Dr Andras Falus, Dr Joe Keane, Dr Doug Veale and Prof Cliona O’Farrelly (ISI president) at the recent ISI Annual Meeting.

I think everyone will agree that the recent Irish Society of Immunology Annual Meeting held in Dublin was one of the most successful meetings to date. The theme of the meeting was ‘Immune Regulation in Health and Disease’ - this encompassed almost every area in immunology and ensured that there was
something for everyone. The line-up of invited speakers was world class and it was a real privilege to listen to speakers such as Jules Hoffman, Andras Falus and Simon Carding. There were also some fantastic talks from those a bit closer to home including David McHugh, David Lynn, Seamas Donnelly, Douglas Veale, Derek Doherty, Joe Keane and Padraic Fallon. The standard of open papers and posters was extremely high and generated lots of interesting discussion. The prize for best open paper went to Ronan Mullan from the Department of Rheumatology, St Vincent’s University Hospital, Dublin for a fantastic talk entitled ‘A novel role for serum amyloid-A in angiogenesis and adhesion molecule expression through an NFkB-dependent signal transduction pathway’. The prize for best poster went to Hameda Asrafel for her presentation entitled ‘Circulating natural killer cells are depleted in chronic HCV infection’. Even though the scientific programme was packed there was still time for a lovely dinner in the Courtyard restaurant and a few drinks afterwards to catch up with fellow immunologists. All in all it was a huge success and a big thank you to all the hard-working committee members for organising it. Looking forward to the next one!!!! Here are some photos of some of the immunologists who attended.
Irish Society of Immunology
Annual Award & Public Lecture

The science of immunology impacts on almost every aspect of human and animal health and immunology research is critical to the discovery of new ways of preventing and treating disease. Immunological expertise is key to designing vaccines against killer pathogens including HIV, influenza virus, TB, malaria and Hepatitis C as well as developing therapies for the major non-infectious diseases in our society, cancer, arthritis, asthma and allergy.

The Irish Society of Immunology has established an Annual Award in recognition of major contribution by an Irish immunologist to the understanding of Immunology. Each year the recipient of the ward is invited to give a Public Lecture on an aspect of their work that will be of interest and relevance to a general audience.

The primary aim of the award is as a vehicle to bring immunology and immunological debate to the general public. It was interesting that during the MMR and foot and mouth crises, no immunologist contributed to the national debates and any immunological information was presented by vets in the latter case and public health specialists in the former. I think one of the aims of our society should be to encourage our members to contribute to public understanding of immunological issues. So we elder lemons should be encouraging all the younger people to go to secondary schools, talk with science teachers, go on television and radio, write newspaper articles etc. Anyone who does this could then be eligible for the award and they could then give the public lecture on the issue of most interest to them rather than just their own research work.

Prof Luke O’Neill, Trinity College Dublin

It would be an honour for me to propose Prof Luke O’Neill for the ISI award for 2004, or indeed for any award within biomolecular/ biomedical sciences, in Ireland. In my humble opinion, he is by far the outstanding biologist of our time in Ireland, and is the one scientist who, within a very competitive discipline, has achieved real international status as an achieving researcher of very high ability.

His consistent publication record in high impact journals, his proven ability to attract significant national and international funding, (although SFI, to their eternal shame did not recognise him first time round!!), his ability as a communicator of his subject, and his enthusiasm for his own research and support for that of others, mark him out, in my mind, as a truly great scientist.

Prof Luke O’Neill has accepted this award and the public lecture will be held in May.

Cliona O’Farrelly
ISI president
ISI members are involved in world class research not only in what would be considered classical immunology such as antibody production and immune regulation but also in many related areas such as – vaccine delivery systems, virology, signal transduction, veterinary medicine and endocrinology. It would be of interest to our readers to know who is publishing what and where. As you all know “The Paper” represents the culmination of all our hard work and the only tangible measure we have of our success or progress. This section of our newsletter highlights recent publications by ISI members. Cytokines are central to the immune response as they form an integral part of the cell to cell communication network at both local and systemic levels. Immuno-modulation via the induction or inhibition of cytokines has recently received much attention both as a therapeutic and as a vaccine development strategy. Altering cell behaviour or immune outcome through manipulation of the cytokine network can be achieved using many agents including antibodies, vaccine adjuvants or cytokines themselves.

Prof. Kingston Mills group based in Trinity College Dublin are involved in vaccine development. They have previously shown that cholera toxin (CT, vaccine adjuvant) induces T-regulatory type 1 cells (Tr1) as well as T-helper type 2 cells (Th2). Their recent study for publication in The Journal of Leukocyte Biology demonstrates that CT synergizes with LPS to induce IL-6, IL-1β and IL-10 production by immature dendritic cells (DC). They propose that CT modulation of DC cytokine production contributes to the induction of Tr1 and Th2 cells thus inhibiting innate immune responses induced by LPS [Lavelle et al. J Leukoc Biol (2004) 2; Epub ahead of print]. Alteration of cell behaviour in vitro in response to cytokines has given us insight into the role of cytokines in vivo. Cytokines act in a dose dependent manner and can have opposing effects at different concentrations. Our estimation of physiological concentrations of a cytokines is largely derived from serum; however, in the context of organ-specific immunity local concentrations may differ greatly from systemic levels. Information on organ-specific cytokine protein levels is sparse in the literature although abundant at an mRNA level. Prof. Cliona O’Farrell’s group (St Vincent’s University Hospital) has a particular interest in liver-specific immunology and has begun to address the issue of tissue levels of cytokines. Their forthcoming paper in the March issue of Cytokine measures the actual level of IL-12 protein in normal and tumour-bearing liver. Using this concentration of IL-12 they demonstrate expansion of specific T cell subsets in vitro. However, direct ex vivo characterization of T cell populations isolated from the liver suggest that the effects seen in vitro are not mimicked in vivo. Cytokines act in overlapping cascades which serve to enhance or inhibit the actions of other cytokines. These findings highlight the difficulty in studying cytokines in isolation. And as they conclude themselves, it is the balance and interplay between many cytokines in the liver that will ultimately determine the outcome of the response [Kelly et al. Cytokine (2004) 25:273-282].

