Medicine

UNIVERSITY OF Southampton

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Medicine New Boundaries | 2013

Immunotherapy to fight cancer

Engineering antibodies and vaccines against tumours

Relief from asthma
Translating lab discoveries into patient treatments

Healthier futures
Breaking the cycle of chronic disease

Reducing antibiotic use
Precautions persuade doctors and patients

In this issue

Welcome to *Medicine New Boundaries*, the University of Southampton's medicine research magazine. In this issue, you will learn how research in Medicine at Southampton is changing not only the treatment of disease, but also the decisions of global partners in government and industry.

From chronicling doctor and patient use of antibiotics to teaching local teenagers how they can reduce their family's chronic disease risk for generations to come. Our research is addressing complex issues like the medicalisation of society and the war on obesity.

Groundbreaking work on treatments for cancer that may someday boost the immune system to provide a less toxic, more durable option to chemotherapy is described on page 4. You can also read about how discoveries by the National Institute for Health Research (NIHR) Respiratory Biomedical Research Unit in the Southampton Centre for Biomedical Research (SCBR) are helping asthma patients cope, on page 10.

Research at Southampton is also influencing social behaviours that affect disease. Our researchers, who have been tracking how chronic diseases are passed on from mother to child are now applying their expertise to the spread of conditions like diabetes in the developing world. Find out more on page 12.

Concerns raised by Southampton researchers more than a decade ago about the links between the over-prescription of antibiotics and drug-resistance are now starting to affect how doctors and patients negotiate treatment of common infections. Read more on page 16.

For more information, visit
www.southampton.ac.uk/medicine

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More highlights

Immunotherapy to fight cancer

Cancer treatments researched and developed at the University of Southampton that use the immune system are revolutionising treatment of the disease and may someday allow tumours to be managed or eliminated in millions of patients.

"We have much evidence that the immune system is critical in not only the development of cancer, but also in how we can overcome it."

Professor Martin Glennie,
Head of Cancer Sciences

Researchers at the University of Southampton Experimental Cancer Medicine Center are developing new immunotherapeutic vaccines for cancer

In July 2012, the University of Southampton received an anonymous gift of £10m – the largest single donation it has ever received – to develop its world-class research in cancer immunology and immunotherapy. This generous donation will allow the University to create a Centre for Cancer Immunology and to build upon its global reputation for bringing treatments from the laboratory bench to the bedside of patients. The new Centre will have links with the new Francis Crick Institute – a major Cancer Research UK biomedical research facility set to open in London in 2015 – which has also received £10m from the same donor.

The University has adopted a lifecourse approach to investigating healthy development and disease: from conception to old age. It has a strong science base from which new discoveries are made and world-renowned links into the clinical world where these can be put to use. By working across disciplines – including chemistry, engineering, electronics and computer sciences, mathematics and social sciences – Southampton researchers are pioneering new ways of approaching challenging health problems.

In recent years scientists in Southampton have made important advances in the development of vaccines and antibodies that stimulate certain cells of the immune system to attack cancerous tumours. "Our research focuses on trying to use the body's immune system to fight cancer," says Professor Martin Glennie, Head of Cancer Sciences. "We have much evidence that the immune system is critical in not only the development of cancer, but also in how we can overcome it."

The team involved in cancer research – including Professor Christian Ottensmeier, Lead of the Southampton Cancer Research UK and National Institute for Health Research (NIHR) Experimental Cancer Medicine Centre and Dr Juliet Gray, Senior Lecturer in Paediatric Oncology – is diverse and demonstrates how the University is able to combine expertise across Medicine, Biological Sciences, Health Sciences and Social Statistics and Demography.

Pioneering research

Antibody research at the University dates back to the 1970s when the founders of the Immunochemistry Laboratory, Professor Freda Stevenson and Professor George Stevenson, described how antibodies could be utilised as treatments. It was not until the 1980s that researchers were able to get special antibodies to attack cancer cells. Since then, researchers have been engineering and developing these antibodies so that they can actually be used for patient benefit.

Southampton scientists are now developing a range of antibodies and vaccines for use as treatments for cancer. Initially, antibody research at the University was focused on lymphoid cancers, but has now expanded to include many other cancers, such as those affecting the skin and pancreas.

The first antibodies used for cancer treatment worked by attacking the cancer cell directly and stopping or slowing its growth. However, antibodies can also act in other ways. A key goal of the University's antibody research is to activate and recruit the body's own immune system so that it may control and ultimately eliminate cancers. Oncologists know that the presence of large numbers of immune cells within a tumour means that the patient is more likely to do well, but without additional treatment, these immune cells cannot clear the disease.

In the late 1990s Southampton researchers started to investigate a group of antibodies known as immune-stimulating antibodies. These don't attack the cancer cell itself, but instead bind to cells of the immune system – such as T-cells or antigen-processing cells – and stimulate them to make a strong response to the cancer, so boosting and revitalising a patient's immune system. Antibody cancer therapies can also activate the patient's immune defences and alert them that there are cancerous cells to be destroyed.

At the same time that Southampton scientists were investigating immune-stimulating antibodies, a group of scientists in the USA were learning more about antibodies known as checkpoint blockers. These also boost the body's immune response against cancer, but rather than directly stimulating the immune cells they act by removing molecular brakes which the cancer applies to the immune response. The drug ipilimumab is an example of this type of antibody. After showing real promise in the treatment of melanoma in clinical trials, it has now been licensed and recently approved by the National Institute for Health and Clinical Excellence (NICE) for use in the NHS. Ipilimumab, which is being developed by the pharmaceutical giant Bristol-Myers Squibb, allows many patients to survive who would otherwise have passed away from their cancer within a few months.

