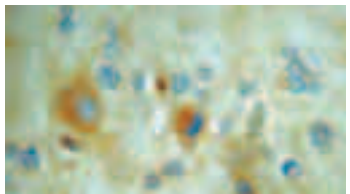
We started with melanoma cells taken from a man who had a mild form of the disease, and we gave the cells a cocktail of proteins that provoked them into becoming more aggressive. We then used gene chips to track the activity in the tumour cells in the laboratory as their 'aggression' levels rose. This revealed several marker genes that we believe could one day be used to characterise a patient's melanoma, diagnosing whether a tumour is likely to stay mild, for instance, or become aggressive and spread. We also discovered that a particular gene, found only in men, is also associated with melanoma: the testis-specific protein (TSP) gene, which occurs on the male Y chromosome. This gene may help to explain why men are more susceptible to developing melanoma.

Brain cancer: stopping brain tumours from spreading

Thomas Flannery and Dr Derek McCormack (Oncology, Belfast City Hospital & QUB) have identified an enzyme that helps some malignant brain tumours to spread

Astrocytoma is a malignant type of brain cancer that is difficult to treat – the tumour typically invades the surrounding healthy brain tissue and becomes all pervasive. This makes it impossible to surgically remove all the tumour without also removing a large part of the brain and causing severe disability or, worse, death. So, we are studying these tumours to see if we can find a drug that will stop them in their tracks. One way astrocytomas spread is by secreting enzymes that digest the surrounding tissue. We identified one of these enzymes, a protein-degrading enzyme (or proteinase) called cathepsin S. It was already known to play a role in other cancers, but we were the first to show its involvement in astrocytomas. Significantly, we also discovered that the more aggressive the tumour is, the more cathepsin S it produces, and the more cathepsin S it produces, the worse the prognosis is for the patient.

Most proteinases are denatured at a neutral pH (about 7.5) such as is usually found in the body, but not cathepsin S: it is stable at pH7.5, which means it is active in tissues for longer and not broken down. Now, one of our colleagues is looking for molecules that will block this enzyme in brain tumour cells. If successful, we might eventually be able to control the spread of astrocytomas with a drug.



Cathepsin S-positive tumour cells infiltrating into normal brain

Blood vessels in a human colorectal cancer

Colon cancer: cell connections and colon cancer

Research fellow Dr Sinead Byrne and Prof Desmond Fitzgerald (Clinical Pharmacology, Royal College of Surgeons in Ireland) have elucidated how one drug controls colon cancer cell growth

Colon cancer is a major killer disease in the Western world – some 1,800 people die every year of this cancer in Ireland alone. Scientists recently discovered that some drugs similar to aspirin, called non-steroidal anti-inflammatory drugs or NSAIDS, are useful in treating and preventing cancers, including colon cancer. But before these can be clinically approved for use in people, we need to know more about how they work. In this project we looked at the effect one such drug had on cells taken from colon cancers.

The drug we study is called a COX-2 inhibitor, which we know induces cell 'suicide' (or apoptosis). We looked at its effects on cancer cells by using gene chip technology: this provides a snapshot of the genes that are active in a cell at any time and, by comparing snapshots 'before' we apply the drug, and 'after', we can see how the cells react. In this way, we discovered that the drug affects genes involved in cell structures, gene processing, protein production and apoptosis.

Next, we focused on one particular gene, gamma-catenin (also called Plakoglobin), which is similar to a gene already implicated in colon cancer. Normally, gamma-catenin controls cell contacts, ensuring they don't become crowded. This gene is altered in cancer cells, however, leading to the disordered cell growth that is characteristic of tumours. We discovered that our COX-2 inhibitor drug acts by turning off this gene in colon cancer cells. This is an important mechanism, and suggests that COX-2 inhibitors could be useful in chemotherapy.

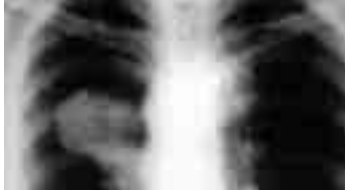
Prostate cancer: killing cancer without collateral damage

Prof Mark Lawler, Prof Donal Hollywood, and PhD student Ruth Foley (Haematology, St James's Hospital, Dublin), and Dr Tracey Robson (UU, Jordanstown) have devised a way of killing prostate cancer cells, without damaging healthy cells

Prostate cancer kills some 500 men in Ireland every year, making it almost as big a killer of men as breast cancer is of women. Treatment typically includes surgery, radiotherapy and 'androgen withdrawal' (in essence: chemical castration) and many patients respond well. However, some tumours resist all our best efforts, so new approaches are needed.

One problem with most cancer therapies is that they kill healthy tissue as well as the tumour, but we have devised an approach we hope will be more discriminating. Our plan relies on a standard chemotherapy drug, 5 fluoro-uracil. But instead of giving this, we would give an inactive precursor, 5-fluoro-cytosine. Then, we would introduce the gene that would convert the precursor into the active (and toxic) form. To ensure only cancer cells die, however, we would first have to engineer the 'vector' (which carries the gene into the cells), so that it is switched on only in prostate cancer cells.

We have now tested our idea on prostate cancer cells in the laboratory and have proved that it works in practice: we successfully transferred the gene into the cells, activated the drug, and killed the cancer cells. We were also able to make the technique more effective by designing our gene vector so that it is switched on by low-dose radiation, of the kind used in radiotherapy. We believe we now have a new, effective technique for killing prostate cancer. Before it could be tested on patients, however, the next step would be to conduct pre-clinical studies. This project was co-funded by the HRB and the R&D Office, Belfast.



Chest X-ray showing lung carcinoma – shadow in left lung

Lung cancer: The puzzle that is bcl-xL

Dr Carmel Daly, Prof Martin Clynes and PhD student Isabella Bray (National Cell & Tissue Culture Centre, DCU) are trying to find out how some cancer cells become resistant to chemotherapy drugs

Cell suicide, a highly regulated process which scientists call apoptosis, plays an important role in our body's healthy development, but also in many diseases. Several drugs now exploit apoptosis, notably chemotherapy drugs which work by persuading cancer cells to commit suicide. Unfortunately, cancer cells can become resistant to these drugs, usually by producing more of some gene that blocks apoptosis and prevent the cells dying. One such gene is called bcl-xL, and our group previously discovered that chemo-resistant lung cancer cells over-express this anti-apoptotic gene. This made us wonder: if we turned down this gene, would the cells become sensitive again to chemotherapy drugs?

To explore bcl-xL's role in drug-resistance, we devised two ways of turning down the gene which would hamper the production of bcl-xL protein. Both methods worked effectively in test tubes as measured by the absence of precursors to the bcl-xL protein. To our amazement, however, when we attempted the same thing in lung cancer cells, we saw, if anything, an *increase* in bcl-xL protein levels. Perhaps bcl-xL is so vital, a cell will not let us interfere with its production? Or perhaps, if you do interfere, the cell compensates in some other way? Clearly, we need to know more about bcl-xL. One possible next step is to use gene-chip technology to look not just at bcl-xL, but at several apoptosis genes simultaneously.

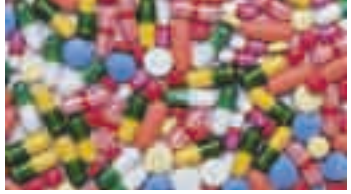
2) Therapies and Treatments
A new cancer drug?

A drug already used to treat paracetamol poisoning could also have anti-cancer potential, as Dr Joe O'Connell and PhD student Raymond Kelly (Medicine, Cork University Hospital) discovered

People with chronic inflammatory diseases will sometimes develop cancer. For instance, some 5-10% of patients with inflammatory bowel disease will eventually contract colon cancer. This link between inflammation and cancer is puzzling and so, working with cell cultures in the laboratory, we are teasing out the mechanisms that might be involved. This research has yielded two important results.

First, we discovered that a protein called tumour necrosis factor alpha (TNF-alpha), which helps perpetuate chronic inflammation, can block another protein, called p53, which normally works to prevent cells becoming cancerous. This is a direct link between chronic inflammation and cancer development – a molecule that is abundant at inflammatory sites suppressing a molecule that maintains DNA integrity and prevents normal cells from becoming cancerous – and sheds light on the mechanisms involved.

Second, while studying the function of p53, we discovered that a drug (NAC) normally used as an antidote for paracetamol poisoning of the liver can also block two proteins that promote the growth and spread of cancer cells. These two proteins are both receptors – the insulin-like growth factor-1 receptor, and the epidermal growth factor receptor – and scientists are currently looking for agents to block them, as possible anti-cancer drugs. Our preliminary finding that NAC can block both of these receptors is very exciting, especially as we know that NAC is a drug with few side-effects in humans. Our next step will be to move from studying cell cultures, to investigating what effect NAC has on tumours growing in mice.



