Medicine

UNIVERSITY OF Southampton

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Medicine New Boundaries | 2014

Breathe easy

Southampton researchers tackle asthma

Beating blood cancer
World-leading breakthroughs in understanding leukaemia

Genetics of diabetes
Improving healthcare pathways

Tackling malnutrition
Influencing public policy on nutrition

In this issue

Welcome to *Medicine New Boundaries*, the University of Southampton's research magazine that showcases the ways our researchers are changing the medical world and impacting on patient care.

In this issue, you will find out how we connect with partner institutions and businesses to tackle some of the most pressing global healthcare issues such as chronic diseases, malnutrition and cancer.

On page four you can read how asthma, which affects 235 million people worldwide is being tackled by our experts. Find out how our partnerships with pharmaceutical companies provide the knowledge to develop the next generation of asthma therapeutics.

The prevalence of diabetes is increasing and currently affects more than 285 million people worldwide. Discover on page 10 how a long-term collaborative project has uncovered the first genetic form of diabetes and led to the advanced understanding of imprinting disorders and ultimately improved care pathways for patients.

Leukaemia accounts for 300,000 new cases a year, as well as 220,000 deaths. Our immunology research has led to greater understanding of the disease and more effective treatments. Find out how a collaborative approach is leading the way on page 12.

Malnutrition is estimated to contribute to more than a third of all child deaths around the world; we are influencing public policy to change healthcare practices and public attitudes to nutrition. Read more on page 16.

For more information on Medicine research, visit **www.southampton.ac.uk/medicine/research**

Please send us your feedback

We are keen to receive any feedback you have about *Medicine New Boundaries*. If you have any comments or suggestions, please send them to **medicineresearch@southampton.ac.uk**

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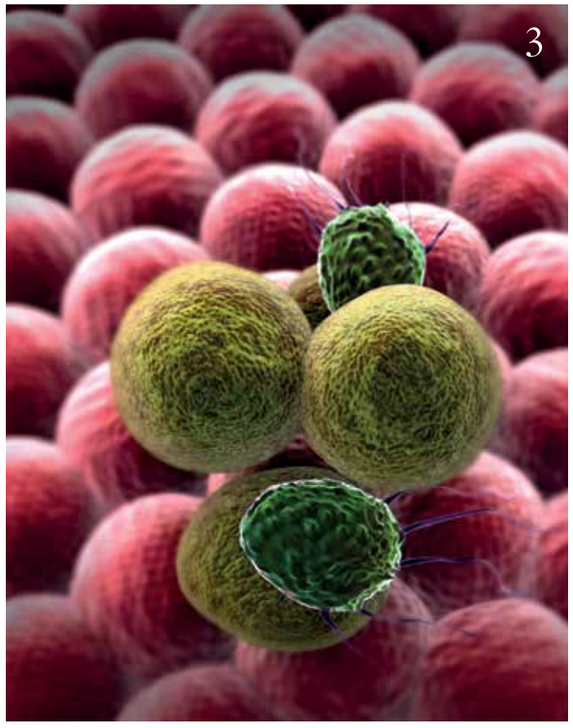
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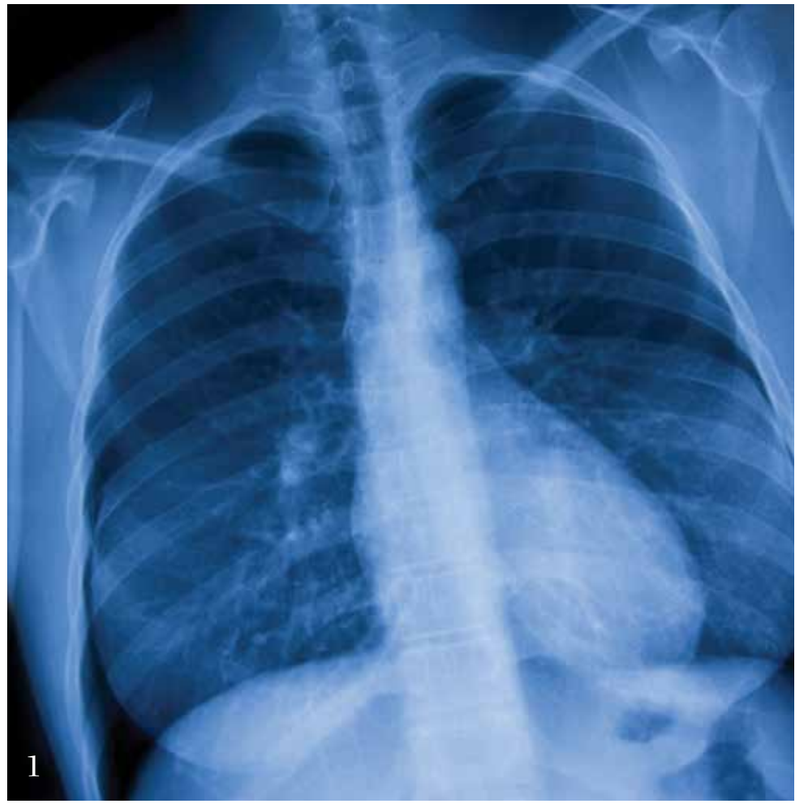
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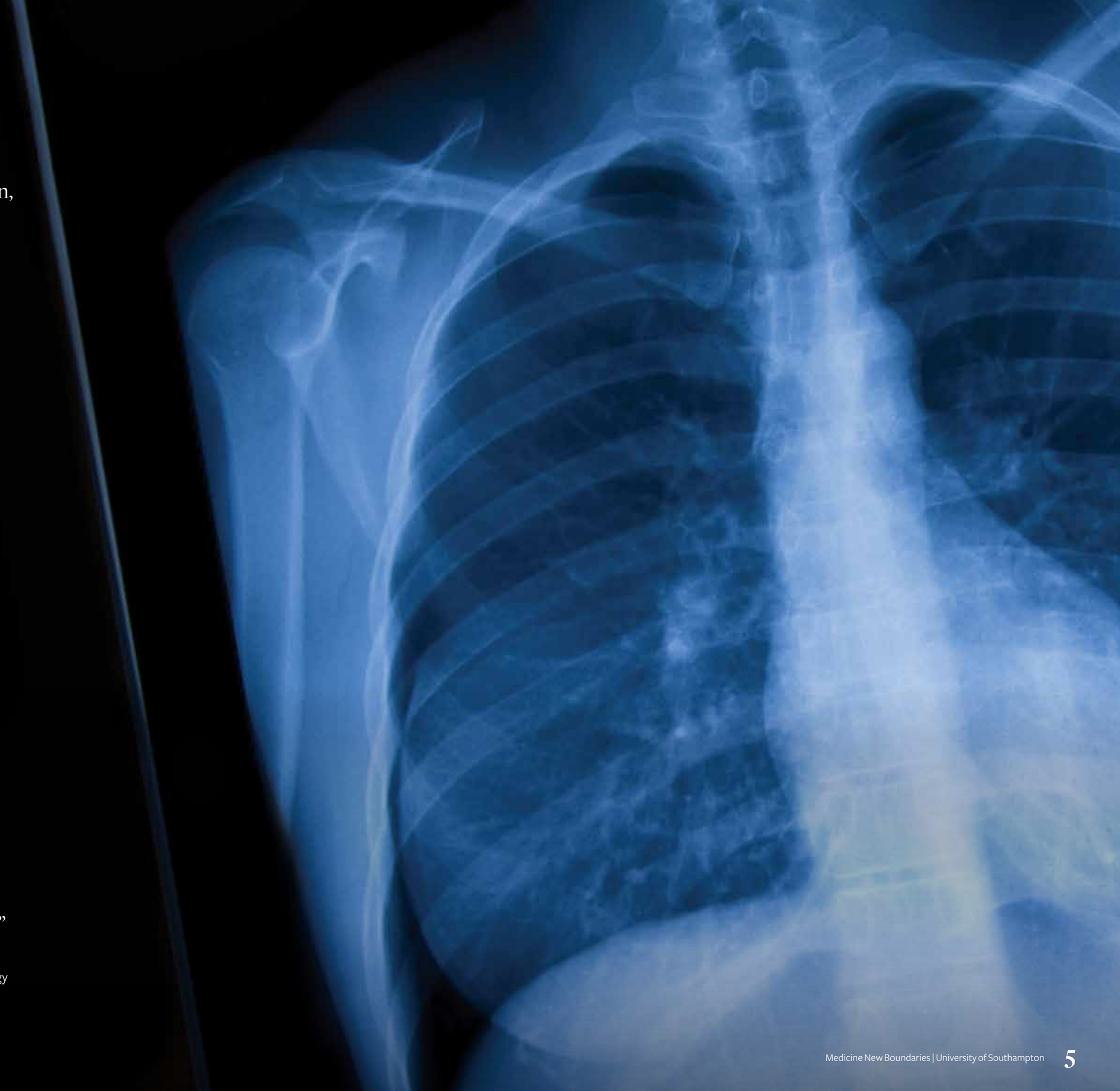
More highlights