"For the first time, we are seeing a proportion of melanoma patients who receive ipilimumab surviving longer than expected," says Martin. "With this, and other antibodies that boost anti-cancer immunity, we will soon be able to direct the body's natural defences more effectively and hopefully trigger responses to a level where they can control cancer for the long-term."

Margaret Warren, a patient participating in the ipilimumab treatment programme, was diagnosed with malignant melanoma in 2009. After trying unsuccessfully to treat the tumour in her left lung with chemotherapy, Margaret's doctor referred her to Christian and in February 2011 she began the first of her treatments.

"Before the ipilimumab treatment I was sleeping poorly, had a constant cough and was so breathless that I could not hold a conversation," says Margaret, "After the second of four treatments, I was already showing signs of improvement and began feeling better. Now I feel brilliant and can engage in mild exercise, like chasing my three-year-old grandson."

> "The future of cancer treatment will be asking not just which vaccine should we use but which combinations of vaccines and antibodies are most effective."
>
> Professor Christian Ottensmeier, Lead of the Southampton Cancer Research UK and NIHR Experimental Cancer Medicine Centre

Mollie Matthews, age 4, consults with Dr Juliet Gray before a series of immunotherapy treatments for her cancer

"It is important that we learn as much as we can in the laboratory, in advance of clinical trial, about how this type of therapy can best be used in childhood cancers."

Dr Juliet Gray,
Senior Lecturer in Paediatric Oncology

Other members of ipilimumab's family of checkpoint blocker antibodies may hold even greater promise in the treatment of a wide range of cancers. "The beauty of immune-stimulating and checkpoint blocker antibody treatments is that they are not confined to one type of cancer," says Martin. "They are able to stimulate immunity against a wide range of cancers." Recent results even show some limited success in the treatment of lung cancer which is notoriously difficult to control.

Novel vaccines

As one of only 15 Cancer Sciences Centres in the country funded by Cancer Research UK and the NIHR, the University of Southampton Experimental Cancer Medicine Centre (ECMC) benefits from a close working relationship with Cancer Research UK to efficiently organise its infrastructure and run clinical trials to the highest standard.

A laboratory group in the ECMC develops new immunotherapeutic vaccines for cancer and combines existing strategies, tests them in patients and measures their impact. ECMC researchers also measure whether tumours are being reduced and if the treatment strategy stimulated an immune response.

In the past 15 years, the team in Southampton has developed a number of novel vaccines for cancer treatment. This work, which has been conceived and developed in the laboratory by Professor Freda Stevenson, exploits the idea of using DNA to stimulate the immune system. The focus has been to stimulate the body's T-cells and, more recently, to educate the immune system to make antibodies against cancerous cells.

These approaches can be used in precancerous or cancerous conditions that are caused by viruses, such as Human Papilloma Virus (HPV). Equally, they can be used to target cancers of the bowel, breast or lung, which are not caused by viruses. The aim is to re-educate a patient's immune system to reduce or eliminate the cancer. The team has completed a series of vaccine studies.

"In the process of conducting our trials we have learned a lot about how the human immune system responds to cancer," says Christian. "The next big step for us is to show that, in a randomised study, these vaccines can make a difference."

Genetic clues

With an encouraging number of patients treated with ipilimumab surviving at least a year after treatment, researchers are asking why others did not survive, whether their immune systems have been exhausted, perhaps, and cannot recover. Their genes may hold the answer. Mark Cragg, Professor of Experimental Cancer Research and Southampton geneticists led by Dr Jon Strefford, Senior Lecturer in Cancer Molecular Genetics, are collaborating with a pan-European team to take population gene samples and see if there might be a genetic factor in those who responded favourably to an antibody treatment for lymphoma.

From a small sample of blood, researchers can also look for changes in the blood proteins of patients when treated with antibodies, a science called proteomics. Research into these protein biomarkers by Dr Spiros Garbis in the Centre for Proteomics Research may help explain which patients will respond favourably to antibody immune stimulation, before considering a course of treatment.

"The future of cancer treatment will be asking not just which vaccine should we use but which combinations of vaccines and antibodies are most effective." says Christian, "Rather than looking at how treatments affect the cancer, as specialists have historically done, we need to understand how these new immunotherapies work systemically."

Paediatric cancer trials

While adult trials for many cancer immunotherapies are proceeding, paediatric cancer researchers face a unique set of challenges in bringing these more specialised treatments to trial. Dr Juliet Gray is developing two antibody treatments for children with neuroblastoma, one of the more aggressive childhood cancers, as a less toxic alternative to chemotherapy.

"There are many different immunotherapy trials going on here in Southampton and around the world in adult cancer patients, yet there are very few for children," says Juliet. "There are a number of things that make conducting this type of clinical trial in children very challenging. Therefore, it is important that we learn as much as we can in the laboratory, in advance of clinical trial, about how this type of therapy can best be used in childhood cancers."

With a Cancer Research UK grant, Juliet is studying how immune-stimulating antibodies, such as ipilimumab may be used to treat neuroblastoma. She is hopeful that a paediatric trial of such antibodies can begin within the next five years. Juliet is also examining how Anti-GD2 antibodies work to kill neuroblastoma cells. These antibodies directly target neuroblastoma cells, and are already used clinically in children. Her work is focussed on monitoring the effects of these antibodies in children, and developing ways of making them more efficient.

The promising results of immunotherapy trials suggest that harnessing the healing power of the immune system is the future of cancer treatment. While chemotherapy and other treatments narrowly target the cancer, the cancer often develops new ways of growing. By focusing immunotherapies at the genetic and systemic levels, it will soon be possible to determine mutations in each person's genes that have caused a cancer and then seek appropriate treatment for those errors.