A cancer drug with fewer side-effects

Pharmacologists at the Royal College of Surgeons in Ireland are investigating two ways of making an anti-cancer drug less toxic and hopefully more effective

Prof Desmond Fitzgerald, and MD students Noreen Dowd and Tom Neilan, found that a naturally occurring molecule called prostacyclin may block the drug's toxic effect

The drug doxorubicin is very effective at treating breast cancer and certain blood cancers but, like many anti-cancer drugs it causes serious side-effects. In particular, doxorubicin can damage a patient's heart, sometimes so severely that the person needs a heart transplant. Doctors usually prescribe only small doses of the drug, to minimise the risk of damage, but this also means the drug is less likely to kill the cancer. We wondered if we could somehow block the unwanted side-effect, while preserving the drug's anti-cancer action.

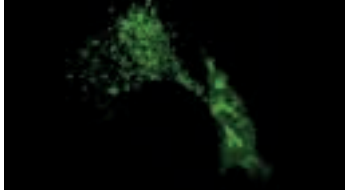
By studying the genetics and biochemistry involved, we identified a gene, COX-2, that blocks doxorubicin's toxic effect. COX-2 codes for a protein that makes a small molecule called prostacyclin, and when we gave prostacyclin to laboratory mice, it protected their heart against the drug. Conversely, when we blocked the action of the mice's COX-2 gene (either with a drug, or by deleting the gene – a technique called 'gene knockout'), we found that doxorubicin caused even more heart damage.

But if prostacyclin protects the heart, might it also protect the tumour we are trying to kill? To investigate this, we studied prostacyclin's effects in laboratory mice that had been injected with a lung cancer. When the mice were given doxorubicin only, their tumour got smaller and their heart was damaged. However, we were pleased to find that if they also got prostacyclin, the drug still killed their tumour. This looks very promising, but before we can contemplate clinical trials of prostacyclin in cancer patients, we need to know how the molecule works, and we are now investigating how it protects the heart against doxorubicin.

Research fellow Dr Michael Scully and Prof Desmond Fitzgerald have made a new chemical that, in laboratory tests, can also block the drug's toxic effect

When doxorubicin is metabolised inside a patient's body, a number of waste by-products are produced. Among these are free radicals, aggressive chemicals which can damage nearby tissues. It is now widely believed that it is these free radicals that injure the heart muscle in 5-10% of cancer patients, causing the problem side effect that limits how much doxorubicin a patient can be given. Obviously, it would be a tremendous benefit to patient care if we could find some way of absorbing these free radicals.

We developed a novel chemical agent in our laboratory called anthranilic hydroxamic acid (AHA). In laboratory tests that mimic doxorubicin's toxic effect on heart muscle, we were able to explore the effect of adding AHA. We found that administering AHA at the same time as the doxorubicin significantly reduced the damage to the heart muscle. This is potentially very promising, but clearly further research on AHA would be needed before we could go from these laboratory tests to clinical trials on cancer patients.



A peptide, bound to the VEGF receptor, neuropilin 1 on tumour cells. This peptide blocks the protective effect of VEGF on tumour cells and increases tumour cell death.

How to starve a tumour

Can gene therapy be used to kill cancer? In the first of two projects, Dr Judith Harmey, PhD student Brian Gibson and researcher Dr Angela Duffy (Surgery Dept, Royal College of Surgeons in Ireland) are developing a new gene therapy technique

Gene therapy holds huge promise for treating diseases. Its use so far has been limited by practical considerations, however, not least the difficulty of safely transferring therapeutic genes into the target cells. One important application for gene therapy is treating cancer: if we could deliver a gene that, for example, stops blood vessels growing in tumours, we would starve and suffocate the cancer. But how to transfer the gene?

Cochleates are unusual lipid-based particles, that are not attacked by the immune system, and that slowly release their contents. Could they work as gene carriers? To test this, we made cochleates carrying a trial gene that codes for a green fluorescent protein. We gave these to cancer cells growing in the laboratory, and to tumour cells in mice, and found that in both cases our test gene was successfully transferred: we could clearly see the green fluorescent protein, proving that our idea works in principle.

Now we want to see if we can safely transfer a therapeutic gene to attack a cancer. We have cloned a gene for an enzyme that inhibits blood vessel growth (called macrophage metalloelastase), and have engineered the gene so that it is switched on only when oxygen levels are low, as occurs inside solid tumours. Next, we will get our cochleates to deliver this gene to solid tumours in mice. If we can safely block blood vessel growth this way using gene therapy, we should be able to block the tumours, and stop them spreading.

How to improve chemotherapy

In a second project, Dr Judith Harmey and PhD student Martin Barr (Surgery Dept, Royal College of Surgeons in Ireland) are looking at ways of making tumour cells more likely to die

If a tumour is to grow and spread, it needs oxygen and nutrients – in other words: a blood supply. Tumours recruit their blood vessels from the surrounding vascular system, by secreting a protein called vascular endothelial growth factor (VEGF). This protein stimulates blood vessel growth by preventing the blood vessels from dying; it does this by blocking apoptosis, the all-important process of cell suicide. Apoptosis is exploited in some cancer treatments, and many chemotherapy drugs work by prompting tumour cells to commit suicide. Some tumour cells are resistant to this, however, and these resistant cells are often found in low-oxygen regions within solid tumours – conditions which arise when tumours are growing so fast that blood vessel growth cannot keep up.

If VEGF blocks apoptosis in blood vessels, might it similarly protect tumour cells by preventing them from dying? And could this explain why some tumour cells are resistant to chemotherapy? To test this, we gave VEGF to tumour cells grown in the laboratory, and found that it does indeed block apoptosis in the cells. Conversely, when we blocked the action of VEGF, we found that tumour cells growing in low-oxygen levels became vulnerable to apoptosis. By studying the biochemistry involved, we identified several molecules crucial to VEGF's action in tumour cells. We then designed some small peptides that can block VEGF and so cause more cells to die. We believe these peptides could be valuable in treating cancer, particularly in combination with chemotherapy or radiotherapy.

Instrument used in keyhole surgery

Less can mean more when cutting out cancer

Recent evidence suggests that tumours removed using 'keyhole' rather than open surgery, are less likely to recur. Prof Paul Redmond and research surgeon Eoghan Condon (Cork University Hospital) may have discovered why

Surgery is often used to remove cancers, but sometimes a tiny piece gets left behind. This occasionally transforms into an aggressive tumour, and doctors increasingly think this transformation is triggered by the operation itself. An important clue comes from patients who have less intrusive, 'keyhole' surgery (laparoscopy), as their cancer is less likely to return. But why is this? Scientists have known for some time that our immune system perceives surgery as a wound and responds with a stream of immune cells and molecules. Could some aspect of this response inadvertently promote tumour growth? And is the response stronger if you had open rather than keyhole surgery?

We looked at what happens when laboratory mice undergo surgery, focusing on changes in their bone marrow. We discovered that when mice have open surgery, their bone marrow responds by producing endothelial progenitor cells. These cells promote blood vessel growth (vascularisation), which brings essential nutrients to fast-growing tumours. Significantly, mice that undergo laparoscopy produce fewer such cells. And if the mice had cancer at the time of the operation, then those undergoing open surgery went on to develop bigger, more vascularised tumours than those given only a laparoscopy.

We therefore believe these endothelial cells explain why patients do better after laparoscopy. Confirmation comes from trials of a new drug (vascular endothelial growth factor (VEGF) blocking antibody), which both blocks endothelial cell growth and reduces tumour growth. While our findings with mice need to be confirmed by clinical trials with cancer patients, they suggest that laparoscopy will be more successful than open surgery, and especially if combined with drugs that block endothelial cells.

SECTION 7

The building blocks of life: genes and proteins

The Human Genome Project

A genome is all the DNA in an organism, including its genes. Genes carry information for making all the proteins required by all organisms. These proteins determine, among other things, how the organism looks, how well its body metabolises food or fights infection, and sometimes even how it behaves. The Human Genome Project (HGP) was an international effort formally begun in October 1990 to determine the complete sequence of the DNA that constitutes all 25,000 human genes, to identify all these genes, and make them accessible for further biological study. The project was planned to last fifteen years, but rapid technological advances accelerated the completion date to April 2003.

DNA is made up of four similar chemicals (called bases and abbreviated A, T, C, and G) that are repeated millions or billions of times throughout a genome. The human genome, for example, has 3 billion pairs of bases. The particular order of As, Ts, Cs, and Gs is extremely important. The order underlies all of life's diversity, even dictating whether an organism is human or another species such as yeast, rice, or fruit fly, all of which have their own genomes which have been fully sequenced through genome projects. Because all organisms are related through similarities in DNA sequences, insights gained from nonhuman genomes often lead to new knowledge about human biology.

Source: US Department of Energy

IVF: What makes a good egg?