Breathe easy

According to the World Health Organization, 235 million people worldwide have asthma. Southampton research is developing new treatments for the disease, helping millions of people to breathe easier.



"We have a serious problem; a rise in the number of cases of respiratory disease, a fall in the number of treatments, and a lack of understanding of what the environmental and societal drivers are for these conditions."

Professor Stephen Holgate,
Medical Research Council (MRC) Clinical Professor of Immunopharmacology

Southampton research is improving the lives of people with asthma

"Southampton has been at the forefront of allergy and asthma research for more than 30 years and we are extremely privileged to have such an array of expertise and talent within our team."

Professor Hasan Arshad,
Chair of Allergy and Clinical Immunology

Respiratory diseases are among the most common conditions, and affect all ages of the population. Asthma is particularly prevalent in children and young adults, while chronic obstructive pulmonary disease (COPD), associated with cigarette smoke, affects the older population. Many, if not all, respiratory diseases are increasingly progressive over time; the last 15-20 years has seen a dramatic increase in the incidence of all of them globally.

Late diagnosis

Stephen Holgate, Medical Research Council (MRC) Clinical Professor of Immunopharmacology at the University, explains that the four main types of non-infectious respiratory disease: asthma, COPD, lung cancer and interstitial pulmonary fibrosis, all present with different symptoms, but that the difference between symptoms of lung diseases compared to other chronic illnesses such as heart disease, is that the symptoms are 'soft'. "In other words the person experiences shortness of breath and coughing, which are the main symptoms, but they tolerate these for a long time before seeking medical assistance," says Stephen. "This means that the diagnosis of a respiratory disease is made much later, when the illness has progressed considerably," he adds.

At present, much of the treatment of chronic and acute lung disease is directed to disease suppression or relieving symptoms rather than dealing with the causative cellular and molecular pathways. Indeed, many of the underlying causes of respiratory diseases are not fully understood, resulting in the pharmaceutical industry having a failure rate of 97 per cent for novel treatments that could intervene on the causative processes in these conditions. "We have a serious problem; a rise in the number of cases of respiratory disease, a fall in the number of treatments, and a lack of understanding of what the environmental and societal drivers are for these conditions," says Stephen.

He explains that one of the reasons it is difficult to develop novel therapeutics for these diseases is that many pharmaceutical companies rely on animal models to predict how humans would respond to new treatments. While in the past such an approach has been helpful, increasingly the animal models used appear not to recapitulate the disease as it occurs in humans, despite superficially appearing similar.

"At Southampton, we have focused on setting up in vitro human-based screening systems, in order to move away from animal models and better predict the effects that therapeutics will have on patients," Stephen says.

Centre of excellence

Southampton's reputation for innovative research that tackles respiratory diseases has recently been recognised by the World Allergy Organisation (WAO). The Asthma, Allergy and Immunology Activity has been named a World Centre of Excellence for achievements in clinical innovation and research, and is currently the only centre in the UK to hold this status.