"Within a decade, oncologists are just as likely to be asking about gene sequences and molecular profiles as they are pathological findings to determine treatment for their cancer." Martin predicts. "Because scientists like myself and my colleagues are developing these new immunotherapies, hopefully patients can be told that their cancer can be managed and that they can live with it."

For more information visit:

www.southampton.ac.uk/understandingcancer

www.ecmcnetwork.org.uk

www.southampton.ac.uk/cancersciences

Relief from asthma

As a joint venture by the University of Southampton and University Hospital Southampton NHS Foundation Trust, the Southampton Centre for Biomedical Research (SCBR) translates the latest innovations made in the laboratories directly into new treatments for patients with nutritional problems, cancer, lung diseases, cardiovascular medicine, and bone and joint diseases. *Medicine New Boundaries* speaks with the SCBR's Director, Professor Ratko Djukanovic.

Professor Ratko Djukanovic, Director of the Southampton Centre for Biomedical Research (SCBR) and the NIHR Southampton Respiratory Biomedical Research Unit, uses a bronchoscope to examine a patient's airway

Q *How did the Southampton Centre for Biomedical Research (SCBR) start?*

In 2008 NIHR made two £3.75m Biomedical Research Unit (BRU) awards to the University of Southampton and University Hospital Southampton NHS Foundation Trust (UHSFT). These units – one dedicated to respiratory medicine and the other to nutrition, diet and lifestyle – were established to improve health by enabling translation of basic research into novel treatments. The awards recognised our track-record in doing just this in both areas over more than two decades.

Q *What are the SCBR's aims?*

The SCBR was established to consolidate and make more cost-effective our entire translational clinical research infrastructure. Physically, the SCBR comprises translational research facilities in Southampton General Hospital, and it builds on the enterprising, collaborative ethos that characterises our university-hospital partnership.

Through SCBR we share investment in people, facilities and technology across several subject areas, making research more efficient and creating intelligent links and collaborations for clinical research in Southampton. A good example of this is our £1.5m investment, in partnership with the UHSFT, in a new molecular sciences hub which will support translational research across all disciplines with industry-standard gene sequencing, molecular microbiology and measurements of immune function.

Q *What impact has the research of the NIHR Southampton Respiratory Biomedical Research Unit had on patients with respiratory disease?*

Our team pioneered the use of research bronchoscopy, an endoscopic camera that enables samples to be collected from the lungs of patient volunteers. This has completely transformed our understanding of asthma by showing that it is an inflammatory disease where the bronchial tissue gets restructured. These findings have had a major impact on pharmaceutical research and treatment guidelines.

We are seen as a world-class facility in creating medical technologies for keeping the air pathways open, such as surfactant, which keeps the lung expanded, fights infection and dampens inflammation. We have also discovered an innate immune response deficiency in the lungs of asthmatics that are unable to produce a key immune system protein molecule called Interferon-β, which fights viruses that cause colds and flu. Virus infections trigger more than 80 per cent of asthma attacks. We were the first to apply Interferon-β to patients with successful results and have created a University of Southampton spin-out drug company, Synairgen, to develop Interferon-β as a medicine, offering hope to millions of asthma sufferers.

Q *What kinds of unique partnerships and collaborations is the BRU engaged in?*

With the University of Amsterdam and Imperial College London, we are leading a research programme with 20 other European universities and several major pharmaceutical companies to better define the many types of asthma, especially its severe forms, and, thus, enable more targeted drug discovery. Funded with €21m from the European Union and major pharmaceutical companies, this Innovative Medicines Initiative (IMI) programme is the world's largest group working to help improve our knowledge of asthma.

Q *What are some links between nutrition and respiratory health you have discovered?*

The SCBR has overseen extensive research into the trans-generational links between nutrition and chronic diseases like diabetes and asthma through lifecourse studies like the Southampton Women's Survey and the Maternal Vitamin D Osteoporosis Study (MAVIDOS). There are some diseases where there is clear evidence that nutrition determines health outcomes; for example, underweight individuals with emphysema do less well than others in terms of both morbidity and mortality. Our collaborative programme seeks to optimise nutrition for patients with chronic obstructive airway disease.

Q *What are some cutting edge discoveries that the BRU has made?*

The role of biofilms is an area in which we have made tremendous impact in the field of respiratory medicine. In some respiratory infections, bacteria create a thin layer of film which acts as protection from antibiotics. Our laboratory researchers have discovered that we can break these biofilms with a gas called nitric oxide and have shown that this restores antibiotic efficacy.

Q *Who are some primary funders of the SCBR's research?*

The NIHR is our primary funder, with over £27m over five years and we also receive major support from the Medical Research Council and Cancer Research UK. The Wellcome Trust has vastly improved our ability to do clinical research through the award of one of five UK Millennium Clinical Research Facilities, as well as funding for our state of the art mass spectrometry equipment. The US National Institutes of Health have also contributed large amounts to paediatric and adult airways disease research. Pharmaceutical companies, like GlaxoSmithKline, have also played a prominent role in funding the Centre's collaborative research.

Q *What is the future of respiratory medicine and Southampton's role in it?*

Starting more than 25 years ago with a focus on asthma, we've grown into a substantial department with new areas of research across chest medicine, with a new focus in interstitial lung disease and critical care. We are developing a programme with allied health professionals, thereby tapping into some of the UK's best physiotherapy and nursing experts from the University's Health Sciences.

I also see a very good research environment developing in the UK for translational research, taking findings from the laboratory and applying them to treatments that help those who suffer from disease. Southampton is working with the pharmaceutical industry in Translational Research Partnerships coordinated by the NIHR to help industry speed up and make more cost-effective their drug development programmes. This consortium is unmatched anywhere in the world and will play a key role in finding new cures.