Working with cattle embryos, research fellow Dr Trudee Fair and Prof Maurice Boland (Animal Sciences, UCD) have found a way of telling good eggs from bad, work which could be useful in human IVF

The test-tube baby techniques of *in vitro fertilisation* (IVF) and embryo transfer, first successfully used in 1978, are now widely used in humans and farm animals. In cattle, however, despite years of research, only 40% of eggs develop to the crucial seven-day blastocyst stage, when the embryo can be transferred to a cow. Our UCD colleagues, under Dr Pat Lonergan, previously discovered that these 'good eggs' complete their first cell division within 27 hours of fertilisation. The 'bad eggs', on the other hand, were much slower, taking at least 40 hours to divide and almost never became a blastocyst. This 'egg-timer test' is now used to some extent in human IVF when selecting which eggs to transfer.

For this project, we wanted to identify the embryo development genes that make an egg 'good' (i.e. fast) or 'bad' (i.e. slow). We collected eggs from cattle at slaughter, fertilised them in the laboratory, monitored the fast and slow ones, and identified which genes were active in each group. Among the genes identified were several involved in DNA synthesis and cell division.

Next, we focused on a gene found in mice and important in cell division and embryo survival. This pre-implantation embryo development (PED) gene codes for a protein that appears on the embryo surface, and may help the mother's immune system tolerate the embryo. By comparing published DNA sequences for mice and cattle, we identified a similar sequence in cattle. Significantly, we then found that our fast dividing cattle eggs had more of this gene transcript than slow ones. Furthermore, embryos produced entirely within cows also had more of this gene than embryos produced in the laboratory – suggesting that laboratory conditions are less than ideal, and that embryos should spend as little time as possible in a lab. It is now thought that people also have a gene similar to PED, so our work with cattle could help to improve the success rate of human IVF.

The science of saliva

Prof Brian O'Connell and PhD student Caroline McDermott (Dental Science, TCD) study salivary proteins that can kill fungi

Saliva is a complex biochemical mix that contains, among other things, many proteins capable of killing bacteria, viruses and fungi. These proteins are thought to be important in controlling the microbes in our mouth, and in protecting us against infection. Our team is interested in one particular family of anti-microbial proteins, the histatins, which are very active against disease-causing fungi such as candida. Intriguingly, histatins are found only in humans and in some monkeys, and not in other mammals. Some HIV patients produce fewer histatins than normal, which may account for why they are more susceptible to fungal infections than healthy people. This suggests that histatins are an important ingredient in saliva, and so we are studying their regulation and function.

There are two histatin genes, which between them produce 14 different histatin proteins (the variations are introduced when the two gene transcripts are processed into functioning proteins). Working with salivary cells in the laboratory, we studied the histatin-2 gene, and discovered that its expression is controlled by DNA sequences nearby. We also discovered that the gene gets switched on when there are fungi in the general vicinity of the cells.

Our next step will be to give histatins to animals that do not usually have them, and see what effect this has. As a first step, we have cloned the histatin-2 gene; next, we plan to breed laboratory mice that carry this gene. This should eventually give us a greater understanding of how these proteins function and perhaps allow us to develop new and better ways of treating fungal infections.

‘Jerky’ development and disease

Dr Tom Moore and PhD student Rosalie Waldron (Biochemistry, UCC) believe that the unusual Jerky protein helps regulate the structure of one specific chromosome

The cells of all mammals contain the Jerky gene, so called because it was first identified in transgenic mice that had a jerky gait. These mice were seriously unwell: they had epilepsy, were poorly developed, and mostly infertile. The reason was a mutation in a gene later named Jerky. We now know that the gene’s sequence resembles both ‘transposable elements’ (aka jumping genes, which can move around the genome, although Jerky itself does not move), and genes involved in controlling chromosome structure and movement during cell division. Clearly, Jerky is an essential gene, which may be important in embryo development and some diseases.

We investigated the Jerky protein in human cell cultures in the laboratory, and have made several significant discoveries. First, we found that Jerky associates predominantly with one specific chromosome, probably chromosome 15, although this has yet to be confirmed. All of the other 22 human chromosomes seem not to be associated with Jerky, and we don’t yet know why one chromosome should be regulated by a different protein. Second, when we trace the Jerky protein in the cells, we can clearly see it form dots in the cell nuclei. These dots are also associated with a protein that is implicated in leukaemia (called pro-myelocytic leukaemia protein). Finally, we speculate that Jerky plays a role in regulating steroid hormones, to explain why many Jerky mice were infertile. These findings are important for understanding normal cellular function, as well as perhaps shedding light on diseases such as cancer, reproductive abnormalities and epilepsy.

The genetics of delayed development

Prof Andrew Green and PhD student Sarah McCabe (National Centre for Medical Genetics, Our Lady’s Hospital for Sick Children, Dublin), are investigating the gene for Rett’s syndrome

Some 1% of children have significantly delayed development. We can usually find a reason for the problem in about half of the cases, but for the others we can offer no explanation to the family to account for their relative’s disability.

One rare cause of developmental delay is a genetic condition called Rett’s syndrome which mostly affects girls. Affected children develop normally for 18 months, but then their heads stop growing, they lose what speech they had, and they develop seizures and unsteadiness and show ritualistic hand movements. Eventually their condition stabilises, but they remain dependent on others until adulthood. A gene for Rett’s syndrome has been found (MECP2) that is involved in switching other genes on and off. We now know that about 80% of girls with classic Rett’s syndrome have an altered form of this gene. But it has also been suggested that this gene could account for some of the other unexplained cases of delayed development.

To investigate this, we analysed DNA samples donated by some 150 children with developmental delay for abnormalities in the Rett’s syndrome gene. These children were attending our clinic for routine genetic testing, and were queried for Angelman’s syndrome, autism or X-linked mental retardation (developmental delay disorders). We found no evidence that the Rett’s syndrome gene was altered in these children, however, suggesting that there is some other factor at work.

Pregnancy and blood clotting disorders

Dr Geraldine Gaffney and PhD student Sara Balbas Sedano (National Diagnostics Centre, NUI Galway) study the genetics of a blood clotting disorder that may contribute to pregnancy complications

When your blood coagulates, two things should happen: a protein called fibrin should bind the blood components into clots and, to prevent clots becoming too large, enzymes should also start breaking down the clots. In blood clotting disorders these processes do not work properly, and if clots are not properly digested, then fibrin can accumulate. One such disorder is activated protein C resistance (APCR), and the most common genetic form of this is a mutation in the blood Factor V gene (the Factor V Leiden mutation).

APCR is associated with certain pregnancy complications, notably pre-eclampsia and low birthweight, perhaps because fibrin accumulates in the placenta, interfering with its function. To investigate this, we screened 930 pregnant women for APCR; 730 of the women have now given birth, and we noted who developed pre-eclampsia and/or low infant birthweight.

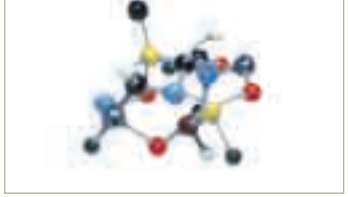
In all, 19% of the women had APCR. We found that they had more fibrin deposited in their placenta, but intriguingly, they were no more likely to develop pre-eclampsia or have a small baby than the other women. Furthermore, they were not producing more fibrin precursor than the normal women, suggesting that the fibrin accumulates not because too much is produced, but because it is not broken down. Finally, 95% of the APCR women had known mutations (mostly the Factor V Leiden mutation) but when we analysed the other 5%, we found no new mutations that altered the function of the Factor V protein. Clearly, this phenomenon is more complicated than was initially realised, and more research is needed if we are to understand this problem.

Pay attention, please!

Research fellow Dr Aiveen Kirley and Prof Michael Gill (Psychiatry, St James's Hospital, Dublin) are investigating the genetic causes of ADHD

Attention deficit hyperactivity disorder (ADHD) is a complex but common childhood condition. Up to 5% of children have it, and they are usually characterised as being inattentive, hyperactive and impulsive. We don't yet know the exact cause of ADHD, but research suggests that about 80% of the disorder is due to genes. Among the genes that have been implicated are several which are involved in regulating and transporting dopamine, an important neurotransmitter in the brain. These genes are associated with ADHD in general, but we wondered if they might be more strongly associated with some of the clinical components of ADHD.

We looked at genetic associations in 180 children with ADHD, and found that two genes are associated with specific conditions. First, the DAT1 gene, which codes for the dopamine transporter protein: we found that children who respond well to the drug methylphenidate (more commonly known as Ritalin), are more likely to have a particular variant of this gene. We also found that they were more likely to inherit this variant from their father. Second, the DRD4 gene, which codes for the dopamine receptor: children who also have oppositional defiant disorder (ODD) or a family history of ADHD, were more likely to have a particular variant of this gene. These findings help shed light on the genetic causes of ADHD, and may eventually help us to revise how ADHD is diagnosed. If our finding with the DAT1 gene is confirmed, it could pave the way for a test to identify the children most likely to respond to Ritalin treatment.