"To be named the World Centre of Excellence is a tremendous achievement and testament to the magnificent progress in patient care and research by some truly exceptional people," says Professor Hasan Arshad, a Consultant at Southampton General Hospital and Chair of Allergy and Clinical Immunology at the University. "Southampton has been at the forefront of allergy and asthma research for more than 30 years and we are extremely privileged to have such an array of expertise and talent within our team."

Through the National Institute for Health Research (NIHR) Southampton Respiratory Research Unit, the Centre's extensive research programme works alongside hospital care and a world-leading education programme to understand the causes of these conditions and prevent the development of asthma and allergy in children by the use of vaccines during infancy.

Linked with the David Hide Asthma and Allergy Research Centre on the Isle of Wight, Southampton is one of only six centres in England to care for both adults and children from diagnosis to treatment of allergic diseases, where the masters in allergy course at the University is one of only two in the world.

The WAO Centre of Excellence status also recognises our allergy education delivery. "To be recognised as a Centre of Excellence for our education programmes, which include our flagship MSc Allergy, is an outstanding achievement. As a Centre of Excellence, in partnership with the WAO, we would like to create education packages using the excellence of the MSc Allergy programme, for people to access around the world," says Dr Judith Holloway, Programme Leader MSc Allergy at Southampton.

"We have just out-licenced our findings to AstraZeneca for $230m. AstraZeneca is going to take the therapeutic forward as well as work with Synairgen to work up some other Southampton discoveries."

Professor Stephen Holgate,
Medical Research Council (MRC) Clinical Professor of Immunopharmacology

Southampton researchers partner pharmaceutical companies to develop novel treatments

Pharma partner

Stephen's work stretches back to the early 1990s when he started to collaborate with Ciba-Geigy (now Novartis) to develop a treatment that would block the action of the allergic antibody IgE from activating the allergic cascade that leads to most asthma – ie an anti-IgE.

"The allergic cascade is part of the chronic inflammation of asthma and most asthmatics will associate parts of the disease with exposure to allergens from dust mites, pollen, fungi and pets," says Stephen. "The idea was to develop a therapeutic that would intervene before IgE can trigger the allergic cascade that results in swelling or coughing," he adds.

Stephen and his team carried out the first clinical trial of an anti-IgE antibody, which was developed by Ciba-Geigy and showed that it was safe for human use, but was also effective at eliminating IgE. "This was the first time any IgE-blocking monoclonal antibody had ever been given to humans with a potential impact beyond asthma," explains Stephen. "Allergic antibodies are a class of antibody that are raised against common allergens that may occur in up to half of the population giving rise to allergic diseases such as asthma, hay fever and food reactions. After demonstrating safety and efficacy, the humanised anti-IgE monoclonal antibody, omalizumab, was developed and successfully trialled in severe allergic asthma. Omalizumab or similar anti-IgE therapeutics could be used to wipe out allergic reactions to all allergens by preventing the initial allergen triggering events involving IgE bound to inflammatory cells such as mast cells and basophils."

Novel breakthrough

Omalizumab prevents IgE from crosslinking receptors on the surface of mast cells and basophils, preventing them from secreting chemicals that cause allergic inflammation (eg histamine, prostaglandins and leukotrienes). By targeting the part of the IgE that binds to the mast cells, the allergic cascade cannot occur. "This was the first really novel breakthrough in asthma treatment in the last 50 years enabling many people with the disease to reduce their other treatments, such as steroids, which have many side effects," says Stephen. "But still only 40 per cent of people with severe asthma have a good response to omalizumab," he adds.

Novartis has now developed a new antibody that is 20 times more effective than omalizumab. "We hope that this new therapeutic will enable the 60 per cent of people who do not respond to omalizumab to see improvements. I am in active discussions with Novartis about a clinical development programme, which will hopefully involve trials at Southampton," says Stephen.

Winter months can be a particularly worrying time for people with asthma because cold and flu viruses trigger more frequent asthma attacks. Collaborating with Donna Davies, Professor of Respiratory Cell and Molecular Biology, Professor Ratko Djukanovic, who pioneered the use of fibreoptic bronchoscopy to obtain airway cells from asthmatics, and expert engineers and physicists at the University, the team studied the epithelial cells from the lining of the conducting airways of the lungs. They found that people with asthma are unable to fight off colds and flu as effectively as people with healthy lungs.

"Asthmatics have a defect in their airway epithelial cells in that when infected with common cold viruses, they don't make enough of a special type of protein – interferon beta – that would normally defend the lung against such normally innocuous viral infections and flu viruses," says Stephen.

Inhaled interferon

The discovery led to the formation of a University spin-out company, Synairgen, in 2003 to develop a treatment to limit virus-induced asthma attacks. The Southampton team designed and then, under the direction of Ratko, carried out clinical trials worldwide to show that inhaled interferon was safe for human consumption, and that in patients with severe asthma, when inhaled at the first sign of or in a few days of the start of a common cold, it could prevent common cold viruses from causing an acute worsening (exacerbation) of asthma attack.

"We have just out-licenced our findings to AstraZeneca for $230m. AstraZeneca is going to take the therapeutic forward as well as work with Synairgen to work up some other Southampton discoveries," Stephen explains.