For more information on Ratko's research visit: **www.southampton.ac.uk/medicine/ratkodjukanovic**

LifeLab students learn more about the health effects of a high cholesterol diet by examining donor DNA samples preserved in an electrophoresis gel

Healthier futures

Southampton's pioneering research into how nutrition can improve health across the lifecourse is helping young people break the cycles of unhealthy behaviour. It will also assist the global effort to combat chronic diseases associated with modern lifestyles, as increasing economic costs associated with obesity approach 7 per cent of total health care costs worldwide.

Professor Mark Hanson, Director of Human Development and Health at the University, believes we urgently need to re-examine our strategy in the global war on obesity and chronic disease.

"The emphasis at the moment in many societies is on adult lifestyle, and a culture of blame, leading to debates over regulating what people should eat," Mark says. "Instead, we should take the opportunity to give children a better chance to have healthier lives and to pass on improved habits to *their* children."

Mark's innovative research has revealed the biology of how risk of chronic disease, such as Type 2 diabetes, is passed from one generation to the next. In 2008, he co-founded an adolescent health literacy programme, LifeLab Southampton. This innovative education programme engages students from local schools with the science behind chronic disease so that they may make informed judgments about their own health and reduce their and their future families' risks. As a partnership between Medicine, Southampton Education School, the National Institute for Health Research (NIHR) Southampton Biomedical Research Centre in Nutrition, the Science Learning Centre South East, the Medical Research Council Lifecourse Epidemiology Unit (MRC LEU) and Southampton schools and local government, LifeLab aims to prevent the development of risk factors for later disease in young people, such as poor diet, lack of exercise and sleep, stress, alcohol intake and smoking. Poor health behaviours are linked with heart disease, Type 2 diabetes and even some forms of cancer.

Clues about how chronic disease risk can be passed across generations emerged from the landmark Southampton Women's Survey (SWS), a study of 12,500 women aged 20-34, that began in 1998. The SWS is run by the MRC LEU, directed by Professor Cyrus Cooper. The study recruited women and their partners before they became pregnant to see if considerations such as diet, employment, social factors, level of fitness and exercise have an influence on foetal and infant development. Looking at that study allowed Mark and his colleagues to think about how lifestyle diseases such as heart disease and obesity get passed from one generation to the next.

The SWS showed that women with lower educational attainment may suffer from health problems like obesity and often do not prepare for pregnancy by changing their diet or lifestyle. As a result, their children are less likely to have a diet conforming to the government's guidelines for nutrition, are more likely to be obese, have a lower IQ and perform less well in school. The chain of cause-and-effect was a powerful indication that something should be done to break this unhealthy cycle.

"It was looking at that cycle that made us realise that waiting until a woman was pregnant or until after her child was born might be too late to intervene," says Mark, "What we needed to do was to go back a step, intervening with adolescents in the hope of changing their behaviour to improve their lifestyle – not only for their health but for that of the next generation." ▸

Dr Kathryn Woods-Townsend, Post-Doctoral Research Fellow, Medicine and Southampton Education School, helps LifeLab students scan their arteries with a portable ultrasound machine, in order to better understand how arteriosclerosis affects their bodies

"We should take the opportunity to give children a better chance to have healthier lives and to pass on improved habits to their children."

Professor Mark Hanson, Director of Human Development and Health at the University

Connecting classroom and university

LifeLab has worked across the city with secondary school pupils. Their interaction with some of the University's leading biomedical scientists allows students to see results of on-going studies such as the SWS and to connect these with their own lives and the LifeLab activities. Activities include scanning their carotid arteries with a portable ultrasound machine, measuring muscle and bone strength and investigating placental function. The activities are designed to stimulate student group discussions on how lifestyle factors such as diet can impact on their own bodies and even influence the health of their future children.

The approach seems to be working, because a recent survey of 14-year-olds in Southampton, comparing the responses of those who had attended LifeLab with those who had not, showed that six months after the visit the LifeLab participants are more likely to agree that the food they eat now will impact their long-term health and that of their children.

"Getting to see the inside of their own carotid artery makes it very real when we talk about what it would look like if its wall was becoming thickened, a risk factor for cardiovascular disease," says Dr Kathryn Woods-Townsend, Post-Doctoral Research Fellow, Medicine and Southampton Education School, who coordinates classroom projects for LifeLab.

In another LifeLab project, highlighting research by Philip Calder, Professor of Nutrition Immunology, students learned that dietary fish oil supplements can stabilise arterial plaques in some patients, reducing their chances of stroke. LifeLab is also seeking ways to show students findings from the MRC LEU's Maternal Vitamin D Osteoporosis Study (MAVIDOS) in which it is hoped that supplementation of women with vitamin D throughout pregnancy will lead to improved bone development in the baby. In one activity students handle decalcified chicken bones to see how flexible they are, helping them to realise how important vitamin D from sunlight and their diet is to developing and maintaining a healthy skeleton.

Encouraging adolescents to act on these lessons in their daily lives is LifeLab's next challenge. To learn how, the BUPA Foundation is helping to finance a large-scale, randomised trial in Southampton (and a corresponding one for a sister programme in Auckland, New Zealand) to evaluate whether LifeLab produces sustainable changes in adolescents' lifestyles and whether it will motivate more of them to study science subjects at school or later. LifeLab researchers are also looking at the value of the interactions between scientists and secondary school pupils to see whether it benefits the scientists' communication skills and allows them to explore the wider implications of their work.

Global ambitions

While LifeLab is piloting education interventions at a regional level in the war on chronic disease, researchers at Southampton are involved in initiatives wider afield. The populations of low and middle income countries are experiencing substantial health challenges, brought on by rapid changes in diet and lifestyle between generations. According to the World Health Organization (WHO), the number of people suffering from diabetes in Malaysia is projected to increase by approximately 163 per cent over the next 30 years, while China and India will experience more than a doubling of people affected.

