The Academy of Medical Sciences

UNIVERSITY OF Southampton School of Medicine

Southampton symposium: Translating new research into clinical practice

Thursday 26 February 2009

Symposium report, June 2009

The Academy of Medical Sciences
The Academy of Medical Sciences promotes advances in medical science and campaigns to ensure these are converted into healthcare benefits for society. Our Fellows are the UK's leading medical scientists from hospitals and general practice, academia, industry and the public service.

The Academy seeks to play a pivotal role in determining the future of medical science in the UK, and the benefits that society will enjoy in years to come. We champion the UK's strengths in medical science, promote careers and capacity building, encourage the implementation of new ideas and solutions – often through novel partnerships – and help to remove barriers to progress.

Acknowledgements
This report was prepared on behalf of the Academy by Dr Jamie Goode and provides a summary of the Symposium held on Thursday 26 February 2009 at the Wessex Heartbeat Centre, Southampton General Hospital.

The Academy warmly thanks Professors Freda Stevenson FMedSci and Stephen Holgate FMedSci for hosting the event, the speakers for their thoughtful presentations and review of this report, and the session chairs and delegates for their participation.

The Academy gratefully acknowledges the sponsorship of the University of Southampton School of Medicine for the event.

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Background

On Thursday 26 February 2009 the Academy of Medical Sciences and the School of Medicine, University of Southampton held a joint symposium on 'Translating new research into clinical practice' at the Wessex Heartbeat Centre, Southampton General Hospital.

Coordinated by Professors Freda Stevenson FMedSci and Stephen Holgate FMedSci, the symposium focused on translational research within two key themes: 'Epigenetic and environmental influences on disease' and 'Immunity and inflammation'.

The symposium was opened by Professor Iain Cameron, Head of the School of Medicine, University of Southampton, and Professor Sir John Bell, President of Academy of Medical Sciences. Presentations were given by Southampton-based Fellows of the Academy and colleagues. In summing up, the Academy's Executive Director, Mrs Mary Manning, reflected on the Academy's role in supporting medical science and scientists, and gave a future outlook.

The event was attended by over 120 delegates, the full programme and list of attendees are annexed. This report provides a short review of each of the presentations.

Introduction

Professor Iain Cameron
Head of the School of Medicine, University of Southampton

Professor Sir John Bell FRS PMedSci
President, Academy of Medical Sciences

The Academy of Medical Sciences' 2003 report 'Strengthening Clinical Research' called for developments to maximise the potential of the UK's strong basic science base by enhancing translational research.[1] The report coincided with the 'Biosciences 2015' report from the Bioscience Innovation and Growth Team which set out an agenda to take forward UK research in translational medicine.[2] In 2006, Sir David Cooksey's 'Review of UK Health Research Funding' drew further support for the translational research agenda, including the creation of a single ring-fenced budget for UK health research and the establishment of the Office for the Strategic Coordination of Health Research (OSCHR).[3] Key UK programmes in translational medicine are now in place, however ongoing challenges include:

- Training sufficient young clinical scientists
- Being responsive to the potential impact of the economic crisis
- Engaging and facilitating the commercial sector in translational research.

The University of Southampton School of Medicine has a flourishing basic science programme, but has particular strengths in undertaking translational research. A deliberate research strategy has been employed to support high quality basic science with a focus on translation into clinical settings. The University has a strong relationship with the local National Health Service, with the School of Medicine itself embedded in Southampton General Hospital. Southampton University's capacity to deliver translational research is supported by key strengths in epidemiology, and the School of Medicine has a strong track record in areas including developmental sciences, respiratory medicine, bone and joint disease, cancer and immunology.

The success of the University of Southampton in punching above its weight in translational research highlights the importance of key factors: infrastructure, cross-disciplinary partnership, and a wealth of talent. The joined-up feel to the way the various research elements work together, including strong collaborations between the biomedical and physical sciences, is another important aspect of the Southampton environment, and exemplifies what the UK aims to achieve in translational research.