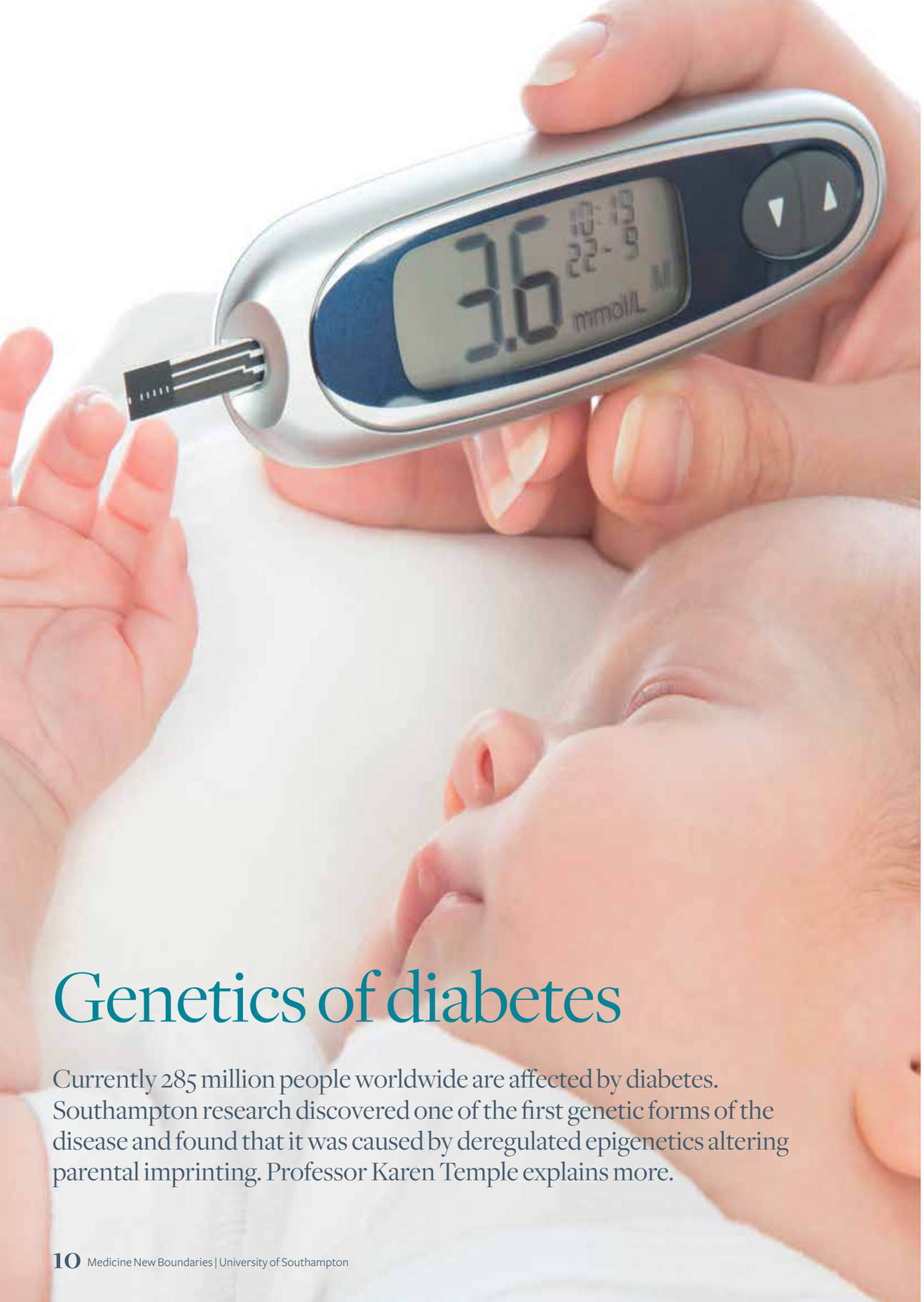
Strong foundation

Researchers are now building on this work to discover what makes asthma a chronic condition that persists throughout life; they are making exciting links between respiratory research and developmental science, with new studies looking at ways to prevent children developing asthma by controlling diet in pregnancy and early childhood. "This links to an area of science that the research community is very excited about: epigenetics – the study of how the genes are switched on by the environment. We're looking at what it is in early life that switches on these genes and makes children asthmatic," says Stephen.

Exchanging ideas with the research community around the world has been key to the success of Southampton's respiratory research. "Southampton is among the top five in the world in asthma research; one of the most powerful things to enable this is the fact that over the last 20 years a lot of very talented people from both in the UK and across the world have come to do their training at Southampton, bringing with them originality and fresh ideas," Stephen says.

For more information about Southampton research on airway diseases, visit **www.southampton.ac.uk/medicine/research/themes.page**

To find out about the MSc Allergy at Southampton, visit **www.southampton.ac.uk/medicine/allergy**



Genetics of diabetes

Currently 285 million people worldwide are affected by diabetes. Southampton research discovered one of the first genetic forms of the disease and found that it was caused by deregulated epigenetics altering parental imprinting. Professor Karen Temple explains more.

What are the challenges diabetes poses?

Diabetes is increasing in incidence and is the end point of a whole load of different ways that insulin stops working in the body.

Classically the disease has been divided into two types: Type 1, resulting from the body's failure to produce enough insulin; and Type 2, resulting from the body not being able to respond to insulin properly. But we know from genomic classification that there are many different types of diabetes, so the challenge is trying to understand the molecular pathway of each type in order to personalise the treatment for each patient.

What does your research involve?

I work closely with geneticist Dr Deborah Mackay, at the University, and one of our strengths has been to come at the questions from both a clinical and a scientific direction. We discovered one of the first genetic forms of diabetes and suggested that the gene was regulated epigenetically by a process called parental imprinting. Patients that had the disease had a problem, not with the way the gene was assembled, but with the way the gene was able to work.

I was first interested in diabetes when I saw a remarkable patient on the ward that presented with the disease at birth. By six weeks old she did not have diabetes anymore and we discovered that she had the condition transient neonatal diabetes (TND). Chromosome testing highlighted that the patient had an unusual inheritance of chromosome 6 resulting from paternal uniparental disomy; the inheritance of both chromosomes 6 from her father with no contribution from her mother. We looked into her case because in fact the mother contributed a very tiny amount of chromosome 6 which was just visible as a small marker chromosome. This was possible because of a Wellcome Trust project grant.

Our subsequent paper on TND was the first indication of an imprinted form of diabetes; a rare inheritance pattern regulated epigenetically via the parent of origin.

Can you explain more about this project?

By genetic investigation of patients from around the world we identified the imprinted TND locus and subsequently developed detection methods for epigenetic mutations in patients. Our laboratory demonstrated connections between imprinting disorders, firstly describing TND patients with a novel 'complex' imprinting disorder, and then demonstrating mutations in a gene, ZFP57, essential for normal epigenetic control of development. This work showed the power of genetic studies in rare conditions for disclosing biological mechanisms, defining novel clinical entities and driving technical developments that have enhanced diagnosis of imprinting disorders in general.

What has your research in this area led on to?