Freight transport in our cells

Dr Mary McCaffrey and Dr Andrew Lindsay (Biochemistry, UCC) study how nutrients are transported in and out of cells

Hundreds of diseases, including cystic fibrosis and haemochromatosis, develop because materials are not properly located and/or transported into, around and out of our cells. We study the proteins involved in controlling this traffic, our aim being to understand what is happening at the molecular level, which may ultimately help us to understand the diseases that develop when these processes fail.

One important group are the Rab proteins, 60 or so enzymes that regulate the transport of cellular freight. In particular we study Rab4, which helps sort material that has arrived into the cell; and Rab11, which controls the transport of appropriate material back to the cell surface (‘recycling’). During the course of our work, we have identified six other proteins involved, called the Rab11-family interacting proteins (Rab11-FIPs). Advanced cell biology and biotechnology techniques allow us to pinpoint where in a cell these proteins are located and what their function is, and we have now characterised the localisation and function of Rab11-FIP2.

We also investigated a segment, called the C2 domain, found in three of these Rab11-FIP proteins, which plays a role in binding to cell membranes. We have now shown that this C2 domain preferentially binds to two particular lipids in the cell membrane. Moreover, when these lipids have been synthesised, the Rab11-FIPs move from the recycling compartment, which is located near the nucleus of the cell, to the cell membrane. We believe this mechanism allows the Rab11-FIPs to deliver cargo to the cell surface on receipt of the appropriate cell signals.

SECTION 8

In the trenches: immune wars

Human blood consists of two major types of cells. The most common are red blood cells or erythrocytes, which carry oxygen to the body tissues, and carry away carbon dioxide. The other group are white blood cells, or leukocytes. These are the immune cells that destroy invading foreign objects, such as micro-organisms, by devouring them or launching chemical warfare.

These white blood cells are made of many different sub-types that are spread throughout the body, each playing different roles and moving about the body as needed. Some leucocytes recognise specific foreign organisms to which the body has been exposed in the past. These specific immune cells are called lymphocytes and are responsible for producing antibodies. Other non-specific cells, such as neutrophils and natural killer cells, patrol the circulation and can attack a range of different foreign organisms.

We make the most of our immune system by manipulating it to give us immunity to serious illness. We do this by using vaccinations.

1) Immunity and infections

Helping wounds to heal faster

Chronically ill people often heal slowly. Mr Malcolm Kell and Prof Paul Redmond (Surgery, Cork University Hospital) have identified immune stimulants that might help after surgery

People who are chronically ill, or who need emergency surgery, often also have a weakened immune system. When this happens, they don't produce enough immune cells and, if they have surgery, their wound usually takes longer than normal to heal. While researching burn injuries at Harvard Medical School some years ago, Malcolm Kell noticed that the wounds healed faster if they had been treated with specific immunological bacterial products. We have now begun to research this potentially important phenomenon.

As a first step, we performed surgical operations in laboratory conditions, and found that, if we treated the wounds with bacterial products, these activated immune cells within the wound. The treated wounds healed as well as the untreated wounds, but much faster – down from about ten days to seven days – and, significantly, were just as strong. This could have important implications for people recovering from an operation, and the compounds we are studying could be commercially useful. Before we could contemplate clinical trials on patients, however, we need a better understanding of what is happening in the treated wounds.

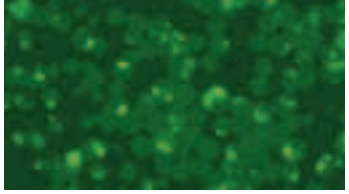
A little labour can be good for you

Research fellow Eleanor Molloy and Dr William Watson (Conway Institute of Biomolecular and Biomedical Research, UCD) have discovered that even a short period of labour boosts the mother's and baby's immune system

Giving birth is an amazing, complex process when lots of things happen. One of these, we have discovered, is that the surging hormones stimulate the mother's immune system, pump-priming the white blood cells so that they are ready to fight in the event of an infection.

We studied the neutrophil cells (which are important in fighting infection), in blood samples taken from mothers and from the placenta of babies born vaginally or by caesarean section at the Coombe Women's Hospital in Dublin. We found that, in general, babies' neutrophils live longer than adult ones. The infant neutrophils were also less sensitive to heat and to low oxygen levels than adult cells, which may be important in helping a newborn baby cope with possible fever or reduced oxygen supply. Significantly, we also found that labour – even a short period of labour – activates the neutrophils of both mother and baby, so that the cells survive even longer and are better at fighting infections.

Our findings suggest that the stimulated neutrophils live longer because the mother's hormones (specifically, oestrogen and progesterone), delay the cells' death. (This sex hormone effect was already known as an explanation for the fact that women are, on average, better at fighting infections than men, at least until the menopause.) The effect of labour on the infant's immune system is perhaps our most important finding, and may explain why premature babies, who miss out on this effect, are more vulnerable to infection and organ damage. Assessing neutrophil condition and stimulating the immune system may help in treating premature babies. Our findings indicate that even a short period of labour would benefit both mother and baby.



Macrophages with bacteria inside, stained fluorescent green

Surviving against the odds

Some bacteria can survive inside the immune cells that are supposed to kill them. Dr Wim Meijer and PhD student Pamela Duffy (Industrial Microbiology, UCD) are discovering the tricks these bacteria use to fool our immune system

The bacterium *Rhodococcus equi* causes a deadly pneumonia in foals. Increasingly, it is also a problem for people whose immune system has been weakened, for instance by AIDS, or immune-suppressing drugs. In such people, it can result in a TB-like infection that is difficult to treat, because *R. equi* has a cunning strategy: it hides out inside the immune cells sent to kill it.

Normally, our body responds to infection by mobilising macrophage cells to engulf and digest the invading bacteria. But *R. equi* subverts this: once inside a macrophage, it takes control and, within about two days, kills the cell. There is also, however, a non-virulent strain that fails to take over the macrophage. Instead, the macrophage commits 'suicide' (a programmed cell death process called apoptosis), taking the bacterium with it.

Scientists now know that the virulent bacteria have a small extra chromosome or plasmid; non-virulent bacteria lack this plasmid, but are transformed if they acquire it. To discover how virulent bacteria control macrophages, we used gene-chips to probe for the genes that are switched on (expressed) when macrophage cells engulf either virulent or non-virulent *R. equi*. We found that when a virulent bacterium (i.e. *R. equi*) takes control it alters the expression of some 150 macrophage genes. Some of these are 'cell suicide' genes, suggesting that virulent bacteria prevent the macrophages from committing suicide. We are now studying the virulence plasmid, to identify which genes make the bacteria virulent. Eventually, we hope our research will lead to successful treatments for this puzzling infection.

In search of stowaway viruses

Dr Dermot Walls, post-doctoral fellow Dr Brendan D'Souza and PhD student Pamela Pegman (Biotechnology, DCU) have discovered how some viruses can stay hidden for years inside our cells

There are several viruses that can remain in our bodies long after the initial infection is over. One such virus is a type of herpes virus called Epstein-Barr virus (EBV). This causes symptoms like those of a mild cold, and most people pick it up during childhood. After the infection clears, however, a few copies of the virus will 'stowaway' in some of our blood cells, and there they stay for the rest of our lives. EBV is surprisingly common, and an incredible 90% of us carry it as a stowaway, usually without any complications. However, the virus is also found in the cells of certain types of cancer, including many lymphomas, nasopharyngeal carcinoma and cases of Hodgkin's disease. We are interested in how EBV manages to stay hidden in our cells, and how it may contribute to the development of these cancers.

When a virus particle infects a cell, the cell will usually respond by trying to commit suicide (a process called apoptosis), in a bid to eliminate the intruder. We have discovered that EBV can prevent this suicide response by forcing the cell to overproduce a protein, called Bfl1, which blocks apoptosis. We believe this to be the key step that allows EBV to become a stowaway. We have now worked out much of the molecular basis of this process and have identified places where it can be blocked. These results have been published in a leading virology journal. Hopefully, these findings may one day lead to the development of new ways of preventing and treating certain cancers.

The liver fluke's Achilles heel

By studying the biochemistry of nerve transmission in parasitic worms, Prof John Dalton and PhD students Elaine McCarthy and Colin Stack (Biotechnology, DCU) have identified a possible new anti-helminthic drug

Parasitic worms can affect people and livestock and are a major problem in developing countries. These parasitic helminths, among them liver fluke (*Fasciola hepatica*) and the schistosoma worms that cause bilharzia, are traditionally treated with anti-helminthic drugs, many of which disrupt the parasite's nervous system. Unfortunately, drug-resistant parasites are on the increase, so the race is on to discover other ways of hitting them. One possible target is the parasites' nerve transmission and nerve signalling system. This is quite different from the system mammals such as ourselves use, so drugs that target these pathways should have little effect on the people or livestock taking the drug.