We would like to hear from you about your area of interest and recent or forthcoming publications. So please do send details to lucy.golden@ucd.ie and we will highlight your achievements in
the next issue of our newsletter.

Lucy Golden Mason, ERC St Vincent’s University Hospital.

Meeting Reports

Annual Congress of The British Society for Immunology, 2-5 December 2003, Harrogate, UK.

The following are two reports on BSI 2003.

It’s getting colder, the days are getting shorter and Christmas is just around the corner. It must be time for the annual lab trip to North Yorkshire. Despite talk of diverting us to another airport because of the fog, we landed at Leeds-Bradford more or less on schedule. And lucky we did, because for me one of the first sessions proved to be the highlight of this year’s conference. This session, intriguingly entitled “The good and bad aspect of horror autotoxicus”, was put together jointly by the Tumour Immunology and Autoimmunity Affinity Groups. Although it was spread over two days and covered a lot of topics, part one largely focused on regulatory T cells (Tregs). Many of the presenters began with an overview showing that Tregs can occur naturally (CD4⁺CD25⁺) or may be induced (Tr1).

L. Taams (London, UK) reviewed her group’s recent work into the presence, phenotype and function of naturally occurring CD4⁺CD25⁺ T cells in rheumatoid arthritis. Whilst 11% of CD4⁺ T cells in the peripheral blood of healthy controls co-expressed CD25, this cell population was raised in the peripheral blood (PB) and synovial fluid (SF) of patients with rheumatoid arthritis. Furthermore, PB CD4⁺CD25⁺ T cells from patients expressed intermediate levels of CTLA-4 and GITR, and less than 10% co-expressed markers of activation such as CD69, MHC class II and OX40. In contrast, SF CD4⁺CD25⁺ cells expressed high levels of CTLA-4 and GITR, and more than 50% were CD69⁺, MHC class II⁺, OX40⁺. When tested in an in vitro model, these synovial Tregs demonstrated increased suppressive ability, compared to patient-derived PB Tregs and also produced lower levels of TNF-α, IFN-γ and IL-10. Taams concluded that her data suggests the presence of a negative feedback system at the site of inflammation.

Moving away from naturally occurring CD4⁺CD25⁺ T cells, S. Gregori (Milan, Italy) showed that Tregs can also be induced. Dendritic cells were differentiated and/or matured in the presence of exogenous IL-10 or anti-CD45RO/RB mAbs and used, with tetanus toxoid (TT), to repetitively stimulate allogeneic naïve CD4⁺ T cells. Following two challenges with TT, anergic cells were generated which, when co-cultured with TT-specific cells, caused a dose-dependent inhibition of proliferation. These generated cells were not CD25⁺ and expressed intermediate levels of CTLA-4 and GITR, however they appeared to be less activated and produced more IL-10 and TGF-β than unmodified cells. Addition of anti-IL-10R inhibited the suppression of IL-10-treated cells, but only partially inhibited the suppression of anti-CD45-treated cells, suggesting that IL-10 is not the sole regulator of Tr1 development.

As part of the meeting’s plenary session, this year entitled “Genetic influences on the immune system”, L. Glimcher (Boston, USA) gave a fascinating overview of the roles of the transcription factor T-bet. Based mainly on research in the mouse, T-bet is highly expressed in Th1 cells and regulates IFN-γ production in CD4⁺, CD8⁺ and NK cells by transcriptionally activating the IFN-γ gene. In CD4⁺ cells, T-bet not only represses the production of Th2 cytokines, but can also redirect fully polarised Th2 cells into Th1 cells. In the absence of T-bet, EAE-susceptible mice...
are protected from EAE (due to decreased IFN-γ and raised IL-10 production), suggesting that blocking T-bet could be important in controlling autoimmune diseases. Moreover, T-bet-deficient CD8+ T cells fail to acquire an effector phenotype following antigenic stimulation. As with CD4+ cells, this is thought to be largely due to diminished IFN-γ production, together with elevated IL-2 and Tc2 cytokine secretion. Finally, DCs also require T-bet for optimal IFN-γ production, a factor which further impacts on Th1/Th2 polarisation.

Human CD8+ T cells were the focus of a presentation by R. Solana (Cordoba, Spain) in a session entitled “Chronic infection and regulation in the immune system”. The data presented showed the distribution of CD8^{bright} T cells, according to naïve, central memory, effector memory and effector phenotypes. Whilst the naïve and central memory subpopulations were predominantly CD28−, effector memory and effector CD8^{bright} T cells contained both CD28 and CD28+ subsets. Moreover CD8^{bright}CD28− T cells more often expressed NK cell markers. CD8^{bright}CD28− T cells are known to be increased in elderly individuals, and the author showed that this is due to an accumulation of effector memory cells, rather than an expansion of effector cells.

On a similar theme, our own Denis Reen presented an overview of the homeostatic expansion and differentiation of newborn T cells. Denis showed how human neonatal CD4+ T cells (recent thymic emigrants) undergo expansion and maturation in response to antigen, and how newborn CD4+, CD8+ and NK-receptor+ T cells demonstrate varying levels of responsiveness to common γ-chain cytokines, in an antigen-independent manner. Notably, following culture with IL-15, newborn CD8^{*}CD45RA+ T cells differentiated into effector memory cells (as defined by production of IFN-γ and TNF-α, together with decreased expression of CD62L, CCR7 and CD45RA). In contrast, although adult CD8^{*}CD45RA+ cells cultured with IL-15 also produced IFN-γ and TNF-α, they divided more slowly and maintained their naïve phenotype.