The Southampton approach to translational medicine fits well with the core strategy of the Academy of Medical Sciences, in promoting advances in medical science and ensuring

[1] Academy of Medical Sciences (2003). *Strengthening clinical research.* http://www.acmedsci.ac.uk/p99puid22.html
[2] Bioscience Innovation and Growth Team (2003). *Bioscience 2015*. http://www.bioindustry.org/bigtreport/downloads.html
[3] HM Treasury (2006). *A review of UK health research funding*. http://www.hm-treasury.gov.uk/cooksey_review_index.htm

these are translated into healthcare benefits for society. As a national body, the Academy of Medical Sciences plays a role in showcasing translational research across all regions of the UK, and works to attract and develop the young scientists needed to build future capacity for translational research.[4]

[4] The Academy's events programme is on-line at: http://www.acmedsci.ac.uk/p43.html

Malnutrition during development and disease in later life

Professor David Barker CBE FRS FMedSci
Professor of Clinical Epidemiology, University of Southampton, and
Professor of Cardiovascular Medicine, Oregon Health and Science University

One arm of translational medicine is improved therapy, but the other is preventing chronic disease, the focus of this paper. Malnutrition and other adverse environmental exposures during development alter gene expression and programme the body's structures and functions for life. Adverse exposures also slow growth. People who were small at birth because they grew slowly have higher rates of coronary heart disease, diabetes, hypertension and other chronic disorders. They are biologically different to other people through their lives. The differences include reduced functional capacity, and altered hormone production and metabolism. After birth children who later develop chronic disease grow differently to other children.

Fetal nutrition is determined by the mother's diet, the nutrients stored in her body, and the placenta's ability to transport nutrients from mother to baby. Chronic disease in the next generation may be prevented by improving (a) the tempo and paths of child growth, (b) the diets of mothers before and during pregnancy, (c) the nutrition of girls and (d) the transport of nutrients across the placenta.

One hypothesis for the origins of breast cancer is that it is initiated *in utero* when developing breast tissue is exposed to the mother's circulating sex hormones. Women's levels of circulating oestrogens are established at puberty and track through their reproductive lives. At puberty oestrogen is responsible for the broadening of the bony pelvis that characterises the growth of girls. The maximal width of the upper hips, the intercristal diameter, may be a marker of a woman's level of oestrogen production and therefore the amount of oestrogen her fetus would be exposed to. In the Helsinki Birth Cohort the daughters of women with large intercristal diameters have a threefold increased risk of breast cancer. They are at a similarly increased risk of ovarian cancer.

These findings suggest that hormonal cancers are initiated by events during the mother's puberty that led to broad hips. The hypothesis is that the mother's sex hormones cause genetic instability in the stem cells of the breast and ovary. These stem cells are laid down around the seventh week of gestation, before the placenta forms a barrier between the fetus and the mother's circulating hormones. The mothers whose daughters develop breast and ovarian cancer have broad hips but only average height. The cancers may therefore be the result of poor nutrition in the mother's early childhood followed by pre-pubertal catch-up growth.

A small placental surface area predicts hypertension and coronary heart disease in later life. This has led to the hypothesis that coronary heart disease is initiated by excess cardiac loading *in utero* as a consequence of small placental size. A large placental surface area is also associated with later hypertension. In some circumstances an undernourished fetus can expand its placental surface to extract more nutrients from the mother. Much is

known about this in sheep. If ewes are well nourished, mated, and then put on poor pasture for days 30–60 of gestation, the placenta expands. When the ewes are returned to good pasture they give birth to bigger lambs than they would otherwise have had. Inducing placental expansion is standard practice in sheep farming. It seems that placental expansion can also occur in human mothers if they were well nourished at the time of conception. This expansion may have long term costs for the fetus that include hypertension and certain cancers.

The relationships between early growth and later disease are part of a life-long trade-off between the requirements of growth, reproductive success and longevity.

Embryo environment and its association with adult health and disease

Professor Tom Fleming
Professor of Developmental Biology, University of Southampton

A newly emerging concept in developmental biology is that of a 'dialogue' between mother and embryo. At the very start of development, before implantation, this important communication sets the level of developmental plasticity, such that the right phenotype is selected to fit the anticipated future environment. This communication is based upon the quality of nutrition the mother is eating and it represents an important decision the embryo makes about its mother.