In the body, neuropeptide molecules involved in nerve signalling first have to be made and, once they are no longer needed, must then be destroyed. In a North-South collaborative project, with Aaron Maule, David Haltona and Gerry Brennan (Biochemistry, QUB), we set out to uncover the biochemical steps that take place when neuropeptides are degraded in the parasite cells, and discovered a particular enzyme which chops up and inactivates the peptides. Using sophisticated microscopes,we could also show that this enzyme, and the neuropeptides, are present in the nerve cells connected to the parasite's muscles. This leads us to believe that the enzyme we discovered plays an important role in the nervous system of parasitic worms. Perhaps, then, if we dose the parasites with inhibitors of this enzyme, we can seriously disrupt their nerve and muscle function. In which case, we may have discovered the basis for a whole new generation of anti-helminthic drugs.

This project was co-funded by the HRB and the R&D office, Belfast. The collaboration continues, with John Dalton's team now funded by the Government of New South Wales, Australia.

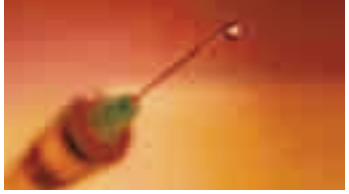
Antibiotic-resistant bacteria in hospitals

What is the best technique for fingerprinting MRSA? Prof Conor Keane and Dr Angela Rossney (National MRSA Reference Laboratory, St James's Hospital), and MSc student Martin Lawrence (Clinical Microbiology, TCD) evaluated three options

The bacterium *Staphylococcus aureus* is found everywhere. Most people carry some on their skin, for instance, where it can cause acne. Occasionally an antibiotic-resistant strain emerges, however; this usually happens in hospitals, and it is difficult to eradicate. The biggest problem are strains resistant to the antibiotic methicillin: the infection is costly and complex to treat because few antibiotics are effective, and hospital patients who become infected with methicillin-resistant *S. aureus* (MRSA) are often already critically ill.

Worldwide there are some 20 different major MRSA strains, and about five occur in Ireland. New strains occasionally evolve, with new properties, so it is important to know which strains are here at any time. Traditionally, MRSA strains were differentiated or 'typed' using a technique called 'phage typing' – this exploits the fact that different strains are sensitive to different phages (viruses). Two new techniques recently became available: antibiogram-resistogram (AR) typing, and the more expensive technique of DNA analysis.

To evaluate which is best for the Irish situation, we compared the three techniques on 426 MRSA cultures taken from hospital patients. Significantly, we found the old technique was poorest, while AR typing was best, and although combining AR and DNA analysis provided some additional information, this was usually not worth the added cost. The National MRSA Reference Laboratory now uses AR typing for most cases.



2) Vaccines Research

Whooping cough and vaccine

Prof Kingston Mills and PhD student Chantelle McCann (Biochemistry, TCD) have discovered that the whooping cough bacterium can disarm the immune system

Whooping cough is an infectious bacterial lung disease caused by *Bordetella pertussis*. The infection is severe in young children and often associated with secondary infections and pneumonia. It appears that, in the lungs, the pertussis bacteria can suppress the child's immune system and so prolong the infection.

Whooping cough bacteria make a protein, called filamentous haemagglutinin (FHA), and we have found that this turns off certain functions of the immune system which would otherwise allow it to fight the infection. FHA works by triggering production of an immune system 'messenger molecule' (cytokine), called interleukin-10, which the body normally produces to limit inflammation and protect against damage from an over active immune response. The bacterial FHA can deliberately induce this anti-inflammatory messenger, however, thus 'calming' or suppressing the immune response and allowing the bacteria to survive for longer in the body.

Significantly, FHA is one of the features of the whooping cough bacteria that our immune system can recognise as 'foreign', and that provoke an immune response. For this reason, it is included in a new three-in-one vaccine for immunising children against diphtheria, tetanus and pertussis. This new vaccine, with FHA in place of pertussis bacteria, was introduced about five years ago because the previous, whole cell pertussis vaccine had some undesirable side effects. However, it is now clear that, with the new vaccine, the immune response to the diphtheria and tetanus components is weaker. Our research suggests that is probably because the FHA in the vaccine suppresses the children's immune system. These findings, which are important for public health, have since been confirmed by other groups.

Hep C: good at hide and seek

The hepatitis C virus can evade our immune system. Prof Cliona O'Farrelly and PhD student Susan Behan (Research Centre, St Vincent's University Hospital, Dublin) are discovering the tricks it uses

Hepatitis C is one of the world's most common infectious diseases, and a leading cause of liver cancer. Despite considerable biomedical research, we still do not know why the infection persists in some people for years, yet others can quickly clear it. Seemingly, the virus can sometimes evade capture by a person's immune system – and we need to understand how it does this, if we are ever to develop an effective vaccine.

We focused on white blood cells, key components of the immune system which are deployed to fight viral infections. To see if the hepatitis C virus is hiding inside these cells, we collected white blood cells from patients with chronic hepatitis C infection. Using sophisticated technology, we looked for evidence of the virus in the cells, and we detected the virus in every case. Next, we wondered how the virus was affecting the cells – was it perhaps hampering their response to interferon-alpha (IFN-alpha), a key immune stimulant that is used to treat hepatitis C infection?

Initially, we observed that genes which respond to IFN-alpha appear less active in white blood cells of infected patients. However, when tested in the lab, there was no difference in the *ability* of infected patients' genes to respond to IFN-alpha when compared to healthy individuals. Rather, the lower activity of IFN-alpha response genes that we observed in infected patients' cells, is due to the virus interfering with IFN-alpha itself. This may explain why the infection lingers so long in chronic hepatitis C infected patients, and why IFN-alpha is not an effective therapy for some people. Our next aim is to determine precisely how the virus shackles the IFN-alpha, information which may one day lead to new treatments for this disease.

Breast cancer; carcinoma of the breast. Photomicrograph showing metastatic ductal tumour

The search for a cancer vaccine

Dr Ursula Bond and PhD student Blanca Arnaiz (Microbiology, TCD) have identified molecules that might be useful in developing vaccines against cancer

When cells become cancerous, some molecules on the cell surface change. These changes make the cell look 'foreign' and alert the immune system to attack the tumour. Unfortunately, because tumours grow very fast, they usually survive the attack. But what if we could boost the immune response, say with a vaccine? Could we then hope to kill the cancer? Many scientists are now pursuing this, and some envisage vaccines customised for each patient. We are interested in general vaccines, however, that might work against, for instance, several breast cancers.

The small peptide molecules found on cancer cells, and which provoke the immune response, are called antigens. Through a complex screening process, we have identified two synthetic peptides that are similar to antigens found on breast cancer cells. These mimics provoke the same immune reaction but, being synthetic (and therefore appearing more 'foreign' to the immune system), provoke a stronger reaction. Significantly, if we first prime the immune system by exposing it to the original antigens, we got an even stronger reaction from the synthetic mimics. This is an important proof of our general vaccine concept. Intriguingly, we also found that, under certain conditions, our two mimics will bind to tumour cells, but not to healthy cells. We are now investigating how they discriminate between the tumour and healthy cells, since this ability could be exploited to deliver drugs directly to tumour cells.

Chasing elusive vaccines

Studying protein evolution in microbes allows Dr James McInerney and PhD students Chris Creevey, David Fitzpatrick and Simon Travers (Biology, NUI Maynooth) to identify targets for vaccines and drugs

Imagine you are a microbe that infects people and causes disease. Any mutation in your genes which meant your descendants had a modified protein that was better at sticking to the host cells, say, or hiding from the host's immune system, would be a major benefit – what biologists called 'an evolutionary advantage'.

Thanks to developments in DNA and protein sequencing, we can now study this adaptive evolution. Our team does this by writing software to compare protein sequences, identifying proteins that are constantly evolving, and others that don't change. We have now studied protein evolution in several important pathogens, including the bacteria that cause meningitis, the malaria parasite, and the AIDS virus (HIV). Our analyses help explain how some microbes successfully cause disease, findings we hope will be useful in designing new vaccines and drugs.

For instance, there is currently no effective vaccine against meningitis B. To be effective, a vaccine must target a bacterial protein that does not change – targeting one that evolves is like chasing a moving target. Of eight proteins we analysed from *Neisseria meningitidis*, seven are constantly evolving; the eighth is relatively constant, so we suggest this could be a vaccine candidate. Similarly, we compared protein sequences for several HIV sub-types. Type C has been particularly 'successful': once rare, it now accounts for 50% of all HIV infections; in contrast, type K remains rare. We have now shown that the type C virus can rapidly change its coat protein, while the type K virus seems unable to. This inability to evolve may explain why it is less successful at infecting people.