Fortunately, our flight back home wasn’t until 8pm, so I spent a happy Friday afternoon immersed in Harrogate’s many second-hand bookshops. Unfortunately, our flight ended up being delayed by over two hours because Dublin was fog-bound….However, despite the trip ending on sour note, this year’s BSI meeting highlighted advances in a range of important issues for anyone working in the field of immunology and as such, provided great food for thought. See you in Betty’s next December?

Sharon Cookson
University College Dublin

BSI Congress 2003 was attended by over 1500 delegates and over 100 invited speakers covered large number of important topics. With so many sessions you could choose to focus on one topic or try and broaden your knowledge of general immunology as I did.

My report concentrates on plenary session devoted to current concept on genetic influences on the immune system and represents only one major topic of the conference. For those interested in other areas covered at Congress 2003, the conference abstracts have been published in Immunology.

The plenary session provided a timely review of the progress made in the field in the past 10 years. C. G. Mathew (King’s College) turned our attention to the contribution of the NOD2 gene (now called CARD15) in susceptibility to inflammatory bowel disease. Mutations in the gene are known to be associated with susceptibility to Crohn’s disease. Inheritance of one of the three common mutations increases disease risk three fold. CARD15 mutations although
associated with Crohn’s disease do not increase the risk of the other form of inflammatory bowel disease such as ulcerative colitis. Recently his group obtained genetic evidence for an interaction between CARD15 and a Crohn’s disease susceptibility locus at the cytokine gene cluster on chromosome 5q31. This lecture clearly showed that the discovery of CARD15 role in Crohn’s disease provides support for efforts to define genetic pathways underlying the pathogenesis of inflammatory disorder.

To commemorate the discovery of the major histocompatibility complex in 1936 by Dr. Peter Gorer, Guy’s Hospital Medical School have endowed a Peter Gorer Lectureship. This is administered by the BSI and a Peter Gorer lecturer is appointed every three years. This year the Peter Gorer Lecture was given by Peter Parham (Stanford University). We were treated to an excellent review of Killer cell immunoglobulin like receptor – species specific components of innate immunity. Killer cell Ig-like receptors (KIR) are encoded by a compact gene-rich family, which forms part of the leukocyte receptor complex on human chromosome 19q13.4. KIR are expressed on the surfaces of NK cells, some γδ T cells and some memory αβ T cells, most of which express CD8. Apparent from this cellular distribution is that KIR have the potential to function in both innate and adaptive immunity. The KIR family includes both inhibitory and activating receptors of various specificity for HLA class I ligands. The inhibitory class I-specific KIR protect autologous cells from NK cell attack and are indirectly responsible for alloreactive NK cell responses toward targets lacking a cognate HLA class I ligand. For patients receiving an HLA-mismatched hematopoietic-cell transplant for acute myelogenous leukemia, an alloreactive response directed toward the recipient’s cells and mediated by donor-derived NK cells can help eliminate residual leukemia and prevent graft-vs-host disease. Although the functions of the activating KIR remain poorly defined, KIR3DS1 is associated with slowed progress of HIV infection for patient’s having a cognate HLA-B ligand. KIR associations have also been reported with autoimmune conditions and with outcome following HLA-matched hematopoietic cell transplantation. KIR-HLA class I interactions are also implicated in the contribution made to implantation and establishment of pregnancy by intrauterine NK cells during the first trimester. Underlying the biological functions and clinical associations of the KIR gene family is a degree of genetic diversity, which may approach that of the MHC class I genes. Human KIR haplotypes differ in the number of genes they contain (7–15 genes) and are further diversified through allelic polymorphism of individual genes. As a consequence, unrelated individuals almost always differ in KIR genotype. Because KIR haplotypes differ in the number of activating receptors they encode. KIR genotypes range from ones biased for inhibition to ones rich in activating receptors. Such range has the potential to modify NK cell responses in qualitative, as well as quantitative, ways. Because NK cells respond early during infection and influence its subsequent course, and the immune response to it, an appealing hypothesis is that KIR diversity is the consequence of past selection by pathogens upon the NK cell response. Comparison and compilation of population studies reveal extensive KIR genotype variability within human populations and among them. Genomic analysis shows the KIR genes to be close to each other and separated by homologous sequences that promote haplotype diversification through asymmetric recombination. In contrast, homologous recombination appears
favoured at a unique sequence in the centre of the KIR locus, and much haplotypic diversity can be explained by recombination between a limited number of gene-content motifs in the centromeric and telomeric halves of the locus. The importance of NK cells for early defences against infection suggests that human KIR genotype diversity is the accumulated consequence of a history of numerous and successive selective episodes by different pathogens on human NK-cell responses.