The embryo develops in a complex of proteins, growth factors, amino acids and energy substrates within the maternal reproductive tract. This constitutes the information system upon which the embryo selects the pathway of developmental plasticity. Obviously, this has implications for assisted conception treatment (assisted reproductive therapy, ART) and reproductive biotechnologies as well as periconceptual maternal diet.

We have used the mouse low protein diet model to investigate the dialogue between mother and embryo. The control normal protein diet (NPD; 18% protein) has been compared with a low protein diet (LPD; 9% protein) and also with the low protein diet given only transiently during pre-implantation development before switching to the control diet at day 4 for the rest of gestation (Emb-LPD). Normal diet is fed to all offspring. LPD is a mild dietary intervention which has no effect on gestation length, litter size and male–female ratio. However, both the LPD and Emb-LPD offspring mice are hypertensive throughout life, show a range of physiological criteria of cardiovascular disease and Emb-LPD offspring also show behavioural abnormalities.

Similar data have been obtained with a rat Emb-LPD model and a mouse cell culture system to determine effects of ART. Interestingly, mouse embryo culture also results in postnatal hypertension. A Dutch study looking at 225 IVF-conceived children compared with matched controls shows that IVF children also have elevated blood pressure that cannot be explained as a result of subfertility.

Emb-LPD mice show enhanced conceptus and postnatal growth in a way that doesn't occur with LPD mice. The hypothesis is that undernutrition, such as the LPD or Emb-LPD diet, induces responses by the embryo to *enhance* nutrient delivery to the conceptus. When this is an appropriate response, as in the LPD diet, normal growth is the result. But when it is inappropriate, as in the Emb-LPD diet, there is excess perinatal growth. Significantly, if these responses to protect growth are activated, this appears to be the factor that leads to adult cardiovascular disease.

The responses to maternal nutrition by the embryo are induced by the blastocyst stage, and they are independent of the later maternal environment. The blastocyst has three major lineages: the inner cell mass, the trophectoderm and the primary endoderm. All three lineages can be affected by early experience. LPD treatment induces an enhanced

capacity for the yolk sac placenta to endocytose and deliver maternal proteins and amino acids to the fetus to underpin the compensatory growth mechanism. This is mediated mainly by upregulation of the expression of Megalin, a transmembrane endocytic receptor important in yolk sac endocytosis. The Emb-LPD treatment also induces an increase in trophectoderm cells and an increase in the invasiveness of the the trophoblast cells, a further compensatory response.

How do embryos sense their mother's nutritional status? Amino acids could be the signal, because LPD causes changes in the maternal serum amino acid profile as well as the profile of amino acids actually present within the uterine fluid which bathes the preimplantation embryos. It is likely that specific amino acids could signal to the conceptus about the mother's nutrient status. Epigenetic mechanisms are associated with this signalling. At the preimplantation stage the embryo undergoes significant changes in DNA methylation that control the developmental programme. Emb-LPD has been shown to induce epigenetic changes in fetal and adult liver, and there is a growing literature suggesting that epigenetic effects are associated with the preimplantation environment.

Novel approaches to the prevention of osteoporosis throughout the lifecourse

Professor Cyrus Cooper FMedSci
Professor of Rheumatology and Director, MRC Epidemiology Resource Centre, University of Southampton; and Norman Collisson Chair of Musculoskeletal Science, University of Oxford

Over the last three decades, osteoporosis has come of age. This period has witnessed a substantial increase in our understanding of risk assessment and in the number of available drug interventions to reduce the risk of osteoporotic fracture. The remaining lifetime risk of fracture among women aged 50 years in the UK approaches 50%, while that in men of similar age is 20%. The economic burden of osteoporosis (£2.1 billion for the acute management of fractures each year) is similar to that posed by chronic obstructive pulmonary disease (COPD). Fracture pathogenesis depends upon both bone strength and trauma. However, many aspects of bone size, shape, material density and microarchitecture, influence its strength; likewise, the intrinsic and extrinsic determinants of trauma are also complex.

There are two major preventive strategies for osteoporosis: the first entails movement of risk in a beneficial direction by increasing bone density in all members of the population; the second is to target those individuals at highest risk (for example, those with bone density falling below an intervention threshold).