SECTION 9

Tummy trouble: bellyaches and gut reactions

Stomach and Duodenal Ulcers (Peptic Ulcers)

An ulcer is an open sore, or lesion, usually found on the skin or mucous membrane areas of the body. An ulcer in the lining of the stomach or duodenum, where hydrochloric acid and pepsin are present, is referred to as a peptic ulcer. When the ulcer is in the stomach, it is called a gastric ulcer. When the ulcer is in the duodenum, it is called a duodenal ulcer.

What causes gastric and duodenal ulcers?

In the past it was believed lifestyle factors, such as stress and diet caused ulcers. Later, researchers determined that stomach acids contributed to ulcer formation, while nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin and ibuprofen can also cause ulcers. Today, research shows that most ulcers (80 percent of gastric ulcers and 90 percent of duodenal ulcers) develop as a result of infection with a bacterium called *Helicobacter pylori (H. pylori).*

Source: US national library of medicine

Be good to your gut

The lining of your gut can keep infections out, and control disease. Research gastroenterologist Seán Cochrane, Prof Alan Baird and Prof Diarmuid O'Donoghue (Veterinary Physiology, UCD) are learning how it does this

Treasure your gut – for this surprisingly complex organ helps keep you healthy. The thin layer of epithelial cells lining the gut is all that separates your inner organs from the bacteria in your gut, and from the 'foreign substances' contained in food and drugs. Specialised M cells patrol this lining, apprehending suspicious bacteria and taking them across to immune cells, so that if more of these bacteria ever appear, the immune system will then recognise them. The epithelial lining itself should ideally be slightly inflamed, and with no gaps between cells. However, the inflammation must be finely balanced: not enough, and harmful bacteria will slip through the gaps; too much, and you get inflammatory bowel disease. Understanding how the bowel lining functions could help us to improve the efficacy of oral drugs and vaccines, and to treat infections and inflammatory bowel disease.

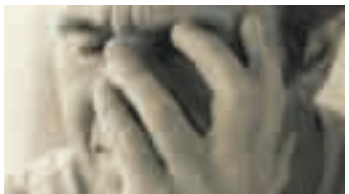
M cells are scarce, however, and difficult to identify and study. In 1997 researchers in Paris developed an artificial gut lining, combining human and animal cells, that allowed scientists to study this complex system in the laboratory for the first time. Our UCD team has now created a more life-like version, with only human cells, and which produces cells that look and behave like M cells. Using this, we have discovered that the *Salmonella* food-poisoning bacteria cross the gut by hi-jacking the M cells. *E. coli* bacteria, however, cross by creating gaps between epithelial cells. They do this by stimulating an important enzyme (called MLCK), which may also play a role in inflammatory bowel disease. By shedding light on the processes involved, we are learning more about the gut's role in health and disease.

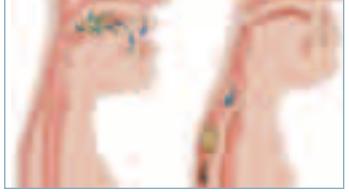
When the drugs don't work…

Dr Ross McManus and PhD student Megan Dring (Institute of Molecular Medicine, St James's Hospital & TCD) are unravelling the genetics of inflammatory bowel disease, and why some people don't respond to treatment

There are two major forms of inflammatory bowel disease: Crohn's disease, and ulcerative colitis. People with these conditions are usually put on steroid drugs, which is the standard treatment for chronic inflammatory diseases. However, up to 20% of patients with inflammatory bowel disease don't respond to the steroids. One reason for this, it seems, is that their genetic background makes them more resistant to the drugs used.

A gene that is probably important is the multi-drug resistance gene (MDR1). It codes for a protein that pumps drugs out of cells. People with different forms of the gene will produce different versions of the protein; these would presumably be more or less effective, and allow different amounts of steroid into the person's cells. In this study, we looked to see if this was true in patients with inflammatory bowel disease. We examined the effect of variations in their MDR1 gene, and in another gene which regulates the MDR1 gene. We found that patients who do not respond to the drugs, particularly patients with Crohn's disease, usually have certain forms of these two genes. Therefore, testing for these genes might allow us to identify in advance the 20% of patients who won't respond to steroid treatment.





Heartburn, bile and cancer

Prof Dermot Kelleher and PhD student Eileen Looby (Gastroenterology, TCD) are looking at the causes of oesophageal cancer

Cancer of the oesophagus is on the increase across the Western world. The disease has its roots in severe inflammation of the oesophagus, and factors such as diet, smoking and alcohol seem to play a role, as do two medical conditions: reflux oesophagitis and Barrett's oesophagus (a pre-malignant condition). These two conditions develop after years of chronic heartburn, when stomach contents are repeatedly regurgitated into the oesophagus, allowing acid and bile to corrode the lining. In a previous study, we identified a gene called p73 that was altered in people with either Barrett's oesophagus or oesophageal cancer. We wondered if this gene might play some role in triggering the inflammation, and if it was switched on by stimulants such as bile.

Working with laboratory cultures of oesophageal cancer cells, we looked at whether adding acid or bile caused the cells to produce more p73. Surprisingly, we found that there was very little p73 in the cells to begin with, and that adding acid and bile had little or no effect on p73. However, we discovered that bile does switch on a set of genes involved in inflammation, including an important gene, COX2, which codes for the enzyme cyclo-oxygenase 2. Significantly, this enzyme promotes inflammation, and it is present at high levels in oesophageal cancer cells. Hence, blocking this enzyme could help stop the inflammation and prevent the cells becoming cancerous. We therefore suggest that the conventional acid-suppressing treatment for oesophageal disease may not be enough, and that drugs which reduce inflammation may also be needed.

Bugs, beasts and bowels

How come some parasites can infect cattle and people, while others infect only people? Dr Billy Bourke and PhD student Amna Osman Yousif Hashim (Our Lady's Hospital for Sick Children, Dublin) and colleagues at the Vet College, UCD, believe they have unravelled this mystery

Our research centre is interested in infections that cause food poisoning and diarrhoea. These include bacteria such as *Campylobacter* and parasites such as *Cryptosporidium parvum*. *C. parvum* is a one-celled animal (or protozoan), which has recently come to attention because it causes diarrhoeal disease that can be fatal in AIDS patients. There are two types of the parasite, however: type I infects only people; while type II infects people and cattle – people often catch type II infection from animals, or from water contaminated by run-off from a cattle farm.

To see what effect *C. parvum* has on cells, we grow the parasites in our laboratory in cells which were taken from cattle at slaughter, or which come from biopsies of patients' bowels. We found that type II parasites can bind to and infect animal and human bowel cells but, significantly, type I parasites can bind only to human cells. Thus the reason type I parasites do not affect cattle, we discovered, is because they cannot physically get into the animal cells.

We also discovered that the two strains are affected differently by certain drugs (notably colchicines) which disrupts the formation of structural proteins inside the parasite. Treating type II parasites with colchicine made them less able to infect cells, but type I parasites were not affected. This suggests that the two strains use different mechanisms to infect bowel cells, and many scientists therefore believe that these strains are distinct species. Our work confirms this, and our next step is to identify what these differences are, information which should be important in treating this cause of severe diarrhoea.

Enzymes at work in oesophageal cancer cells

Research fellow Dr Orla Barry (Cancer Research Centre, UCC) and Prof Desmond Fitzgerald are studying how oesophageal cancers proliferate

Cancer of the oesophagus is on the increase worldwide. Risk factors include diet, obesity, smoking and gastro-oesophageal reflux disease, which brings corrosive stomach acid into the oesophagus. To develop an effective treatment for this growing problem, we need a better understanding of both oesophageal cancer and the secondary cancers that can spread from the oesophagus to elsewhere in the body.

We found that two families of enzyme are important in oesophageal cancer. First, the Pak family (short for 'p21-activated serine threonine kinases'). Working with cells from both primary and secondary tumours, we discovered that two Pak enzymes (the Pak1 and Pak4 variants, or isoforms) are involved in oesophageal tumour development. Among other things, Paks play a role in cell proliferation, cell migration and cell death, which may explain their role in creating aggressive tumours resistant to chemotherapeutic drugs.

The second group we studied are the PKC (protein kinase C) enzymes, a family of at least ten different isoforms. Early studies showed that when these enzymes were activated, the cells synthesised DNA, suggesting that the enzymes played a role in stimulating cells to proliferate. However, it now seems that in some cell types over-activating these enzymes can actually stop the cells growing, and/or trigger them to differentiate. We have now discovered that higher than normal levels of one particular PKC (PKC delta), reduces the proliferation of oesophageal cancer cells. This suggests that the effect of the PKC enzyme – whether it is in promoting cell growth, or inhibiting it – depends on which isoform is activated, and that targeting specific PKC isoforms could lead to new drugs for fighting oesophageal cancer.

A virtual ID of possible bowel cancers?