L Glimcher (USA) presented his data on T-bet transcription factor in control of type 1 immunity. T-bet, a T helper 1 (Th1)-specific transcription factor previously isolated and characterized in his laboratory, has been shown to be required for the development of the CD4+ Th1 subset. T-bet directly activates transcription of the IFN-γ gene and has the remarkable property of redirecting committed Th2 populations to a Th1 phenotype. The importance of T-bet in Th1 immunity has been most clearly illustrated through the analysis of mice with a targeted disruption of the T-bet locus. CD4+ T cells lacking T-bet are severely impaired in their ability to produce IFN-γ, yet secrete elevated levels of the opposing Th2 subset cytokines, IL-4 and IL-5. Furthermore, T-bet-deficient mice, on the otherwise resistant C57BL/6 background, are highly susceptible to Leishmania major infection, are protected from autoimmune inflammatory bowel disease, and spontaneously develop inflammation and airway remodelling resembling human asthma, indicating a marked in vivo shift of the Th1/Th2 balance toward the Th2 pathway. Dr. Glimcher and his team also demonstrated that the generation and function of the effector CD8+ T cell compartment relies on the transcription factor T-bet. T-bet therefore directs lineage commitment and effector function of naïve progenitor cells of both major T cell subsets, making it an overall regulator of type 1 immunity. Although roles in both CD4 and CD8 T cell function have been described, the mechanism by which T-bet directs effector differentiation in these two cell types is not fully understood. No doubt, T-bet should prove an attractive target in designing strategies to augment type 1 immunity against known and novel microorganisms.

The session was concluded with Promega Young immunologist of the Year Award presentation. The prize was given to B. Javid of Addenbrooke's Hospital Cambridge for his work on presentation of mycobacterial heat shock protein/antigen complex by human dendritic cells.

As every year Congress social activities were well organised and provided an opportunity to meet old colleagues and to set up new collaborations and friendships with immunologists sharing a common interest.

Greg Skibinski
Queen's University of Belfast

**TUBERCULOSIS – The most successful bug in the world**

One in 3 people worldwide are latently infected with *Mycobacterium tuberculosis* (Mt), the causative agent of tuberculosis (TB). Eight million new cases of TB are reported each year, leading to 3 million deaths, and these numbers continue to rise. The mycobacterium has been interactive with all that our genome can throw at it for millennia. There is more TB than ever, so it looks like the bug is winning, and the human immune system is losing. In Ireland, the incidence of active TB was 11.7 per 100,000 in 1998 (424 cases), which is higher than in countries such as Norway, Sweden and the USA, but lower than in countries such as Austria and Germany. In those countries up to 50% of the patients are foreign-
born, whereas in Ireland foreigners accounted for only 8% of the reported cases in 1998 [Smith et al. 2000]. This percentage may increase however, because globally the incidence of TB continues to rise. One of the challenges is for the Irish health system to offer new immigrants to this country, a chance to have latent TB infection diagnosed and treated to prevent the immigrant and the community suffering for further TB.

Tuberculosis is primarily a pulmonary disease (75% of cases), spread by inhalation of aerosol droplets containing tuberculosis bacilli, but it can also spread to other organs and tissues. TB meningitis is a particularly deadly form of disseminated TB. Early detection and appropriate treatment are crucial to stemming the spread of tuberculosis. The gold standard for the diagnosis of tuberculosis is the culture of $M. tuberculosis$ from a patient sample, but this can take up to 7 weeks, as pathogenic mycobacteria grow very slowly. TB is treated with a cocktail of antibiotics, which have to be taken for up to 9 months. Drug resistance is becoming a grave concern globally but the incidence of drug-resistant isolates in Ireland is still low (1-1.5%). It is important that the molecular techniques for the rapid identification of TB drug-resistance be set up and available in Ireland.

The incubation period for TB can extend for decades. You can be infected as a child, and suddenly reactivate to develop active disease in your 70’s. The immune system is crucial in containing the disease, as reactivation can follow an episode of immunosuppression. TB is an AIDS-defining illness, but the incidence of HIV-TB co-infection in Ireland is not known. Recent data suggests that TNF-blocking agents can cause reactivation tuberculosis. This has informed us on the important of this cytokine in the host response to infection and in maintaining the bacillus dormant in the confines of the protective human granuloma.

The only current vaccine against TB is the Bacille Calmette-Guerin (BCG), a live attenuated strain of $Mycobacterium bovis$. The vaccine does not appear to prevent infection with $M. tuberculosis$, but may protect from development of active disease in children. Most infants in Ireland receive the BCG vaccine, but we need to develop a more effective replacement. It is especially important for us to understand better the immune response to this agent so that we can design a more effective vaccine.

Macrophage apoptosis is an important aspect of the immune response to Mt. A lab in Germany are working on a vaccine that maximises macrophage apoptosis after infection. This in turn will result in better antigen presentation and better Cell Mediated Immunity to the bacillus. Tuberculosis bacilli survive and multiply intracellularly after having being phagocytosed by macrophages. To do this, they have devised the most ingenious immune evasion strategies. They are able to actively inhibit phagosomal acidification, maturation, and fusion with lysosomes, thereby effectively crippling the macrophage’s ability to eliminate the infection. However, the macrophage can respond to infection by going into apoptosis. Macrophage apoptosis is a known defence strategy against intracellular pathogens, including viruses. Macrophage apoptosis is abundant in tuberculosis granulomas and in broncho-alveolar-lavage from tuberculosis patients. $M. tuberculosis$ induces apoptosis of human alveolar macrophages in a TNF-dependent manner [Keane, 1997]. Apoptosis of infected macrophages prevents bacterial dissemination and ingestion of bacilli contained in apoptotic cells results in efficient killing of $M. avium$, another pathogenic mycobacterium [Fratazzi, 1997]. These data suggest that apoptosis
is a beneficial element of the host response to tuberculosis infection. The ability of mycobacteria to avoid host cell apoptosis correlates with mycobacterial virulence [Keane, 2000]. Infection with avirulent mycobacteria such as BCG results in macrophage apoptosis and bacillary killing, which is IFN-\(\gamma\) independent [Keane, 2002]. Virulent mycobacteria such as \(M.\) \(tuberculosis\) prevent this apoptosis and continue to replicate inside the macrophages [Keane, 2000]. Transcriptome analysis of infected macrophages demonstrates that virulent mycobacteria manipulate gene expression to prevent apoptosis [Spira, 2003]. This suggests that mycobacterial virulence determinants act to avoid the apoptotic response to infection.