A World Health Organization working group recently produced a fracture risk assessment tool (FRAX), whereby information on nine independent risk factors is utilised to generate a 10-year risk of fracture for any given individual. This 10-year risk is then used to determine whether drug therapy is indicated, or not.

A large-scale MRC trial (Screening of Osteoporosis in Older People [SCOOP]) is now underway. The trial includes seven centres and will aim to recruit 11,580 women aged 70-85 years. They will be randomly allocated to the WHO FRAX risk assessment/ treatment algorithm, or to conventional care, and will be followed-up for seven years, with the principal outcome being the incidence rate of any osteoporotic fracture.

Most of our research on osteoporosis has been focused at the other end of the life course: the period of early development. The term ‘developmental plasticity’ refers to the capacity of the genome to respond variably to the prevailing environment, at critical periods of intrauterine and early postnatal development. When there is a mismatch between the predicted later environment, and that encountered, disease risk is particularly accentuated. Several common, chronic disorders in developed populations (cardiovascular disease, obesity and osteoporosis) appear to have such developmental origins to their later risk. Research at the MRC Epidemiology Resource Centre addresses the developmental origins of adult disease using two types of population study.

The Hertfordshire Cohort Study was based on a series of birth records in the 1920s and ‘30s, with these individuals followed up when they reached age 60-75 years. The study

showed a significant contribution of early development, as indicated by birthweight or weight in infancy, to adult bone mass. The trajectory of intrauterine and early postnatal growth also predicted later risk of hip fracture. The environmental contribution to this relationship was established in a UK twin study, in which the relationship between birthweight and bone mass could not be removed, even when contrasts were made in genetically identical twins.

Further data emerged from mother-offspring cohort studies such as the Southampton Women's Survey. In this study, 12,500 non-pregnant women aged 20-34 years were interviewed in depth and the 3,000 who went on to have children, were studied in detail. The study showed that several maternal characteristics had an effect on bone mass in the offspring. Thus, mothers who smoked, had poor nutrition, and high exercise levels in late pregnancy, all gave birth to infants with reduced bone mass. Most important, from the point of view of intervention, maternal vitamin D status in pregnancy was found to correlate with childhood bone mineral content at age 9 years. The principal determinants of maternal vitamin D status were sunlight exposure and the use of vitamin D supplements. This finding led to the establishment of a randomised controlled trial of vitamin D supplementation in pregnancy, as well as interventions aiming to influence the nutritional choices of women before and during pregnancy, in the city of Southampton.

We have established an animal model in which to replicate these phenomena and study further the underlying mechanisms. Pregnant dams are fed a low protein diet, and their offspring are transferred to a normal diet. Studies of bone samples from these offspring reveal that maternal protein insufficiency results in altered bone mass, shape, microarchitecture and strength. The precise mechanism whereby these effects are induced during pregnancy remains the subject of much interest. It is likely that epigenetic changes are part of the explanation. These entail altered genetic expression by DNA methylation or histone acetylation. Our laboratory studies have demonstrated that glucocorticoid receptor (GR) methylation and expression in the embryo is affected by maternal diet, with reduced methylation on the GR promoter in the low protein diet. Folate administration in the animal model reverses this methylation.

Our future research will continue to explore both the underlying mechanisms for the developmental origins of osteoporotic fracture, as well as interventions to reduce fracture risk throughout the lifecourse.

Metal fume and risk of infectious pneumonia

Professor David Coggon OBE FMedSci
Professor of Occupational and Environmental Medicine, University of Southampton

Our research on metal fume is an example of the use of epidemiology to characterize a previously unrecognised occupational hazard. It started 15 years ago when the Health and Safety Executive (HSE) and Office of Population Censuses and Surveys (OPCS) commissioned us to carry out a national analysis of occupational mortality. This was one of a long-running series of analyses, which have summarised associations using standardized mortality ratios (SMRs) and proportional mortality ratios (PMRs), both being indices of relative risk. We were aware of data from the previous analysis for 1970–72 which showed 66 observed deaths from pneumonia in welders, when the expected number would have been 42, giving an SMR (with 95% confidence interval) of 1.57 (1.21–2.00).