Some of the insights from LifeLab may be employed to help young people in these countries. Mark and his colleagues are partnering with the pharmaceutical company Novo-Nordisk, the Malaysian Ministry of Health, and local religious authorities to establish a public health campaign in community health centres aimed at reducing risk factors for diabetes, which is increasing rapidly in Malaysians in their 20s and 30s.

"In Malaysia, we would like to educate young couples around the time when they marry and before they conceive a child," says Mark. "Diabetes is most commonly occurring during pregnancy as gestational diabetes. Usually the condition reverts at the end of pregnancy, but it puts the woman at a higher risk of diabetes afterwards and also increases the risk in her children."

The proposed Malaysian programme, currently in the detailed design phase, will soon run its first pilots and is scheduled to launch in autumn 2013.

Influencing policy

LifeLab's partnerships are helping to translate findings from University research into public policy. Mark believes that the opportunity to explain to adolescents what goes on in a hospital, including clinical research, and for them to engage and consider careers in science, could lead to stronger ties between Southampton General Hospital, the University and the City, some of the largest employers in Hampshire.

"City and County officials recognise the same problems in adolescent health that we researchers do. They want Southampton to be a healthier city. They also know that there is a need for better dissemination and uptake of health messages in some groups of the population," says Mark.

Many problems may not be solved without engaging the food industry. Together, Mark, Keith Godfrey, Professor of Epidemiology and Human Development, and Professor Cyrus Cooper, Director of the MRC LEU, founded the EpiGen Consortium (along with the University of Singapore and the University of Auckland) to help identify epigenetic links between factors such as diet and human development. EpiGen has been very successful in developing collaborative research programmes with industry that may lead to easier access to healthy diets and greater awareness of the importance of lifestyle.

In 2013, construction of a permanent facility for LifeLab at Southampton General Hospital will enable approximately 5,000 students per year to participate in LifeLab education modules. The University of Southampton, Garfield Weston Trust Foundation and the University Hospital Southampton NHS Foundation Trust (UHSFT) are all helping to finance the project.

For more information, visit:
www.southampton.ac.uk/medicine/lifelab

Reducing antibiotic use

Paul Little, Professor of Primary Care Research, first researched key problems associated with the over-prescription of antibiotics in a 1997 study. With the annual, global cost of infections caused by antibiotic resistance estimated at $4-5 billion, Paul's findings are now widely cited in a precautionary movement among General Practitioners in the UK and elsewhere. He talks to *Medicine New Boundaries* about his research.

Q *What does your research involve?*

The goal of most of my research is to help people manage their own acute or chronic health problems, where feasible, to limit 'medicalisation' – creating unnecessary dependencies upon the health care system.

There is no doubt that antibiotics provide some benefit to many patients, and for serious infections, save lives. However, the prescription and use of antibiotics has expanded beyond their effectiveness and over use complicates essential treatment for others by creating bacteria that are resistant to antibiotics. The challenge is to reduce antibiotic use for the majority that do not need them and target them to those where it is really necessary

As my colleagues and I demonstrated in our 1997 *BMJ* study and in subsequent studies of doctor–patient interactions involving prescription of antibiotics, patients often ascribe too much of their healing to antibiotics, (thus, belief in antibiotics) and are 40 per cent more likely to return for more antibiotic treatment when they have another infection. This wouldn't be a problem if our antibiotics remained effective for another thousand years, but they won't be, since bacteria continue to outsmart them.

Q *What attracted you to do your work at the University of Southampton?*

I've been here since the early 1990s. Southampton has always had one of the leading faculties for primary care. I received training in secondary care, but got interested in researching the things primary care physicians deal with day-to-day, the huge challenges of being a GP, and the complexities of GP–patient interactions.

Q *How did your research interests in this subject develop?*

My wife is a speech therapist who works with ear, nose and throat surgeons. Many years ago a UK charity in Nepal hired both of us to quantify the extent of ear, nose and throat infections in rural areas there. Seeing the contrast between the malnourished population there with very limited access to primary care or antibiotic treatment, and the easy access and over-use in the UK, prompted my interest in the use and abuse of antibiotics.

Q *What impact have your findings had on the prescribing behaviour of physicians and public health policy?*

It usually takes a while for the evidence in primary care to change minds and practice. However, following publication of our first paper in 1997 where we demonstrated the effectiveness of delayed prescribing strategy (the advice to delay use, and only use them if necessary), we've seen a twenty per cent gap between primary care physicians prescribing antibiotics and the number of patients who actually fill them.

I was appointed by the National Institute for Health and Clinical Excellence (NICE), as chair of the guideline development group for antibiotic prescribing strategies, to coordinate the development of guidance for the medical community in the UK. Our work has encouraged investigators elsewhere, such as the United States, to look at the issue and it now appears in their physicians' guidance for treating ear infections. In Israel, too, they've seen a reduction in physician antibiotic use through implementing the delayed prescription strategy.

Q *Is multidisciplinary collaboration important in your research?*

Yes. If you want to understand how effective treatments or strategies are and why patients and doctors behave as they do, then you need a whole range of disciplines like statistics, epidemiology, health economics, sociology and health psychology. A key collaboration is with Professor Lucy Yardley in the Health Psychology Group. She has developed software called LifeGuide that helps researchers and clinicians develop interventions in a structured way to support behaviour change.

Q *Who is helping to fund your research?*

The Medical Research Council, the National Institute for Health Research and a range of UK funders. In the European Union, EC Framework 6 Funding has made a significant contribution.