The induction of apoptosis by mycobacteria is dependent on TNF-\(\alpha\) signalling, but the precise mechanism is not known, nor is the mechanism of blocking of the apoptosis response by virulent mycobacteria. We are attempting to dissect this important part of the innate immune response to mycobacterial infection in our newly established TB Immunology laboratory, which is part of the Dublin Molecular Medicine Centre at St. James’s Hospital. We study the interaction of mycobacteria and human macrophages in vitro by biochemical techniques and microscopy. We have established fruitful collaborations with the Molecular Signalling group of Yuri Volkov and with the National Mycobacteria Reference Laboratory at St. James’s Hospital, headed by Noel Gibbons. In addition we are collaborating with Cellestis Ltd to evaluate the Quantiferon assay as a possible diagnostic tool for early diagnosis of tuberculosis infection. The long term goal of our research is to identify the mycobacterial virulence factors which manipulate the host immune response; and to use that information to design therapies or improved vaccines against tuberculosis.

\[\text{Dr. Annemieke ten Bokum PhD & Dr. Joseph Keane MD, Institute of Molecular Medicine, St James's Hospital}\]

**ISI Travel Bursaries**

The ISI will be awarding 5 travel bursaries this spring of €300 each to graduate students whose work has been accepted for presentation at an international meeting. Applications for consideration should be submitted to Michelle Armstrong (ISI secretary), Dept. Biochemistry, TCD, by the 31st March for review including a copy of the abstract. Please make sure to send in applications in plenty of time, as the deadline will be strictly adhered to. All those who receive a bursary will be expected to write a short meeting report for publication in the ISI newsletter.

**ISI MEMBERSHIP**

**Annual Membership: € 40**

**Benefits:** Reduced registration for ISI meetings  
Free admission to ISI events (public lectures, workshops, etc.)  
Reciprocal membership: Ulster Immunology Group  
Access to ISI directory  
Free subscription to ISI newsletter

**Postgrads** - Eligibility for travel bursaries  
- Oral & poster prizes at ISI
Prof Colm O’Morain (President ISG), Dr Lucy Golden Mason and Mr Enda Scott, AstraZeneca.

Irish Society of Gastroenterology Winner

Dr Lucy Golden-Mason, from St Vincent’s University Hospital Education and Research Centre, was awarded first prize for Best Oral Presentation at the Irish Society of Gastroenterology Winter Meeting. Lucy’s presentation identified the chemical pathway underlying biliary cirrhosis and highlighted the balance between cytokines in the liver. The ISI would like to congratulate Lucy on her fantastic achievement.

A causal link between bone disease and intestinal inflammation

Bone destruction and intestinal inflammation in certain autoimmune disorders are closely linked with deregulation and hyper-activation of autoreactive CD4 T cells. How these T cells are activated and mediate disease is not clear. One family of ligands and cell-surface-receptors that has been shown to have an increasing role in regulating a variety of cellular functions including differentiation, survival and death are those of the TNF superfamily. The TNF family molecule, Ligand for Receptor Activator of NFκB (RANKL) and its receptor RANK are important regulators of bone turnover and are essential for the generation and activation of bone-resorbing osteoclasts (Theill et al, 2002). Of particular
interest to our own work were studies suggesting that RANK/RANKL interactions may also serve as molecular links in other systems, including the immune system. RANKL-expressing T cells has been shown to mediate the survival, activation and cytokine secretion by RANK-expressing, bone marrow-derived dendritic cells (DC) in vitro (Anderson et al, 1997; Josien et al, 1999, 2000; Wong et al, 1997). Most intriguing was the finding that treatment of mice with a recombinant chimeric form of RANK (RANK-Fc) enhanced the induction of oral tolerance to prototypical protein antigens (Williamson et al, 2002). Together these observations suggested that RANK/RANKL interactions might be important in regulating and determining the outcome of immune responses in a variety of tissues and in particular, the intestine. Abnormalities in the regulation of RANK/RANKL interactions might therefore be a common feature of autoimmune disorders characterised by chronic or uncontrolled T cell activation.

To investigate this further we examined Interleukin-2 deficient (IL2−/−) mice that spontaneously develop an autoimmune disorder, a hallmark of which is hyperactivation of CD4 T cells leading to production of autoantibodies and anemia, and an inflammatory bowel disorder (IBD) that resembles ulcerative colitis (Schimpl et al, 2002). Intestinal inflammation is mediated by CD4 T cells which inappropriately respond to members of the commensal gut microbiota (Contractor et al, 1998).

In this study (Ashcroft et al, 2003) we showed that these animals also develop a profound osteopenia characterised by a progressive loss of bone mineral density, cortical bone thinning, and the accumulation of osteoclasts within the trabecular bone. The absence of osteopenia in T cell-deficient, IL2−/− (TcRβ− x IL2−/−) mice and the ability of (CD4+) T cells from IL2−/− mice to transfer disease to otherwise healthy (Rag1−/−) mice identified T cells as being the cause of bone disease in vivo. The mechanism of T cell-mediated bone disease was shown to be related to excessive production of RANKL as demonstrated by increased RANKL mRNA and protein levels in bone marrow mononuclear cells and serum, respectively of affected mice. IL2−/− T cells also expressed abnormally high levels of cell surface RANKL, consistent with them being a major source of RANKL in vivo. Confirmation that abnormalities in the regulation of RANKL/RANK interactions was the cause and not an effect of bone disease was obtained by treating IL2−/− mice with recombinant osteoprotegerin (OPG), a naturally occurring decoy receptor. OPG treatment completely reversed bone loss, resulting in increased bone density, increased trabecular bone and absence of osteoclasts in treated compared to non-treated animals.