In our data, covering 11 years (1979–80; 1982–90), we were able to break down pneumonia cases into more specific diagnostic categories. The PMR for pneumococcal/lobar pneumonia was 2.55 (1.92–3.32). As well as welders, moulders, furnacemen and sheet metal workers also showed an increased risk of lobar pneumonia. This excess was restricted to men of working age. Our conclusion was that metal fume exposure reversibly increases susceptibility to death from lobar pneumonia. We then went back to data from the 1930s and found the same pattern of excess mortality in men of working age exposed to metal fume.

This work was complemented with a case-control study of 525 men admitted to 11 hospitals in the West Midlands with community-acquired pneumonia, comparing them with 1122 in-patient controls. All were interviewed about their exposure to metal fume. Among the cases, 325 had never been exposed occupationally to metal fume; 142 had last been exposed more than a year previously (odds ratio (OR) 1.1); 11 had last been exposed 8 days–1 year previously (OR 1.8); and 47 had been exposed ≤7 days previously (OR 1.6). There was a clear association with exposure to ferrous metal fume, but because of small numbers, it was not possible to rule out an effect also from non-ferrous metal.

At least two mechanisms might account for this. Oxidant damage leading to impaired immunity is one possibility; another is that free iron in the lung acts as a nutrient for microorganisms.

We then did a biomarker study investigating 27 welders and 31 controls with a range of assays of induced sputum and venous blood. There was increased iron in the sputum of welders, but otherwise the findings in the two groups were remarkably similar. This prompted the hypothesis that repeated inhalation of metal fume blunts the normal

inflammatory response to inhaled particles. In collaboration with the University of Aberdeen, we are now testing this theory by experimental challenge of welders and non-welders.

Vaccines in the treatment of cancer

Professor Freda Stevenson FMedSci
Professor of Immunology, University of Southampton

Some 10–20% of cancers are associated with an infectious agent. It follows that if we can prevent these infections we will prevent the associated cancers. This has already proved to be a successful strategy in some cancers. For example, immunization against hepatitis B virus has led to an associated reduction in liver cancer. Another example is the success of the vaccine against papilloma virus, known to be highly associated with cervical cancer.

But can we harness the immune system in people with cancer? In some cancers this may occur naturally: there are data on the natural suppression of colon cancer by the immune system, where infiltration by T cells accompanies good prognosis.

There are two routes for the immune system to attack cancer: antibody production by B cells, and cytotoxic CD8+ T cells. Passive antibodies can be effective in cancer, usually in conjunction with chemotherapy. Examples would be anti-CD20 in lymphoma and anti-HER2 in breast cancer. Passive transfer of T cells can also work, as evidenced by the graft versus leukaemia effect in allotransplantation. Also, transferred T cells can kill melanoma cells or EBV-infected cells.

Active immunity is even more attractive as an option, but it is hard to induce immunity when cancer cells are already present, because of phenomena such as silencing, immune suppression and tolerance, and also the death and exhaustion of T cells. Vaccination against viruses post infection can be effective (for example, against rabies or smallpox). This sort of strategy is most likely to succeed in cancer where the disease load is minimal.

Molecular genetics has provided us with tools for identifying tumour antigens and then designing appropriate vaccines. In particular, DNA plasmid vaccines show great promise. Mammalian cells are particularly good at sensing bacterial DNA. It is possible to place the sequence of the antigen of choice in a plasmid that contains both immunostimulatory sequences and also the antigen of choice.

It is necessary to 'pep' up weak antigens with microbial sequences, raising the immunity to both. This strategy activates T cell help and breaks tolerance against tumour antigens. For this, we can use fragment C of tetanus toxin, which contains a domain that induces T cell help.

We have conducted a trial looking at the response to DNA vaccines in patients in remission with follicular lymphoma. We detected induction of immunity in 37.5% of these patients, and those who produced stronger responses did better. In order to move to larger trials we have changed the vaccine, first, to use a single antigen for all patients and second, to improve DNA delivery. We are now conducting a range of clinical trials in a number of cancer types.