Q *Can doctors and patients do more to prevent antibiotic resistance?*

We know that across countries, resistance levels are quite closely related to antibiotic use; studies show that nations with the highest rates of antibiotic-resistant bacteria have the highest use of antibiotics and those with the lowest rates have lower use (such as the Netherlands). We need to reduce the 60-70 per cent of patients who are prescribed an antibiotic for a sore throat or a chest infection down to 20-30 per cent. This could potentially make a huge difference in reducing the number of antibiotic resistant strains of bacteria.

When they follow antibiotic prescription guidance, doctors are put in a difficult situation since there isn't much else they can offer patients. So we need much better evidence about how best to manage patients' symptoms, such as the optimal use of over-the-counter medicines and potentially, alternatives such as use of herbal medicines.

We also need to understand the drivers that keep patients coming back for antibiotics and the drivers for doctors to prescribe. Given that there are almost no new classes of antibiotics and most pharmaceutical companies are not now investing in development, we will also probably need public investment working with pharmaceutical companies to develop new classes of antibiotics.

For more information on Paul's research, visit: **www.southampton.ac.uk/medicine/paullittle**

Paul Little is Professor of Primary Care Research, Primary Care and Population Sciences (PCPS)

In brief

Common cure for flu

Researchers from Southampton, the University of Oxford and Retroscreen Virology Ltd offer potential relief for flu sufferers with their discovery of a series of peptides, chains of amino acids, found on the internal structures of all flu viruses. The breakthrough discovery and subsequent vaccination trial could grant people immunity against all strains of the disease.

Influenza, an acute viral infection, affects hundreds of thousands of people around the world each year. Flu pandemics like the outbreak of swine flu in 2009 , which claimed 457 lives, put severe strains on healthcare providers.

Dr Tom Wilkinson, Senior Lecturer in Respiratory Medicine at the University, who led the study, says that the team discovered that T-cells, part of the body's immune response to flu viruses, also attacked the peptides within them.

"Most influenza vaccines only protect us against known influenza strains by creating antibodies in the blood but the influenza virus has the ability to rapidly change itself and new strains can emerge which rapidly spread across the globe by escaping this immunity," says Tom. "Through this discovery we hope to improve vaccines for future strains of influenza; and potentially protect against the next pandemic."

The vaccine research may be further assisted by the recent addition of Professor Robert Read, who joins the University after many successful years at the University of Sheffield. Professor Read specialises in developing and testing novel vaccines for rapidly lethal infectious diseases such as influenza, meningitis and pneumonia.

Molecular medicine for arthritis

Rheumatoid arthritis, an auto-immune disease that causes severe inflammation in joints, connective tissues, muscles, tendons and fibrous tissue, affects as much as one per cent of the global population, especially women. Without effective treatment most patients will eventually become disabled and many lose their jobs within five years of onset of the disease.

Stephan Gadola, Professor of Immunology and Consultant Rheumatologist, is trying to unravel the mechanisms of this disease at the molecular level and provide a cure for not just rheumatoid arthritis, but for other auto-immune disorders. Funded by Arthritis Research UK and the Biotechnology and Biological Sciences Research Council (BBSCRC), and with the assistance of several experts in Chemistry, his research programme focuses on how a subset of specific white blood cells, called Invariant natural killer T-cells (iNKT-cells), are activated by lipid-binding proteins to drive the outcome of an immune response – like a switch – when an infection, auto-immune disorder or cancer occurs. Unpublished results from testing of the iNKT repertoire in patients with early rheumatoid arthritis suggest new ways of how iNKT-cells could be used in the future to treat or even eliminate this debilitating disease.

"As a practicing rheumatologist, I see patients with rheumatoid arthritis and other auto-immune diseases. Currently, these patients are treated, lifelong, with immuno-suppressing drugs that, while effective, put them at risk of serious infections or diseases like cancer," says Stephan. "Since immune tolerance is something the body must maintain, we are pursuing this research with iNKT cells to allow patient's bodies to re-balance their immune systems internally."

More efficient blood testing

Medicine researchers at Southampton are collaborating with their colleagues in Electronics and Computer Science (ECS), taking advantage of the latest advances in nanotechnology and micro-devices to deliver new therapies to patients.

For Professor Donna Davies and Dr Judith Holloway this means working with Professor Hywel Morgan in ECS to develop a point of care micro-impedance cytometer capable of measuring blood cells from a finger prick of blood and automatically relaying that information to clinicians. Such a device would improve the rate of diagnosis of new illness and the monitoring of ongoing illness.

The device would also make doctor-patient interactions more efficient. It could reduce or even eliminate the numerous visits a patient must make to their doctor and to the hospital for diagnosis, to receive a blood test and then discuss its results.

"Imagine a patient on chemotherapy treatment, with drug cycles every three weeks," says Judith. "They could do a home blood test with the cytometer, with the results being uploaded to a 24-hour manned ward. The patient could then be advised appropriately to stay at home, come in to hospital tomorrow or call an ambulance immediately."

Breakthrough on chlamydia treatment

Chlamydia is the most common bacterial sexually transmitted infection in the world with approximately 100 million new cases each year. If untreated, complications from chlamydial infection can result in serious reproductive and other health problems.

Current tests for chlamydia do not capture differences between strains, so a patient receives only a positive or negative result, without distinguishing the nature of the infecting strain. This makes it impossible to determine whether a person who tests positive again after antibiotic treatment has picked up a second infection or if their treatment has failed.

Thanks to a breakthrough in the study of the bacteria's genetics by Professor Ian Clarke and Southampton's Molecular Microbiology Group, new treatments and a vaccine for this silent epidemic may soon be possible. Using whole genome sequencing, they are showing that the exchange of DNA between different strains of Chlamydia to form new strains is much more common than expected. The more we learn about these different strains, the better we can understand how they spread in human populations and how to treat them.