Most strikingly, OPG treatment also had a beneficial effect on the development of colitis in IL2−/− mice. There was a preservation of colonic tissue architecture and organisation with an accompanying decrease in the inflammatory cell infiltrate in treated compared to non-treated IL2−/− mice, although OPG-treatment did not completely return the colonic mucosa to that seen in healthy animals. A detailed comparative analysis of the colonic mononuclear cell populations in treated and non-treated IL2−/− mice identified a specific and selective loss of DC. Together with the constitutive expression of RANK by DC in the colon of non-treated IL2−/− mice these findings suggests that RANK/RANKL/OPG system plays a pivotal role in regulating intestinal inflammation by modulation of colonic DC survival. They also suggest that colonic DC can function as antigen presenting cells for pathogenic (CD4) T
cells. Consistent with this was the redistribution of DC in the inflamed colon where they were seen to move from the lamina propria and into the epithelial layer and in close proximity to the lumen, similar to that described for DC in the small intestine (Rescigno et al., 2001).

These findings have significant implications for the treatment of human inflammatory conditions associated with both bowel and bone complications such as ulcerative colitis, Crohn's disease, and Coeliac disease (Fickling et al., 2001; Klaus et al., 2002). In these disorders bone disease often presents at diagnosis (Lamb et al., 2002) and is not necessarily induced by steroids alone (de Jong et al., 2002). OPG may therefore offer a means of treating both the osteoporosis-like bone destruction found in these conditions and reducing gut inflammation, which would provide significant improvements in the quality of life and reduce complications associated with these diseases.

**PEER-REVIEW-An Editors view**

As scientists, most of us will have endured the sometimes nail-biting anguish of submitting a research paper for publication. The trepidation of pitching to the right journal, the seemingly endless tweaking as you strive for perfection in your prose, the ritual encasement in the FedEx package (or electronic upload as is now more often the case) and then, of course, the agonising wait for a reply. During my time as a practising scientist, journals often seemed to me like 'black holes', indifferently gobbling-up my precious cargo, only to later eject it back out with a letter of 'no-hope' attached. Or, perhaps, there would be a laundry-list of seemingly impossible experiments, suggested by a referee who had clearly lost the plot! Such frustrations of getting one's work published only seemed to me to be compounded by not knowing what was going through the minds of the editors as they made their decisions. Occasionally, a paper would meet with approval of the referees and be accepted for publication: days for which I think most scientists strive!

I'm now on the other side of the fence as an editor at *Science* with a slightly different perspective of the peer-review process. Perhaps I can share with you a little of what I’ve learnt (without giving too much away, of course!) about my role as an editor and offer some general tips on preparing and submitting a paper. I’m not certain I will be imparting anything wildly profound, but rather some things to which I did not often give much consideration when I was authoring papers myself, but which I think I would have found quite useful.

"I think you should be more explicit here in step two."
I’m frequently asked what exactly is the role of an editor at a journal like *Science*? Well firstly, editors do just that; they edit. I spend about one fifth of my time reworking manuscripts, frequently guiding authors in revising their vast tracts of script down to three, or so, relatively intelligible magazine pages. Ultimately, this is a satisfying, if sometimes involved process and I get a great sense of vicarious pleasure when a paper is finally published in the pages of the magazine. Even so, this is just the final stage of an intensive review process, which the editors are responsible for steering from beginning to end.

With every paper, I first make a general assessment of the work, usually also passing the paper by members of *Science’s* Board of Reviewing Editors. These are expert practising scientists who help us with the first evaluation of the many of the manuscripts we receive. The criteria we use when deciding on in-depth review is whether the work represents a significant advance likely to be of interest to the broader readership of the magazine. Because *Science* represents all disciplines, there is very limited space in the journal for each subject. This means that competition is always stiff, with fewer than a quarter of submitted papers making it over this first hurdle.

In-depth peer review is the next stage for the remaining papers, usually with two or three experts in the field. Although some of these may be suggested by the Board and others by the authors themselves, I try to use referees who I know will offer constructive and fair evaluations. Once a paper comes back from review, I consider all the evaluations and circulate the manuscript to garner further comments from some of my colleagues. And then it’s decision time! Of course, most papers do not get accepted without at least some level revision and the editor’s task is to help interpret the reviewer comments and decide if there is sufficient merit to ask the authors to revise their paper. Most papers are not considered for revision, leaving about only 5-10% of the original submissions eventually accepted for publication.

For me, a large appeal of the job is that while every paper receives vital input from several directions, it’s the editors ultimate decision whether to publish or not. In this respect, I always remember that research in a journal such as *Science* can have considerable influence and I try and keep this position of responsibility in mind when deciding on the small handful of submitted papers that finally make it to publication.

After making an initial decision to consider publishing a paper, my next task is to present it to my colleagues at the weekly editor’s meeting, which is held between *Science*’s two main offices in Washington, D.C., and Cambridge, UK, *via* video and phone link. This gathering, affectionately known as the ’Space’ meeting, allows each editor to explain the science in the paper and detail what the Board and reviewers thought of it; ultimately justifying why it deserves space in the journal. For me, this meeting is absorbing because of the wide range of disciplines the editors bring to the table: On any given week I can hear from my colleagues topics as diverse as the life of a neutrino, evidence for water on Mars, how elephants remember, or how a nerve cell ‘knows’ which direction to grow.