We now hold a national register of patients with TND which enables us to inform patients of new discoveries and organise patient study days. Most importantly when we have a big enough cohort we need to try and understand why diabetes in these patients comes back in later life. Our work on TND has also broadened out into investigating the genetic origins of all the other imprinting disorders. A lot of the research I am doing now is in fact on other imprinting disorders such as Russell-Silver syndrome that causes extreme short stature. We have also identified a new condition which causes short stature and obesity in later life if treatment isn't started young, which is called Temple syndrome.

We are not carrying out experiments to try and answer hypothetical questions; we are looking at the mechanisms causing exceptions ie rare diseases, so that we can not only help the individuals to a healthier life, but also to get insight into molecular pathways of processes in the body that may go wrong in more common disorders. It's a way of research that is underexploited. It is often easier to look at the conditions that set people apart first that can inform us about conditions that are more common. Many so called 'common' diseases are in fact a common endpoint for a lot of rare mistakes in a common pathway.

What is the impact of your research?

This long-term collaborative research has transformed the management and intervention for TND and our diagnostic programme successfully diagnoses 95 per cent of TND, supporting care for 1,500 infants all over the world.

However, diagnosis is only the first step in deciding how to treat someone with the condition. Working with professors Andrew Hattersley and Sian Ellard at the University of Exeter, who discovered many other genetic causes of diabetes, we have been able to use the diagnostic test to decide treatments for babies with the illness. We hope that over time the number of sub groups of diabetes will increase so that a patient will receive personalised treatments depending on the type they have.

Is collaboration important in your research?

Yes, collaboration is very important. As well as our colleagues at Exeter and the patients who contribute in so many ways, we collaborate with many other teams across the world. This has helped us to introduce our TND diagnostic test so widely. There is now a European network working together to understand more about these disorders of growth and metabolism (www.imprinting-disorders.eu). We are also heavily supported by Diabetes UK; part of the reason we have been able to grow our research is due to our relationship with the charity.

For more information on this research, visit **www.southampton.ac.uk/geneticimprinting**

Beating blood cancer

Globally, there are 300,000 new cases of leukaemia each year and 222,000 deaths from the disease. Research at Southampton has helped to predict the rate of progression of the commonest leukaemia in the western world. This informs clinical management leading to better healthcare outcomes for thousands of people each year.

There are more than 200 different types of cancer and its complexity is the greatest challenge facing scientists. A cancer of apparently the same type in two people can carry completely different sets of genetic alterations and multiple sub-cancers can be present at the time it is diagnosed, which evolve over time and enable it to evade treatment.

"We are only just developing the methods for unravelling all this complexity; each type of cancer has a different type of complexity and the next decade will see us grappling with the vast amounts of data that can now be generated to describe cancers at the molecular level," says Peter Johnson, Professor of Medical Oncology at the University.

Leukocytes and lymphocytes

One group of cancers that affect the blood is among those being tackled at Southampton; each year around 9,000 people in the UK are diagnosed with a form of blood cancer known as chronic lymphocytic leukaemia (CLL). This affects lymphocytes in the blood, which are an important part of our immune system that fights infection. A related cancer of lymphocytes where cells reside mainly in lymph glands rather than in blood is lymphoma.

Professor of Immunology at Southampton, Freda Stevenson explains that CLL is the most prevalent leukaemia, and tends to occur later in life. Prognosis varies greatly between patients and life expectancy has been difficult to predict.

"Before 1999 when we uncovered a major prognostic marker, CLL was considered to be a single disease with a variable and unpredictable clinical course," says Freda. "Our studies showed there are actually two subsets of CLL with significantly different progression rates, requirement for treatment and overall survival. Previous research worldwide had missed this subdivision due to the inability to reveal the two subsets by cell morphology and phenotype," she adds. ▸

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Freda Stevenson,
Professor of Immunology

As a world leader in cancer sciences, Southampton will be home to a new Centre for Cancer Immunology

"With the new Centre, we expect to double the number of people working on cancer immunology at Southampton and, as a result of this activity, to double the number of patients on clinical trials by the time the Centre is fully operational."

Professor Martin Glennie, pictured above left
Head of Cancer Sciences

Sequencing techniques

By establishing modern DNA sequencing techniques in the laboratory, the team analysed human immunoglobulin (Ig) variable region (V) genes in B-cell malignancies and in normal B-cells. These IgV genes undergo a natural hypermutational process during production of antibodies, and tumour cells carry these mutations as marks of the cell of origin.

Correlations with disease behaviour revealed a connection between IgV gene mutational status and the clinical course. "The aggressive form of CLL was derived from B-cells prior to somatic hyper mutation in the IgV genes, whereas the indolent form of CLL was derived from B-cells that have accumulated mutations. "We found that 40 per cent of patients had the more aggressive disease, with a shorter survival rate, and 60 per cent had the less aggressive variant with a 25-year life expectancy," says Freda.

Freda explains that thanks to her team's discovery CLL patients can know at an early stage what the likely course of the tumour will be, using the simple prognostic test. "Patients with the more aggressive form can be treated early with new drugs. Patients with the less aggressive form may not require any treatment. Not only are the IgV genes providing prognostic information, but a new generation of drugs is aimed at the IgV proteins."

Peter explains that although cancers can develop from lymphocytes, the normal immune system can be activated to fight cancer cells. Cells of the immune system have several features that make immune attack a very powerful potential ally in cancer treatment: "It is highly specific, it is capable of great amplification in its response and it can give lifelong protection. However, it is also a very complex system and the fact that we develop cancers in the first place is down to their ability to evade the immune system," he says.

"There are many challenges in reversing this tolerance to the presence of a cancer, but we are starting to see the first signs that this can work. Up until now we have had fairly crude methods of switching on immune responses to cancer, but this is beginning to change and cancer immunology is attracting more and more attention worldwide," he adds.

Antibody attack

Martin Glennie, Professor of Immunochemistry and Head of Cancer Sciences at the University, and his team have been investigating the use of monoclonal antibodies (mAb) to fight lymphoma tumour cells for more than three decades.

For lymphoma, the fifth most common cancer in the UK, the standard treatment is intensive and toxic chemotherapy. However this can cause multiple complications for patients and is ineffective for those with chemotherapy-resistant lymphoma.