Software that automatically reads bowel scans and identifies possible cancers is being developed by vision system engineers at DCU – Prof Paul Whelan and PhD student Robert Sadleir – working with radiologist Dr Helen Fenlon (Mater Hospital, Dublin)

Every year, some 1,000 people die in Ireland from large bowel cancer. The disease can be prevented if the precursor growths (polyps) can be detected and removed before they develop into cancer, and the standard technique for this is a colonoscopy, using a fibre-optic camera scope. This is accurate, but it is also invasive and there is a risk the scope could perforate the colon. So there is growing interest in a new, less invasive scanning technology, virtual colonoscopy (VC). In this, X-rays are used to generate 2D and 3D images of the patient's colon; a radiologist then examines these for polyps.

Our multidisciplinary team is now developing sophisticated software to process these images: it 'reads' the scans automatically, then compiles a virtual reality model of the patient's bowel, and flags any suspect structures, based on their size and shape. This 'computer aided diagnosis' saves valuable time: the radiologist does not have to examine all the scans, and can focus on areas that are more likely to be cancerous.

We have compared the computer's performance with conventional colonoscopy examinations at the Mater. Results to date are promising: the software is almost as good at spotting early tumours as a radiologist. However, it can be over-cautious, sometimes flagging structures which are not polyps. Once we eliminate this error, we believe we will have a marketable product.

A computer-generated image of an X-ray of a human colon

SECTION 10

Problem solving: tackling disease

What is Cystic fibrosis?

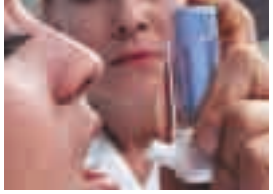
Cystic fibrosis (CF) is Ireland's most common life-threatening inherited disease. Approximately 1 in 20 people are carriers of the CF gene and where two carriers parent a child together, there is a 1 in 4 chance of the baby being born with CF.

CF primarily affects the lungs and the digestive system. A build up of mucus can make it difficult to clear bacteria and leads to cycles of lung infections and inflammation, which can eventually lead to damage of the lungs.

CF can also make it difficult to digest and absorb adequate nutrients from food. Mucus blocks the duct of the pancreas, preventing enzymes from reaching the intestines to digest food.

The result is that people with CF are prone to constant chest infections and malnutrition. However as therapeutic options have expanded over the last decade, significant advances have been achieved in both life expectancy and quality of life. What's more, due to scientific advancement, medical research has given rise recently to hopes of a cure for CF.

Source: The Cystic Fibrosis Association of Ireland



Cystic fibrosis: a potential therapy?

Prof Gerry McElvaney, Dr Clifford Taggart and Dr Catherine Green (Respiratory Research, Royal College of Surgeons in Ireland) have uncovered some of the mechanisms involved in cystic fibrosis, which may help scientists develop an effective treatment for this debilitating disease

People with cystic fibrosis (CF) have a mutation in their CFTR gene, which codes for a protein involved in transporting ions across cell membranes. These individuals suffer chronic inflammation of the lungs, and some years ago it was thought that we could treat this by delivering a working copy of the CFTR gene to the epithelial cells lining the airways. Unfortunately, it is not going to be that simple: our research indicates that we also need to knockout the inflammation associated with the malfunctioning gene, and target other cells, notably neutrophil white blood cells.

CF patients have numerous neutrophils in their lungs, fighting the chest infections to which they are prone. We have discovered that these neutrophils are abnormal: they cannot cope with acidic conditions because their ion channels do not work properly; and, when stimulated, they secrete twice as much of an enzyme (elastase) as normal neutrophils. Elastase exacerbates the lung inflammation, and we have discovered that it acts via a biochemical pathway which is used by other inflammatory proteins. So, rather than target elastase, it would be more effective to block this common path. We have successfully blocked it with anti-inflammatory molecules in CF cells in the laboratory, and plan to determine whether this has therapeutic potential.

Any gene therapy for CF will need to target different types of cell, and eradicate the inflammation associated with the abnormal CFTR protein, as well as providing a functioning copy of the gene. We have now prepared ways of doing this using two relatively new techniques (‘dominant negative’ DNA and peptido-mimetic therapy), which we will shortly test on cells in the laboratory.

Genes, lungs and cystic fibrosis

Dr Clare O’Connor, post-doctoral researcher Dr Clare Whelan (Medicine & Therapeutics, UCD) and Prof J. Stuart Elborn (Medicine, QUB) discovered a genetic difference that could explain why some cystic fibrosis patients have less severe lung disease than others

People with cystic fibrosis have chronic and constant inflammation of the lungs, and over 90% of them will die of lung disease. Some will die in their teens, despite intensive treatment and physiotherapy, while others will live well into their 40s. If we understood why some people survive longer, perhaps we could prevent the lung damage that kills so many others so early. Genetic background is certainly important: for example, women, and patients with the delta-F508 cystic fibrosis gene mutation (the most common cystic fibrosis mutation in most populations) are among the worst hit. But these genetic differences do not fully explain why some patients die young. Clearly, other factors are at work.

A protein called alpha-1-proteinase inhibitor (aPI), is important in fighting inflammation, and people who lack this are susceptible to another inflammatory lung disease, emphysema. Could aPI also be important in cystic fibrosis? Working with colleagues in Belfast, we found that CF patients with an uncommon form of the gene for this protein do develop less severe lung disease. They also have better lung function and require fewer hospital admissions for intensive antibiotic treatment than those with the usual form of the gene. These differences were greatest in women and in patients with the delta-F508 mutation. Intriguingly, we had expected that the aPI mutation would make their lung disease worse, so our next step is to investigate how this protein ameliorates lung damage in cystic fibrosis patients.

This project was co-funded by the HRB and the R&D office, Belfast.

Diet and cystic fibrosis

Research fellow Eileen Savage (School of Nursing & Midwifery, UCC) and Prof Peter Callery (University of Manchester) looked at problems children with cystic fibrosis have sticking to their recommended diet

Children with cystic fibrosis must eat a special diet. They need extra energy from weight gain to fight recurrent chest infections, which develop when mucus accumulates in their lungs. They also suffer from digestive problems - the mucus blocks their gastro-intestinal tract, so digestive enzymes can't reach the intestine, and their food is not properly absorbed. It is recommended that they eat a high-energy diet, some 20-50% more than a healthy child, with 40% of their energy coming from fats. Although this diet is important for their health and long term survival, some children with CF do not follow these recommendations. To find out why, we interviewed 32 children with CF and their parents about food, diet and health.

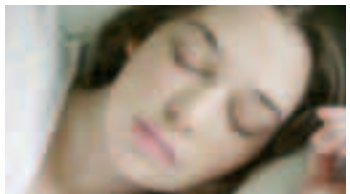
Our most important finding is that parents and health professionals worry about keeping a child's weight up, because they see children with chest infections rapidly losing weight. Children, on the other hand, think of their health in terms of energy levels - having enough energy for football or hip-hop dancing, for instance. In other words, being healthy has different 'meaning' for children and parents. Consequently, urging a child to put on weight is unlikely to succeed, but suggesting they need energy reserves to prepare for dancing or next week's match, probably will. So, changing the message and tailoring it to the way children think, could help them stick to their diet. We are now telling healthcare professionals and CF groups about our findings, which will hopefully bring long-term health benefits to children with cystic fibrosis.

While you were sleeping . . .

Dr Philip Nolan, Dr Stephen Ryan and PhD student Lisa Fleming (Anatomy & Physiology, UCD) are investigating the muscle reflexes that help keep you breathing when you are asleep

When we go to sleep, we take it for granted that we will continue to breathe normally. Fortunately, this happens for most of us. But when some people's tongue and throat muscles relax during sleep, they have difficulty pulling air into their lungs. Result: snoring. However, in a few people the throat becomes completely blocked, a situation called obstructive apnoea, which affects nearly 3% of men. In obstructive apnoea the person tries repeatedly to breathe, their blood oxygen levels fall, their heart rate and blood pressure change greatly, and death is prevented only because they wake briefly and open their throat so that breathing can begin again. This happens repeatedly each night, disrupting their sleep and damaging their heart. We study the mechanisms that help prevent this in healthy individuals, so that we can understand what causes the obstructive apnoea.

Working with laboratory animals, we study how an important muscle in the upper airway, the genioglossus, responds to both changing pressure in the airway and to falling blood oxygen levels, as happens when the airway is blocked. We find that, if the pressure drops or blood oxygen levels fall, the muscle becomes more active than normal, attempting to keep the airway open. When both conditions happen together, then in most cases the muscle becomes even more active. This dramatic response to the combined stimuli is a vital reflex that restores and stabilises the airway, particularly when the upper airway becomes blocked. These findings provide information that is important in understanding the causes of obstructive apnoea.