A crucial part of the job is keeping up with important developments in one’s own field. Aside from reading the literature, a useful way to do this is by visiting labs and attending meetings and this offers a great opportunity to travel to new places, while exercising my brain and acquiring fresh ideas! Combined with previous research experience, keeping up with the field is important
because I need to be able to grasp, in quite a lot of detail, the science presented in the papers I read and in the conversations I have with scientists. Of course, this does not mean that all papers (or all scientists for that matter!) are inherently comprehensible--some are not, and it is therefore also important to exercise patience. This is equally true in other aspects of the job. For example, I often have to impart news of a paper's rejection to people who, sometimes understandably, disagree with the decision, or at least experience natural disappointment. I think it is important to listen to those authors and to think over and discuss their concerns--perhaps it is here that my own experiences of rejection and dejection mentioned earlier come into play!

The role of an editor is considerably more varied than I'd ever imagined it might be and I've been inspired by the numerous opportunities I've had for contributing to the delivery of the scientific discoveries we publish. These experiences as an editor have enabled me to continue learning, not just in developing a much broader understanding of my own subject of immunology, but also about the importance of clear communication of exciting science and good public relations.

**Some tips for preparing and submitting your research.**

**Decide where to submit**
Ask yourself where your paper should be pitched: a top non-specialist journal, or a more specialized publication? Consider your study in the context of other work in your field and ask does your work represent a major advance, or perhaps overturn conventional thinking on the subject? Some journals consider pre-submission enquiries, where the editor may be willing to offer some preliminary feedback on whether your study might be of interest to the journal.

**Invite your own critique**
Run your own "mini-review" process by obtaining feedback from others in your department or institute. Include someone in your own specialty, someone in an unrelated specialty, and someone who is a good editor for the English language.

**Think about presentation**
Outline and organize your thoughts before you write. Be concise; check the journal's instructions to authors, and stick to the journal's criteria for length and format for submitted papers. Always aim to keep your writing succinct and to the point.

**Keep your reviewers in mind**
A reviewer who enjoys reading your paper will likely see the science more clearly and come away with a more generally positive opinion. This may also help them offer more constructive criticism of your work than if they had been obliged to struggle through poorly presented arguments. Before submitting, ask yourself what else you would like to see if you were reviewing the manuscript. Is the paper clearly written; does the message come across well and are there other interpretations you might consider that the reviewer might bring up.

**Keep your readers in mind**
A clear introduction is always important, but for a journal like *Science* it is especially valuable to have the general, as well as specialist reader in mind. Try not to assume a great deal of specialist knowledge on the part of the reader: Although it is not always possible to explain every basic concept when introducing your work, do so where possible. Outline the larger context of
your study and articulate why your work represents a major advance. This is especially important in the abstract of the paper.

**Avoid over-interpretation**

Papers frequently, don’t do as well as they might at review because, although the data may be correct, the claims of the authors have been stretched. Where interpretations are made, keep the language moderate and avoid wild claims of novelty in your writing. Remember; observations without interpretations aren’t helpful, but interpretations without observations are worse!

**Work with your editor**

Keep in mind that in helping you revise your paper, the editor is working on your behalf, as well as for the readers of the journal. Try and work with that person to incorporate the reviewers’ suggested revisions—as well as those of the editor—as completely as possible. If you’re resubmitting a revised manuscript, offer a concise written outline of how you have revised your paper in responding to reviewers’ requests. Include in this any objections and clear explanations of why you haven’t revised according to a specific suggestion. Offer a good level of detail in the response letter, but don’t let the editor or reviewer fall asleep as they wade through page upon page of text!

*Steve Simpson  
Science Editor*
Changing paradigm through a genome-based approach to clinical and basic immunology

1st International Conference on Basic and Clinical Immunogenomics
3-7 October, 2004, Budapest, Hungary
(www.diamond-congress.hu/bci2004/)

Genomics or, in other words, genome-based biology offers an entirely new prospective on strategies applicable to the study of distinct physio-pathological conditions through a “discovery-driven” approach that may complement traditional “hypothesis-driven” scientific thinking. Indeed, analysis of genomic variation at the DNA level and functional genomics that addresses transcriptional variations of biological material have been extensively used by bio-scientists to study distinct pathological conditions and this trend has spread, more recently to applications in basic and clinical immunology. This shift in paradigm in the study of biology and, in for the purpose of this Conference (1st International Conference on Basic and Clinical Immunogenomics, 3-7 October, 2004, Budapest, Hungary, (www.diamond-congress.hu/bci2004/), in immunology may very well be suitable for the understanding of immune regulation in sickness and in health which represents a particularly complicated biological matter due do the extreme biological versatility of the immune system in adaptation to environmental changes. The study of immune regulation in response to pathogen invasion, presence of malignant or allogeneic tissue and, in some cases, or toward normal autologous tissue may require global approaches that could study in parallel the behavior of whole-systems as the study of single immunological parameters has, so far, failed to unlock several questions related to the immune-system complexity.

In fact, new tools have been developed that allow a global vision of genetic processes in parallel at various levels that encompass genetic variation (single nucleotide polymorphism analysis), epigenetic changes...
(i.e. methylation-detection arrays or comparative genomic hybridization that can detect gene methylation or deletion / amplification respectively) and global transcription analysis (i.e. cDNA- or oligonucleotide-based microarrays like the lympho-chip or the peptide-MHC microarrays that combined with bioinformatics tools provide a new approach to the description of complex immunological phenomena. It is likely that, database mining will supplement classical experimentally-driven scientific thinking with a more interactive “in-silicon” processing of information integrated by software programs capable to link information accessible from the literature with extensive data bases from different laboratories with the simple purpose of increasing the data pool from which generate new hypotheses. Thus, we propose the new word: “immunogenomics” to describe the switch from the paradigm of solely hypothesis-driven immunological research to a more interactive and flexible relationship between classical research and with a discovery-driven approach. It also appears to us that immunogenomics may particularly suit clinical immunology for the simple reason that genetic variation of patients and their diseases is not as controllable in humans as it is in inbred animal models.