Martin explains that mAb represent a multi-billion dollar industry with at least five attaining blockbuster drug status. The team's work underpins the clinical development of a new class of anti-cancer mAb, such as anti-CD20 to treat lymphoma. The most advanced is a next generation, fully human drug, ofatumumab, which was commercialised by GlaxoSmithKline/Genmab with the trade-name Arzerra, and was approved in 2009 to treat advanced CLL.

Million-dollar drug

"Arzerra is now a multi-million-dollar drug, launched so far in 26 countries and is being used in 19 clinical trials worldwide for diseases ranging from lymphoma to rheumatoid arthritis and multiple sclerosis," says Martin. The team's work has inspired follow-on funding from government and industry in excess of £12m.

Peter explains that the use of anti-CD20 reagents represents the single biggest improvement in lymphoma survival rates over the last two decades. He and his team directed two innovative trials which exposed for the first time the relationship between lymphoma and how the antibodies work in treatment. A further trial in Hodgkin lymphoma established the chemotherapy treatment that delivered the best outcomes, and confirmed the vital role of radiotherapy in optimising cure rates.

"Our research has driven major advances in international standards for lymphoma care and resulted in the development of new antibodies for its treatment. This has greatly improved survival rates and quality of life for people affected by the disease and reduced healthcare costs across the NHS," Peter says.

The same programme of Southampton research has also been instrumental in the selection of a second anti-CD20 mAb, named GA101 (obinutuzumab), in association with Roche. This was the first type II anti-CD20 mAb to be humanised for clinical work. Capable of killing a significantly higher number of cancerous cells than its type I counterpart, it is currently in multicentre phase III trials and when combined with chlorambucil demonstrates a significant 86 per cent reduction in the risk of leukaemia progression, relapse or death.

Long-term protection

"CD40 is another class of antibody that we discovered. This antibody switches on the body's own immune system," says Martin. He explains that CD40 initiates an immune response, which gives the patient long-term protection. "The idea is that you give a treatment that doesn't target a tumour, but switches on the immune system to protect against the tumour. We are now carrying out human clinical trials on CD40."

At present the cancer sciences industry seems to be focusing on finding improved treatments for cancers such as leukaemia and lymphoma, but Martin explains that the real challenge is finding successful treatments for melanoma and lung cancer for example.

As a world leader in cancer sciences, Southampton will be home to a new Southampton Centre for Cancer Immunology, which will push the boundaries of immunology. "The new Centre will allow us to find out what the differences are between patients that respond well to the treatments and those that don't," says Martin. "One of the strengths of Southampton is that we link groundbreaking research with clinical trials. By utilising our collaborations with colleagues at the new Francis Crick Institute, due to open in 2015, our new Centre will make the transition from research to viable drugs much quicker," he adds.

Martin continues: "With the new Centre, we expect to double the number of people working on cancer immunology at Southampton and, as a result of this activity, to double the number of patients on clinical trials by the time the Centre is fully operational."

"We are never going to find one thing that cures all cancers, but we are making good progress by developing new types of surgery, radiation and drug treatments, finding ways to detect cancers earlier and in many cases preventing them altogether. This is why it is such an exciting area to be involved in," he adds.

For more information on our new Centre for Cancer Immunology, visit **www.southampton.ac.uk/cancerimmunology**

Tackling malnutrition

According to the World Health Organization (WHO), malnutrition is estimated to contribute to more than a third of all child deaths around the world. Researchers at Southampton are influencing public policy to change healthcare practices and public attitudes to nutrition; Marinos Elia, Professor of Clinical Nutrition and Metabolism at the University, explains.

What is your research about?
My research, at the National Institute for Health Research (NIHR) Southampton Biomedical Research Centre (BRC) in nutrition, focuses on tackling malnutrition in the UK. It is sometimes easy to believe that malnutrition is only a problem in developing countries, but it is also a clinical and public problem in the UK. Malnutrition affects more than three million people in Britain, costs an estimated £13bn a year or more and continues to go under-detected.

What is malnutrition?
When people are malnourished, their basic health and social care outcomes are significantly affected, making malnutrition an important patient safety issue. Our latest national surveys suggest that in England, at least 29 per cent of adults admitted to hospital, 18 per cent in mental health units, 12 per cent in sheltered housing and 35 per cent in care homes are malnourished, or at risk of malnutrition. In the whole country this equates to five per cent of the population being malnourished or at risk of malnutrition and expenditure on malnutrition is the same, if not greater, than expenditure on obesity in the UK.

What can malnutrition lead to?
Malnutrition is a major problem and predisposes to disease; it adversely affects its outcome and delays recovery from illness and has detrimental effects on every single system of the body. It leads to a decrease in quality of life and means a person can't function properly. If left untreated, a person can die from malnutrition, but also wound healing is impaired, energy levels are reduced and psychological problems could develop. Frequent malnutrition can cause anxiety and depression and social interaction problems.

How does your research help with malnutrition?
My teams at the University and the University Hospital Southampton NHS Trust, together with BAPEN, a charitable association that raises awareness of malnutrition, have developed a bedside tool that assesses whether a patient is malnourished or not.

The Malnutrition Universal Screening Tool (MUST) is based on three criteria: whether the patient has experienced weight loss, what the patient's weight is now, and whether the patient is likely to lose more weight in the near future.

How does MUST work?
MUST measures a person's body mass index (BMI) and is based on a simple scoring system between zero and two. If the patient has a very low BMI, they score a two. Similarly, if the patient has lost a lot of weight they get another high score, and if they are acutely ill or unlikely to receive nutritional intake over the next five days, then again they score two. The three scores can then be added up and if the score is two or higher they are at a high risk of being malnourished.

Based on the score from MUST, using a simple chart system, healthcare professionals can then decide the best course of treatment for the patient.

What is the impact of MUST on healthcare?
Over the last few years, MUST has been incorporated into the majority of hospitals and care homes in the UK. Supported by the Department of Health, the Royal College of Nursing, the Royal College of Physicians, the Registered Care Home Association and the National Institute for Health and Care Excellence (NICE), MUST is now in use by over 80 per cent of healthcare institutions in the UK.