One example is our prostate cancer trial. Prostate cancer expresses many potential targets. We chose one of them, prostate-specific membrane antigen (PSMA), which we used to construct a DNA vaccine. We found improved performance if we delivered this using electroporation during injection. In a small clinical trial of 30 patients with prostate cancer 71% of patients showed a peptide-specific response, which is unusually high for cancer vaccines, and these responses were durable.

These results are very promising, and we are now moving into a trial of patients with leukaemia. Although regulatory issues raise costs and slow clinical testing, we should soon have defined and objective data on the performance of these novel vaccines in patients.

Anti-cancer monoclonal antibodies: a success for translational medicine

Professor Martin Glennie
Chair of Immunochemistry, University of Southampton; and Director of Tenovirus Cancer Research Laboratories

Monoclonal antibodies (mAb) represent a supreme example of translational research. We can now make human mAb against any specificity in limitless amounts, and more than 20 different mAb are now on the market. The real need, however, is to provide more targets and improved efficacy. A shortage of targets is seen as the primary 'bottle neck' in delivering new drugs and to date only eight mAb have been approved for use in cancer.

There are three ways that mAb can target tumours. They can target the tumour for immune destruction by killer cells or complement, or can block signalling from growth receptors, or can target the tumour environment.

One of the most critical factors for a successful target on a tumour cell is that it must stay on the membrane rather than be endocytosed and thereby no longer be available for recruiting immune destruction by macrophages or complement. In this respect, CD20 on lymphoma and leukaemia seems to be an ideal target because it appears not to internalise when bound by antibody.

Professor Glennie and his team have shown that anti-CD20 antibodies are of two types: Type I (rituximab like) or Type II (tositumomab like). The target specificity of these two types of mAb is indistinguishable at this stage. However, the most striking difference is that Type I mAb activate the complement cascade while Type II do not. Exciting new data however, shows that the Type II mAb, when bound to CD20, remain on the tumour cell surface for much longer than Type I mAb. This result suggests that it might be possible to improve CD20 mAb even further by selecting reagents that persist on tumours longer. When these two types of reagent were used in transgenic mice expressing human CD20 on their B cells, it was found that Type I antibodies are relatively ineffective at removing target cells. There is an initial rapid removal, but target cells start to return after about 7 days. However, Type II mAb cleared B cells for up to 2 months.

How can two antibodies binding to the same epitope have such differences in efficacy? The research team looked at the effector mechanisms and found that the clearance of target cells by both Type I and II mAb was completely dependent on Fc receptors that bind to antibody. These Fc receptors are found on many cells but it is the macrophages that seem responsible for clearing Ab-coated B cells. Thus there was no obvious difference in their mechanism to explain the differences in efficacy. Interestingly, however, they found that the rituximab (Type I) reagent was internalised much more readily by target cells resulting in Ab consumption and short drug half-life.

These data show how important basic science with good animal models can be in understanding mechanisms of action and improving efficacy. The Southampton Ab team are repeating this work with human cells, and think that the results will be highly relevant

to human malignancies such as leukaemia and lymphoma. For example, rituximab is currently the treatment of choice for lymphoma where most data suggest that it does not modulate. However, it doesn't work on chronic lymphocytic leukaemia (CLL), where it is consumed in huge amounts. The results from Professor Glennie indicate that this might be because of internalization and breakdown by the tumour.

Currently, seven CD20 mAb are in advanced stages of development to replace rituximab. The competition to provide an improved rituximab is huge, driven by the US$3–4 billion annual income from this drug alone. The work from Southampton suggests that a Type II mAb might provide a good replacement.

The lessons from this work are that a fuller understanding of basic Ab biology, particularly epitope binding, will deliver improved drugs for humans.

The identification of novel therapeutic targets in asthma

Professor Stephen Holgate FMedSci
MRC Clinical Professor of Immunopharmacology, University of Southampton

Despite five decades of massive investment in asthma research, the management of this disease has not advanced that much. We have just two types of drug available: bronchodilators and corticosteroids. However, various combinations of these give relatively good clinical benefit for the majority of patients providing they take their treatment regularly.