"This is a very significant advance in the study of chlamydia and we are proud to be the first people to achieve this," said Ian. "Previously people have been unable to study chlamydial genetics and this has created a barrier to the comprehensive study of this disease."

In brief

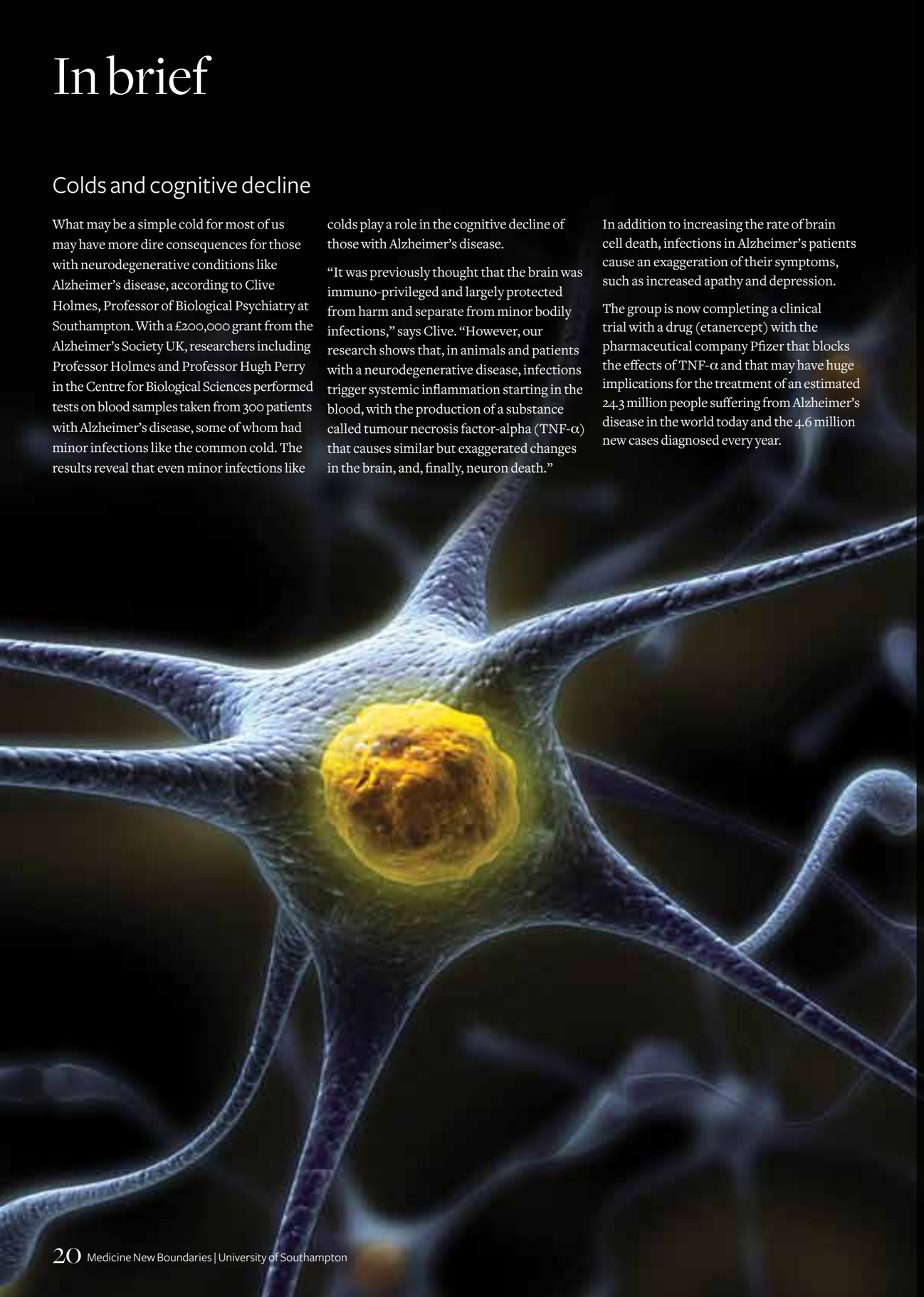
Colds and cognitive decline

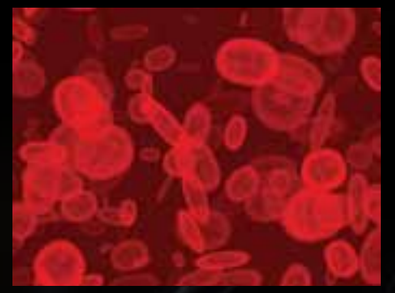
What may be a simple cold for most of us may have more dire consequences for those with neurodegenerative conditions like Alzheimer's disease, according to Clive Holmes, Professor of Biological Psychiatry at Southampton. With a £200,000 grant from the Alzheimer's Society UK, researchers including Professor Holmes and Professor Hugh Perry in the Centre for Biological Sciences performed tests on blood samples taken from 300 patients with Alzheimer's disease, some of whom had minor infections like the common cold. The results reveal that even minor infections like colds play a role in the cognitive decline of those with Alzheimer's disease.

"It was previously thought that the brain was immuno-privileged and largely protected from harm and separate from minor bodily infections," says Clive. "However, our research shows that, in animals and patients with a neurodegenerative disease, infections trigger systemic inflammation starting in the blood, with the production of a substance called tumour necrosis factor-alpha (TNF-α) that causes similar but exaggerated changes in the brain, and, finally, neuron death."

In addition to increasing the rate of brain cell death, infections in Alzheimer's patients cause an exaggeration of their symptoms, such as increased apathy and depression.