The advantage of using MUST is that it can be used in different care settings, and we have created electronic versions and apps to simplify the technique to reduce the workload and move towards an automated system that patients can use themselves. Our recently published work is encouraging since it suggests that patients attending a hospital outpatient clinic can accurately screen themselves in just over a minute using an electronic system linked to Wi-Fi.

How does your work influence policy?
In the UK, policy development and quality standards around malnutrition can only be built on a sound platform of solid and consistent evidence. In Southampton at the BRC, the work that we have carried out has greatly influenced the National Institute of Health and Care Excellence (NICE) quality standards for nutrition support in adults. I have also chaired the group that produced the NICE Quality Standard on nutritional support in adults, providing the essential research knowledge, experience and leadership to develop the new standard that will transform the delivery of care. I have also chaired the NICE Evidence Update Group on nutritional support in adults, to ensure that policies are based on the latest information.

Is collaboration important?
Yes, collaboration is key in the way we work. The BRC, which illustrates the importance of collaboration between the NHS, the MRC and the University, has played a key role in developing the International Malnutrition Taskforce (IMTF), a major influencer and developer of global malnutrition policy and practice.

Using research from the BRC, the IMTF has identified two key research priorities that focus on the needs and care of children with severe acute malnutrition and moderate malnutrition across the world. The research priorities are: the need to be able to accurately determine the pattern of growth in children recovering from malnutrition, and the need to better understand the nutritional requirements of children recovering from malnutrition.

We work with healthcare providers to identify the research priorities of importance to clinicians and patients so that better studies can be designed and delivered that more effectively address malnutrition issues. And we work with industry to develop therapeutic pathways to maximise the quality and effectiveness of nutritional care.

For more information about Southampton research on nutrition, visit **www.southampton.ac.uk/medicine/research/centres.page**

In brief

Preventing pneumococcal disease

Southampton research is helping to save lives among workers exposed to metal fumes through vaccination against pneumococcus to protect against life-threatening infections to which they are unusually susceptible.

In 1992, a team led by Professor David Coggon, was commissioned by the Health and Safety Executive and Office of Population Censuses and Surveys to undertake a national analysis of occupational mortality covering 1979-90. The study indicated a marked excess of deaths from pneumonia in welders and other occupations exposed to metal fumes.

"Among welders of working age, there were more than twice as many deaths from lobar pneumonia as would be expected, but there was no similar excess after retirement age. This suggested an occupational hazard that disappears after exposure ceases," says David.

David's team subsequently confirmed the hazard in a large study of hospitalised community-acquired pneumonia, and in further analyses of occupational mortality for later periods.

Largely on the strength of this evidence, the Department of Health has recommended that employers consider offering vaccination against pneumococcus to welders and other workers exposed to metal fumes – a move which could prevent significant numbers of deaths and serious infections at relatively young ages.

"Other countries are issuing hazard warnings on the strength of our work and we are pressing the Health and Safety Executive to give further guidance on vaccination for metal workers," he adds.

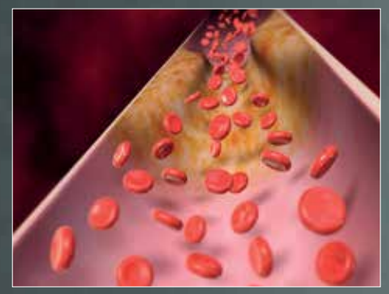
Understanding Alzheimer's

Research at Southampton into amyloid beta protein (Aß) immunisation to treat Alzheimer's has changed the way the disease is understood, and was pivotal in initiating major clinical trials of immunotherapy agents, which led to the pharmaceutical industry investing $3bn in the area.

The theory that accumulation of Aß in the brain plays a key role in Alzheimer's by disrupting normal cognitive function was questioned after clinical trials to remove Aß plaques from the brain displayed side effects. Previous animal studies showed that immunisation with Aß via the bloodstream may reduce the amount of Aß in the brain, and improves brain function.

Southampton's Memory Assessment and Research Centre (MARC) participated in the first human clinical study of active Aß immunisation. Results from this and subsequent studies found that even the effects of complete Aß plaque removal are insufficient to halt cognitive decline, and that early intervention is crucial.

"Our findings were presented in the House of Lords," says Professor James Nicoll. "Subsequently Prime Minister David Cameron announced a doubling of funding for Alzheimer's disease to £66m and a programme of early detection screening. Recommendations based on our research have also led directly to a policy change by the US for the safe monitoring of patients receiving immunotherapy for Alzheimer's."



Treating heart disease

Southampton research on the anti-inflammatory effects of omega-3 fatty acids has directly improved the treatment of cardiovascular disease, leading to lower death rates in patients, reduced healthcare costs and improved clinical practice.

Omega-3 fatty acids are found in foods such as oily fish and are known to help protect against heart disease; however the way in which they work is not fully understood.

Since 1995 our researchers, including Philip Calder, Professor of Nutritional Immunology, have focused on the anti-inflammatory effects of omega-3 fatty acids and investigated whether these acids might act within hard, fatty deposits in blood vessels to reduce illness and death due to cardiovascular disease.

The team found that people awaiting surgery to have their plaques removed who were given omega-3 fatty acids, had a reduced chance of their plaques rupturing, and therefore had a reduced chance of having a stroke or a heart attack. "We then found that this effect was due to the anti-inflammatory actions of omega-3 fatty acids within the plaques," says Philip.

"Our findings have helped set UK and European guidelines on nutrition, and have been licensed in several countries. It also provides further evidence that omega-3 may be useful in treating a wide range of inflammatory diseases such as rheumatoid arthritis and asthma."

Assessing depression

Research at Southampton into the management of depression informed policy and healthcare practice, resulting in improved patient assessment across the UK.

According to the World Health Organization, more than 350 million people of all ages suffer from depression around the world, and in 2010 the estimated cost of mental illness was $2.5tn, with a projected increase to over $6tn by 2030.