We have over-simplified asthma to the point where we thought we understood it, but some key questions have yet to be answered. What is it? Who gets it and why? And what causes exacerbations? Allergic pathways are only partly responsible.

The healthcare burden of exacerbations is enormous, and this represents an unmet clinical need. Because of these sudden, unexpected attacks, having asthma is like living on a knife-edge for many people.

Data on hospitalizations from asthma show that respiratory infection is at least as important in triggering exacerbations as the allergy component, because of extreme peaks in autumn and winter months which correlate with the winter peaks in infections.

In conjunction with the late David Tyrell FRS, we developed a new molecular test for the common cold virus (rhinovirus), and then using this to detect viral infection, undertook a longitudinal study in children. Virus was detected each time where there were episodes of exacerbation. Airway biopsies showed that virus was present in the epithelial cells of the lung. Alergy is also associated with asthma: exposure to allergens gives an increased risk of hospital admission with an odds ratio of 2. With both virus infection and allergen exposure this rises to an odds ratio of 9.

In experiments where young asthmatics are infected with rhinovirus, they show increased lower respiratory symptoms than normal subjects. Also, if epithelial cells from asthmatic subjects are grown in culture and infected with virus, they respond differently to epithelial cells from controls. The epithelium is abnormal in asthma, showing a defect in innate immune responses to rhinovirus. In particular, these cells fail to produce Interferon β (IFNβ) in response to infection. In normal epithelial cells, IFNβ is responsible for suppressing viral replication in the cell.

The logical translation of this work is that inhaled IFNβ may help prevent asthma exacerbations caused by rhinovirus infection. The medical school at Southampton helped us set up a university spin-out company called Synairgen, which raised sufficient funds for us to do this translational research. We have passed the safety study and are currently about to enter efficacy studies.

But this is not the end of the story. We are also interested in what is wrong with the asthmatic epithelial cells. The Toll-like receptor 3 (TLR3) is important in signalling the innate immune response of the epithelium to virus infection, and this is impaired in asthma. Asthmatic epithelial cells are capable of inducing a good secondary response to interferon with upregulation of all the anti-viral genes; the problem seems to be at the initial signalling through TLR3 to initiate the IFNβ response. We now have the opportunity to pull together the infection with the allergy story, and it is likely that the allergen pathways and viral pathways converge at some point. The current thinking in the field is moving towards considering asthma as a disorder of innate immunity, and therapies concentrating on enhancing innate immunity in the airways may prove to be effective.

Impact of systemic infection on the diseased brain

Professor Hugh Perry FMedSci
Professor of Experimental Neuropathology, University of Southampton

While translational science has been effective in many disease areas, it has not done well in the treatment of neurological disease. One of the problems has been the hunt for a 'cure'. What does 'cure' mean in the context of Alzheimer's disease, for example? Attempts to arrest disease progression and improve quality of life may matter more for chronic neurodegenerative disorders than cures.

Our specific interest is the contribution of inflammation to neurodegenerative disease, and it turns out that looking below the neck - even though we are dealing with the brain - is important.

Microglia, specialized types of macrophages, are the immune cells of the brain. They are quiescent in healthy brain but when injury occurs they change their morphology and become activated. They can have many different phenotypes, and are dynamic, capable of being switched from one phenotype to another.

Between one-quarter and one-third of 80 year olds will have Alzheimer's disease, which is progressive, irreversible and largely untreatable. It is characterized by the presence of amyloid plaques and neurofibrillary tangles. In addition, resident microglia are activated, and appear to produce pro-inflammatory cytokines.

An animal model for human Alzheimer's disease is prion disease in mice, a fatal, progressive neurodegenerative disease in which misfolded amyloid protein accumulates in the brain, with associated activation of microglia. We looked in this mouse model for the presence of the same pro-inflammatory cytokines, but didn't find them. The inflammatory response in mouse prion disease is benign and there is no evidence that this contributes to the behavioural deficits at the early stages of disease.

What is the explanation of the difference between mice and people? It could be co-morbidity. Most people who die of Alzheimer's die with systemic infections. The reason people feel ill or sick when they have infections is because the local inflammatory response to infection is generating cytokines, which in turn communicate with the brain in part via the microglia, causing changes in behaviour.