Comprehensive reviews on this subject, contrary to those detailing technical information, are scant and communication between bench and clinical scientist remain below a threshold likely to produce efficient therapy development and ultimately benefit patients. Based on a growing attention we decided to organize the 1stInternational meeting on Immunogenomics (Budapest, October 3-7, 2004).

We hope, that high-throughput technologies will allow, when applied to relevant samples, the efficient screening in humans of theoretical models generated from animal experimentation, in vitro studies or speculation and, in turn, the discovery of new patterns through the direct observation of human pathology but this will only occur through the integrated efforts of multiple basic and clinical research disciplines. During this Conference we try to facilitate meeting of people from all over the world interested to start with a sparkingly new thinking in basic and clinical immunology and genomics.

Prof. Andras Falus, PhD, CMA
Semmelweis Medical University, Budapest
faland@dgci.sote.hu

Education at the DMMC

The Dublin Molecular Medicine Centre (DMMC) is a partnership involving University College Dublin, Trinity College Dublin, and The Royal College of Surgeons in Ireland with the goal of creating a world-class cluster in molecular medicine. A cross-institutional education and training programme and efficient sharing and presentation of information are fundamental to the broad aims of the DMMC: providing an environment for collaboration of scientists and clinicians across Dublin, developing core technologies and resources and facilitating access to them, building partnerships with other academic institutions and industry worldwide, attracting and retaining the best researchers.

In developing a DMMC education and training programme, important requirements include providing short courses to supplement research degrees, providing career-long training, and making the best use of a limited resource – time to teach. DMMC courses are freely available to all postgraduate students, technical, postdoctoral, academic, and clinical staff with an interest in molecular medicine, primarily from UCD, TCD, RCSI, and the affiliated teaching hospitals. The potential benefits of a cross-institutional programme are significant. Individual
institutions do not have to run similar courses for small audiences, lecturers can share the workload with a Dublin-wide pool of expertise, users have free access to all that expertise, and there is a stimulating mix of participants from different backgrounds. The DMMC Directorate helps to develop and organise the courses (together with a cross-institutional education advisory group), and administers applications. Students and staff at all levels of their careers, from different disciplines and institutions, have attended the DMMC courses run so far. The courses currently available are lecture-based, but it is our intention to include practical courses and offer individual in-lab training in various techniques. We also want to involve the biopharmaceutical industry and make selected courses available to researchers outside Dublin and Ireland. The DMMC is aiming to help provide the interdisciplinary training essential for clinician-researchers and scientists with business acumen.

The primary source for information on the DMMC is the website (www.dmmc.ie). This contains information on the courses, how to apply, and presentations to download. There will soon be an easily navigated interface to identify scientists and clinicians from various starting points: disease area, biological process and technology. An information-rich website listing up-to-date events, news, opportunities and expertise will be invaluable to the local molecular medicine community. Interested parties worldwide will see Dublin projected as a vibrant centre of learning and translational research.

What I have described is very much a work in progress. Use the DMMC: take a look at the website; contribute to the education and training programme, both as users and providers; let us know what’s going on so that we can publicise it; if there’s nothing for you, tell us what’s missing. The DMMC is building a community in molecular medicine that transcends boundaries.

Dr Mark Watson  
Education & Information Coordinator  
Dublin Molecular Medicine Centre  
Email mark.watson@dmmc.ie
Irish Society for Immunology Annual Meeting 2004
16th –17th September, National University of Ireland, Maynooth.
Preliminary Programme: Sessions/Confirmed speakers

**Thursday 16th September**

12.00 – 13.30 Registration
12.30 – 13.30 Lunch

**Session 1: Infectious Disease Immunology (13.30 – 17.00)**

Brian Adair, Belfast (porcine/chicken viruses)
Grace Mulcahy, Dublin (parasitology/helminthes)
17.00 - 18.30 Wine reception, posters and trade exhibition.
19.30 - late Conference Dinner, The Glenroyal Hotel, Maynooth.

**Friday 17th September**

**Session 2: Immune Regulation (09.30 – 13.00)**

Kingston Mills, Dublin (T regulatory cells)
David Wraith, Bristol (autoimmunity/EAE/T regulatory cells)
13.00 – 14.00 Lunch, posters and trade exhibition.

**Session 3: Immunology: Novel genomic and proteomic approaches (14.00 – 17.00)**

Steve Pennington, Liverpool (proteomics)
Mike Dunn, London (proteomics)
17.00 End of Conference

Students who are ISI members will be eligible for best oral presentation and best poster prizes of €150 each!

Onsite accommodation will be available at the NUI, Maynooth for conference attendees at student and staff rates
A note from the editor

Hi all. I hope you enjoyed this edition of the ISI newsletter. The job of the editor is a difficult one – my time is spent convincing people to write articles and then constantly bombarding them with emails begging them to actually submit the agreed article for publication!!! The next issue of the newsletter is due for publication in the summer so I’m giving you all plenty of notice to get your writing heads on and come up with something. I welcome any article as long as it will be of interest to our readers. Those of you attending conferences could write a meeting report and young researchers are encouraged to submit articles highlighting their area of research. Illustrations are cartoons are particularly welcomed. Thank you to all of you who contributed to this issue and I hope that the rest of you will contribute in the future. All articles should be emailed to me at loscherc@tcd.ie. I look forward to hearing from you all soon (of your own free will!!!!).