The group is now completing a clinical trial with a drug (etanercept) with the pharmaceutical company Pfizer that blocks the effects of TNF-α and that may have huge implications for the treatment of an estimated 24.3 million people suffering from Alzheimer's disease in the world today and the 4.6 million new cases diagnosed every year.



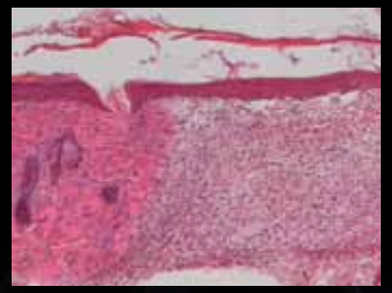


Discovery helps treat heart disease

A recent discovery by Southampton researchers about the regulating effects of arteries could help provide more effective treatments for an estimated 17.8 million patients suffering from cardiovascular disease around the world.

The team, led by Dr Graham Burdge, Reader in Human Nutrition, has found that polyunsaturated fats manufactured in the artery walls are converted into fat-like molecules, called eicosanoids, in order to make the arteries constrict. In a healthy person, the arteries are able to constrict and relax more easily than in someone who is at risk of developing high blood pressure or atherosclerosis. Graham and the team were able to reduce the constriction of arteries and, therefore, the risk of high blood pressure, by blocking the action of two enzymes that create polyunsaturated fats. The researchers also observed changes in the epigenetic 'switches' that control the key genes for making these fats.

"This is an important finding. Cardiovascular disease is an increasing public health issue," says Graham. "In 2009, over 180,000 people died from cardiovascular disease in the UK – that is one in three of all deaths. Currently, it is difficult for doctors to screen people at risk of cardiovascular disease before symptoms develop. However, a test based on the epigenetic changes we have found could provide a new way of screening people for risk of cardiovascular disease, and, in time, it might also be possible to correct this epigenetic defect."



Growing a thicker skin

Nicholas Evans, Lecturer in Bioengineering, is developing therapies for stimulating skin regeneration that may someday benefit millions of people each year recovering from surgeries like caesarean sections, or from skin cancer, accidents and burns.

"When we have a skin wound, keratinocytes – the predominant cell type in the outermost layer of the skin – need to know that there is a wound and how to crawl back over it," says Nick. "In my research I am asking questions about the stiffness and topography of a wound and how its three-dimensional shape affects this healing process."

For years, medical researchers have observed that a cut made to a foetus at an early stage of its development will heal without a scar. Nick is probing the secrets of why this happens by growing skin cells in vitro on synthetic wound surfaces to see how they affect the behaviour of cells in wound healing. He is collaborating with colleagues in Engineering and the Environment, who help create the simulated wounds on polymers through a process called micro-fabrication.

Though their research is in its early stages, Nick believes that the questions they are asking about the mechanical characteristics of skin wounds – like the amount of tension on the wound site – along with advances in technology, point the way to a hopeful future for skin healing.

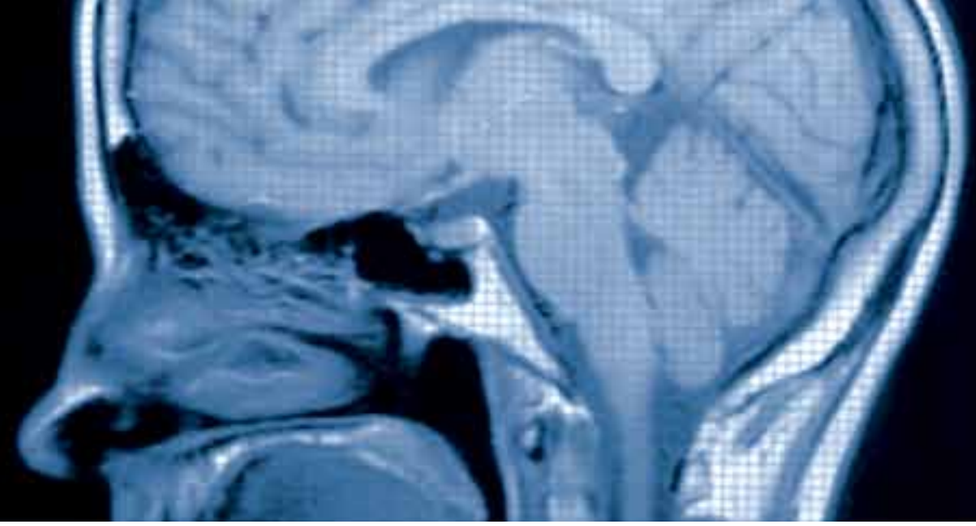
Stopping drug cheats in sports

A test for the presence of human Growth Hormone (hGH), developed by a team of researchers from Southampton and two other universities, has been successfully applied to catch cheating athletes in global competition. On 8 September 2012, the International Paralympic Committee announced that two powerlifters from the Summer Olympic Games had received two year suspensions for Anti-Doping Rule Violations involving Growth Hormone following an adverse laboratory finding using the new markers test.

The test – the first to detect human growth hormone use over many weeks – measures two proteins in the blood, insulin-like growth factor-I (IGF-I) and the amino terminal pro-peptide of type III collagen (P-III-NP) which increase in response to growth hormone. Richard Holt, Professor in Diabetes and Endocrinology at Southampton, has led the team, known as GH-2004, over the last 10 years with funding from the World Anti-Doping Agency (WADA) and USA Anti-Doping Agency and support from UK Anti-Doping.

"We are pleased to have another effective and reliable means to catch cheats and help deter harmful drug misuse," said Richard, "There has been a tremendous amount of team work to develop this test and I am delighted that this dedication has finally succeeded."

A selection of recent papers published from 2008 – 2012



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