So we gave our mice with prion disease a small dose of endotoxin. This causes fever in the mice and all sickness behaviours are exaggerated. We found that the microglia are switched from a benign phenotype to an aggressive proinflammatory phenotype, which is associated with a rapid increase in the number of neurons undergoing apoptosis.

These results led us to do a clinical study of 300 subjects with Alzheimer's disease. Their carers kept a diary of the presence of infections, and we measured blood cytokines. At least half got one or more infections over a six month period. Using the Alzheimer's Disease Assessment Scale (ADAS) cognitive score we monitored cognitive decline, and found that it was significantly accelerated in patients with infections over this six month period.

It appears that systemic infection switches the innate immune memory state of microglia from a benign to an aggressive response. Because of these observations, we would like to consider a therapeutic intervention in Alzheimer's patients to treat systemic infections and appropriate anti-inflammatory drugs.

Appendix I programme

Translating new research into clinical practice: Southampton symposium

Thursday 26 February 2009, Wessex Heartbeat Centre, Southampton General Hospital

09.30 Registration

Morning session chaired by Professor Freda Stevenson FMedSci

Welcome

10.00 Professor Iain Cameron, School of Medicine, University of Southampton

Academy of Medical Sciences: translational medicine and the Fellowship

10.10 Professor Sir John Bell FRS PMedSci, President, Academy of Medical Sciences

Epigenetic and environmental influences on disease

10.20 Malnutrition during development and disease in later life
Professor David Barker CBE FRS FMedSci, Professor of Clinical Epidemiology, University of Southampton

10.50 Embryo environment and its association with adult health and disease
Professor Tom Fleming, Professor of Developmental Biology, University of Southampton

11.30 Novel approaches to the prevention of osteoporosis throughout the lifecourse
Professor Cyrus Cooper FMedSci, Professor of Rheumatology, University of Southampton & Director of MRC Epidemiology Resource Centre

12.00 Metal fume and risk of infectious pneumonia
Professor David Coggon OBE FMedSci, Professor of Occupational and Environmental Medicine, University of Southampton

12.30 Lunch

Afternoon session chaired by Professor David Barker CBE FRS FMedSci

Immunity and inflammation; friend or foe?

13.30 Vaccines in the treatment of cancer
Professor Freda Stevenson FMedSci, Professor of Immunology, University of Southampton

14.00 Anti-cancer monoclonal antibodies: a success for translational medicine
Professor Martin Glennie, Chair of Immunochemistry, University of Southampton & Director of Tenovus Cancer Research laboratories

14.40 The identification of novel therapeutic targets in asthma
Professor Stephen Holgate FMedSci, MRC Clinical Professor of Immunopharmacology, University of Southampton

15.10 Impact of systemic infection on the diseased brain
Professor Hugh Perry FMedSci, Professor of Experimental Neuropathology, University of Southampton

Academy of Medical Sciences: future outlook

15.40 Mrs Mary Manning, Executive Director, Academy of Medical Sciences

Closing remarks

16.00 Professor Stephen Holgate FMedSci & Professor Freda Stevenson FMedSci

16.10 Tea (close 17.00)

Appendix II Symposium delegates

Dr Peter Adura, Clinical Research Fellow, Roger Brooke Laboratory, Division of Infection, Inflammation and Repair, University of Southampton

Jennifer Allison, Senior Nurse Manager, Wellcome Trust Clinical Research Facility, Southampton General Hospital

Dr Qian An, Senior Postdoctoral Research Scientist in Leukaemia Genetics, Cancer Genomics Group, Cancer Sciences Division, University of Southampton

Dr Frazer Anderson, Senior Lecturer in Geriatric Medicine, Division of Developmental Origins of Health and Disease, University of Southampton

Professor Nigel Arden, Professor in Rheumatic Diseases & Consultant Rheumatologist, MRC Epidemiology Resource Centre, University of Southampton

Dr Michael Ardern-Jones, Senior Lecturer in Dermatology, Division of Infection, Inflammation and Repair, University of Southampton

Dr Ayodeji Asuni, Research Fellow, CNS Inflammation Group, School of Biological Sciences, University of Southampton

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