The portal pressure puzzle

Portal hypertension is a major complication of liver disease. Dr Aiden McCormick, Prof James Docherty, Dr Catherine Vandeputte and PhD student Soteria Bexis (St Vincent's University Hospital, Dublin and Royal College of Surgeons) are trying to understand how it develops

Nutrients, toxic waste, bacteria . . . All these and more come from your intestine, via the portal vein, to your liver, where the blood is filtered and cleaned. In patients with liver disease, however, this blood flow is obstructed and so the pressure rises in the portal vein. To compensate, new 'bypass' blood vessels develop. These form varicose veins in the stomach and oesophagus which can burst, causing life-threatening bleeding. In addition, toxins now bypass the liver and reach the brain causing intermittent confusion. Ironically, your body responds by trying to push more blood through the partially blocked system, increasing the pressure in the portal vein. Hence the search is on for drugs that would selectively prevent this secondary increase in blood flow, and reduce or perhaps even prevent the complications of portal hypertension.

One drug target is nitric oxide (NO), which is important in regulating blood flow. Two forms of the enzyme that make NO are believed to be important in blood flow. We study genetically modified mice, that have portal hypertension, and that lack one or other of these enzymes. We found that when mice who lacked one enzyme (iNOS) were given drugs to constrict their blood vessels, we saw a response in their intestinal blood vessels but not in other vessels. This is the first time that such a selective effect has been seen in portal hypertension. If confirmed, it could lead to the development of treatments specifically targeted at this condition.

Eye spy: a study of inherited blindness

A cure for retinitis pigmentosa could come from work on how eye cells die by Prof Tom Cotter and PhD student Francesca Doonan (Biochemistry, UCC)

Retinitis pigmentosa (RP) is a progressive form of blindness that develops when the photoreceptor cells in the retina, which are responsible for vision, start dying. Most forms of RP are inherited and caused by a mutation in a gene, but there are many forms of RP, depending on which gene is affected. Rather than develop a separate treatment for each form of the disease it would be nice if we could find a 'one cure fits all' solution. We know that in all cases of RP, regardless of cause, the photoreceptor cells die by committing suicide (a programmed cell death called apoptosis). So perhaps we could exploit this common feature to develop a general treatment?

Cell suicide is a complex, tightly controlled process. To understand its role in RP, we studied apoptosis in laboratory cultures of mouse retinal cells, and in mice that develop a blindness very similar to the human disease. Classical apoptosis involves certain enzymes known as caspases, and indeed, we found these were important both in the cell cultures, and in the eyes of infant mice. However, caspases do not seem to be important in the diseased eyes of adult mice. Instead, we found a different and previously unknown pathway there, involving enzymes called calpains which are activated by calcium. We are now investigating if these calpains play a direct role in RP, and are starting to test molecules that inhibit calpain to see if they stop retinal cells dying. If successful, it could lead to a way of treating this distressing disease.

Photograph of a resin cast of a normal kidney

When your kidney fails

Research fellow Dr Niamh Kieran, Prof Hugh Brady and Prof Catherine Godson (Mater Misericordiae University Hospital, Dublin) have found a potential drug to minimise acute kidney failure

Some 25% of patients admitted to intensive care have acute kidney failure, often in addition to other problems. The most common cause is ischaemia, or a lack of blood supply to the kidney. Ischaemic kidney failure is serious: there is no effective therapy – instead, patients are supported with measures such as dialysis, and hopefully their kidney will spontaneously recover over 2-3 weeks – and half the patients will die.

We want to understand what happens in kidney failure, and use 'gene chip' technology to reveal which genes are switched on and off when a kidney is damaged. We mimic kidney failure in mice, by cutting off the blood supply to their kidney for 30 minutes. When we looked with a gene chip 24 hours later, we discovered that the expression of some 500 genes was significantly altered: some were turned up, some down. They included genes previously implicated in ischaemic kidney failure, genes not previously implicated, and genes whose function is not yet known.

When blood flow is cut off, the kidney becomes inflamed. So, we treated our mice with a new anti-inflammatory molecule called lipoxin A4, to see if it stopped them developing ischaemic kidney failure. Now, when we examined their kidneys there was less damage; there was also less serum creatinine (a marker for kidney failure) in their blood; and our gene chip showed that gene expression had also changed. This suggests lipoxin A4 could be valuable in treating kidney failure, but more tests are needed before it could be tried in patients.

Stopping unwanted kidney cell growth

Lipoxins are natural anti-inflammatories, and Prof Catherine Godson and PhD student Derick Mitchell (Medicine & Therapeutics, Conway Institute, UCD) have discovered that they could help control inflammatory disease of the kidney

Inflammation is the root cause of many diseases – well-known diseases such as arthritis, and less well-known conditions such as glomerulonephritis, an inflammatory disease of the kidney. There are now several anti-inflammatory drugs available to treat these conditions, but many have toxic side-effects, or work only for some patients. We are studying how glomerulonephritis develops, work which we hope will help identify more effective therapies for this condition at least.

One of the first things that happens in inflammatory diseases of the kidney is that certain important cells (mesangial cells) start dividing rapidly, a process triggered by proteins known as 'growth factors'. The proliferation of these cells reduces the kidney's ability to filter blood, leading ultimately to kidney failure, at which point the patient has to undergo dialysis.

Our body also produces several anti-inflammatory molecules, among them certain lipid (or fat-like) molecules, called lipoxins. We have now discovered that these lipoxins can stop the mesangial cells from proliferating by counteracting the action of the growth factors. We found that this happens at the level of the cell surface, where lipoxin receptors 'cross-talk' with receptors for the growth factors, effectively switching them off, and shutting down the unwanted cell division. As well as shedding light on how cells proliferate, our findings suggest that these natural lipoxins should be investigated as possible new anti-inflammatory drugs for treating kidney disease.

Drosophila ovaries stained for actin/purple and DNA/orange.

Hormones and diseases

Two adrenal hormones are controlled by the same master switch, yet their levels can vary independently. Dr Leonie Young and PhD student Sinead Kelly (St Vincent's University Hospital) are investigating how this trick is achieved

Women with poly-cystic ovarian syndrome have high levels of androgen, a male sex hormone. Their symptoms can include facial hair and male-pattern baldness, yet the disorder often goes undiagnosed, or is discovered only when the woman attends an infertility clinic. This is a puzzling disease, because androgen is produced in the adrenal gland, along with several other steroid hormones. Here, its levels are controlled by the same master switch (ACTH) that also controls cortisol levels (a hormone responsible for glucose metabolism), yet cortisol is not affected by the disease. So what is going on?

The outer adrenal cortex, where steroids are produced, is divided into distinct zones, and it was once thought that each zone was responsible for a different hormone. In previous research, however, we showed that cells from the various zones can all produce a range of hormones, suggesting that control takes place at the biochemical level.

To investigate this, we looked at the regulation of two key enzymes involved in synthesising cortisol and androgen (17-hydroxylase and 21-hydroxylase). One cell factor (called SF-1) was known to control the transcription (or expression) of both these enzymes, but by studying the DNA sequences for these enzymes, we identified a second factor (Nur77). Significantly, we found that Nur77 controls only the cortisol pathway. We have therefore discovered one way in which control of androgen and cortisol differs, information which may one day help us to treat disorders such as poly-cystic ovarian syndrome.

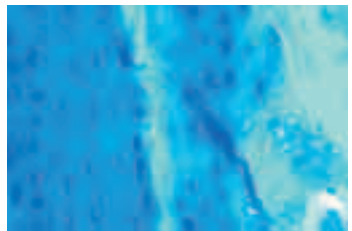
Brittle bones and breaks

Prof Clive Lee (Anatomy, Royal College of Surgeons in Ireland), and Dr Thorfinnur Gunnlaugsson and PhD student Raman Parkesh (Chemistry, TCD) have found a way to spot the tiny cracks that occur in fragile, osteoporotic bones

Nearly 4,000 people broke their hip in Ireland in 2000 – more than double the number seen in 1990. Most of these fractures were due to osteoporosis, which weakens bones especially in older people. Osteoporosis is a major health problem: up to 50% of elderly people who break their hip never live independently again, and up to 20% die within six months. The estimated cost to the exchequer is €13 million a year.

Doctors currently identify people at risk by scanning their 'bone mineral density'. However, this measures only bone *quantity* which accounts for up to 70% of bone strength; the rest is due to bone *quality*. If doctors are to prescribe appropriate therapies and help prevent fractures, they need to measure bone quality as well. An important aspect are small cracks caused by everyday activities such as walking. In healthy bone, these cracks are eventually removed, but in people with osteoporosis these micro-cracks accumulate, reducing bone quality and strength.

In this multi-disciplinary study, we successfully identified several chemicals that specifically label micro-damage in bones. Thanks to these chemicals, we were able to see micro-cracks in samples of cow bone both under a microscope and, significantly, for the first time, using a non-invasive technique called microCT scanning. The non-invasive scanning would be particularly useful in diagnosing patients at risk. However, our new technique needs to be refined before it can be tested in patients. Interestingly, two of our chemical agents could have wider diagnostic uses as they also detect zinc in insulin-secreting cells and cadmium in blood samples.



Micro-crack labelled with basic fuchsin viewed under UV epifluorescence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