In the UK, more than 80 per cent of depression cases are managed in primary care, making effective management in this setting crucial. Tony Kendrick, Professor of Primary Care at the University, and his team discovered deficits in how depression was assessed and treated by GPs.

In the 1990s GPs were failing to recognise around one-third of cases, and most patients received either no treatment, or their treatment was inadequate. The Southampton team launched a groundbreaking trial, the Hampshire Depression Project, which highlighted that guideline-based GP education alone did not improve recognition of depression or patient outcomes.

The team's findings were included in National Institute for Health and Care Excellence (NICE) guidelines leading to questionnaire assessments being introduced into GP contracts.

"Our research contributed to the introduction of assessment at diagnosis and follow-up, and our studies showed that it appeared to influence GPs' decisions to change treatment appropriately," says Tony. "The 2009 NICE depression guidelines directly referenced our findings and the subsequent introduction of formal rating scales had immediate and widespread impact on care."

In brief

Tackling obesity

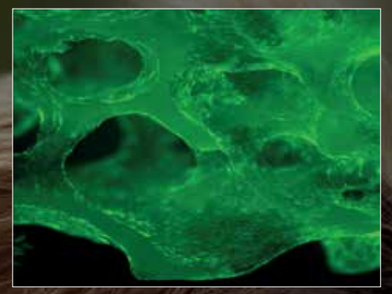
Southampton research has led to a transformation in the medical approach to obesity, osteoporosis and other non-communicable diseases (NCDs). Through an international alliance of researchers, more than £10m in research funding has been raised to further explore this area.

Scientists have long known that chromosomes passed from parent to child form a genetic blueprint for development. But genes are not fixed to a predetermined programme, they can be turned on and off by experiences and environment.

Professor Cyrus Cooper and colleagues at the University's Medical Research Council (MRC) Lifecourse Epidemiology Unit (LEU) are conducting unique lifecourse cohort studies to evaluate relationships between genetic influences, early growth, adult lifestyle and risks of age-related disorders.

"We have discovered that patterns in diet and lifestyle are set before pregnancy, that pre-pregnancy diet quality is the strongest predictor of an infant's diet quality, and both of these are associated with better later health," says Cyrus. "We also showed that undue weight gain in pregnancy is associated with an increased risk of childhood obesity," he adds.

The research has led directly to a change in international and national policy aimed at preventing NCDs, and influenced training and education programmes, leading to health benefits for millions of people.



Bone stem cell therapy

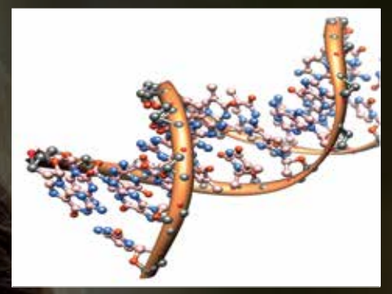
University of Southampton researchers have developed a unique approach linking nano-bioengineering and stem cell research, which could transform treatment for 4,000 UK patients each year and reduce a huge cost burden on the NHS.

Among the challenges posed by our ageing population is the need for novel and cost-effective approaches to skeletal reconstruction. One in three women and one in five men are at risk of osteoporotic fractures worldwide.

For the 30–50 per cent of people requiring revision surgery after hip replacement operations, many will need subsequent bone augmentation. Current practice using donor bone is costly, dependent on availability and commonly leads to complications including infection and immunological rejection.

Work pioneered by Professor Richard Oreffo and his team at the University demonstrated the practicability of using patients' own bone stem cells together with a unique nanotopographical substrate to drive bone formation or maintain bone stem cells as well as biocompatible scaffolds to create a 'living bone composite', essentially regrowing a patient's own bone.

"The stem cells will act like a glue to help with tissue integration," says Richard. "We also discovered how to control stem cells on nanosurfaces and were able to induce hard tissue to form directly onto an implant surface enhancing bone integration and reducing the prospect of revision surgery," he adds.



Gene mapping tools

Southampton research into the genetic causes of diseases has led to gene mapping techniques and applications benefiting patients worldwide. Our work has improved prediction, diagnosis and treatment for common diseases with a complex genetic basis.

With the race to find the genetic causes of diseases gathering pace the focus has shifted from diseases caused by rare single gene mutations to diseases with a complex genetic basis. These are the common diseases which affect millions of people, such as breast cancer, Type 2 diabetes and age-related blindness.

Professor Andrew Collins and his team at Southampton focus on developing novel gene mapping techniques which enable the identification of specific chromosome sections where the causes of diseases lie.

The team has established the advantages of case-control versus family-based gene mapping strategies, and this work has informed the design of genome-wide screening panels which have had profound impacts in medicine.

"We have identified novel genes underlying metabolic syndromes in large birth cohorts and genes causing age-related blindness, and this body of work has contributed to the development of the personal genomics industry," says Andrew.

"The impact of an individual's genetic makeup is now quantified in terms of risk to develop age-related blindness. This has significant bearing on the 20 per cent of the population at risk of the disease. At least five commercial genetic testing kits are available with clinical trials of genetic therapy underway."

Detecting childhood hearing impairment

Research at the University of Southampton was central to the introduction of universal new born screening (UNS) for permanent childhood hearing impairment (PCHI) in the UK and USA.

Affecting over one in 900 babies born each year, PCHI impairs neuronal development, language skills and educational outcomes.

Prior to 2001 screening for PCHI in the UK depended upon a less reliable test at seven months old, but is now achieved in the newborn period by detection of low level sounds originating in the cochlea combined with automated auditory brain stem testing.

Research by Professor Colin Kennedy from Medicine and colleagues from the Institute of Sound and Vibration Research at the University was central to this policy change in the UK and also in the USA.

"Three million UK babies were screened and 5,000 cases identified by UNS over five years benefiting literacy and academic success. We expect that this will also bring lasting improvement in their well-being and employment prospects," says Colin.

"The introduction of UNS has greatly reduced the age of identification of PCHI and the proportion benefiting from greater family awareness and hearing aids in the first year of life," he adds.

Selection of recent journal papers

This sample of journal papers indicates the breadth of research in Medicine, at Southampton. For more research papers, please view individual staff profiles online.

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