

# Education and Research Centre



## Contents

### Education and Research Centre

<b>Reviews and Personnel</b>		<b>Endocrinology &amp; Diabetes Mellitus</b>	70
Review by Medical Director of the E.R.C.	56	Post Graduate Department	73
Introduction	57	<b>Academic Activities</b>	
E.R.C. Principal Investigators - 2003	58	Annual Biomedical Research Symposium 2003	75
Research Laboratories – Personnel 2003	59	Lecture Series	76
Review by Director, Research Laboratories	60	Research Seminars	77
Research at the E.R.C.	61	ERC Journal Club 2003	77
<b>Research Activities</b>		Prestigious Invitations to E.R.C. Researchers	78
Department of Surgery	62	Honours, Awards and Prizes 2003	80
Tumour Biology Group	62	<b>Publications</b>	
Bioinformatics Group	63	Published or Accepted for Publication in International Peer Reviewed Journals 2003	81
Innate Immunity Group	64	Chapters in Books	84
Liver Research Group	65	Invited Reviews	85
Haematology Group	67	<b>Grants Active</b>	
Sleep Research Laboratory	67	Grants Active in 2003	86
Centre for Colorectal Disease	67		
Rheumatology Department	68		
Respiratory	69		



## Review by Medical Director, Education & Research Centre

Education and Research Centre

In 2003, researchers associated with the Education and Research Centre (ERC) continued to make a highly valuable contribution to research and education activities at St.Vincent's University Hospital (SVUH) and indeed to the international research community. Research activities at SVUH are by no means confined to what takes place within the physical infrastructure of the ERC and each of the departmental reports will highlight the considerable body of research, which is taking place throughout the hospital campus. The ERC does provide a focus for research activity and throughout the year many individual research groups hold their weekly meetings and host local symposia, national and international meetings. The highpoint of the ERC year is the annual symposium held in November and this year again with the title of "Common Molecular Mechanisms in Inflammation and Malignancy". This was a most successful symposium ending with a lively discussion on the future of bio molecular research. The symposium offers young SVUH scientists and clinicians an excellent opportunity to present their research findings and to interact with top national and international researchers. I am grateful for the support of Wyeth who this year hosted the symposium gala dinner at their new state-of-the-art facility at Grange Castle.

Perhaps the most significant development in 2003 was the decision of the Board to commission a strategic review of Research at SVUH going forward over the next 5-10 years. The board appointed Professor Patrick Fottrell, formerly President of National University of Ireland, Galway and currently chair of Science Foundation Ireland (SFI), and Mr. Leo Kearns, a consultant to the Public Sector on Management, Policy and Strategy matters, to undertake this review on behalf of the board. Professor Fottrell and Mr. Kearns consulted widely throughout the hospital in late 2003 and also met with key individuals based at the Conway institute and in UCD. A draft high-level report has now been presented to the Board and it is hoped that the Board will soon be in the position to adopt its findings and to implement its recommendations.

The other major development in 2003 going forward was the confirmation of funding to proceed with the development of a Genome Resource Unit (GRU) based at SVUH. The GRU, which is linked to the Dublin Molecular Medicine Center (DMMC) and which is being spearheaded at SVUH by Dr. Seamas Donnelly, will allow for the co-ordinated clinical and genetic phenotyping of large cohorts of patients attending SVUH. This in turn will undoubtedly open up new avenues for treatment in conditions as divergent as prostate cancer and rheumatoid arthritis. With plans for development at an advanced stage of planning, it is expected that the GRU will be operational in 2005.

Researchers throughout the hospital and at the ERC have continued to publish in top quality medical and scientific journals. They have also been successful in attracting research funding from agencies such as SFI and the Health Research Board. A number of scientists and clinicians have successfully been awarded higher degrees and many have been invited to contribute to both national and international meetings. Details of these publications, grants and achievements can be found in the individual departmental reports. The challenge ahead of attracting a major, collaborative grant such as a CSET proposal should and can now be addressed.

It remains for me to thank the other members of the ERC management team – Professor Diarmuid O'Donoghue, Professor Walter McNicholas, Professor Cliona O'Farrelly and Mr Eamonn Fitzgerald – whose enthusiasm helps drive the research agenda forward. I would also like to acknowledge the first-class support provided by the ERC management office – Geraldine Lanigan Ryan, Louise McCormack and Alan Garton; and also the support provided by Mr. Saul Lugoye, UCD Information Technology Officer based in the ERC.

Prof. Oliver Fitzgerald



## Introduction

Education and Research Centre

St.Vincent's University Hospital (SVUH) is renowned in Ireland for the excellence of clinical care given to its patients. For decades, this excellence has been supported by a commitment to research. In more recent years, SVUH has extended this reputation with the development of the Education and Research Centre as one of its key initiatives for increasing the knowledge base in the hospital and improving patient care. With dedicated laboratory and clinical research facilities at the ERC, research programmes have developed which complement the primary clinical, diagnostic and treatment challenges faced by healthcare workers at SVUH. In particular, clinical and basic research into arthritis, liver disease and breast cancer are now integral components of Ireland's premier Early Arthritis Clinic, the National Liver Transplant Programme and the National Breast Cancer Unit which are all based at SVUH. A major clinical and basic research initiative in Respiratory Medicine over the years has also resulted in the development of expertise in integrative biology, respiratory physiology and sleep disorders as well as a nationally recognised expertise in the management and research of Cystic Fibrosis. Continuous clinical research over two decades in Endocrinology has made significant contributions to clinical management of Diabetes and Infertility at SVUH. More recently, an ambitious combined clinical and basic research programme in Colorectal Disease is contributing to the emerging research profile of SVUH.

SVUH researchers from clinical and scientific backgrounds collaborate with clinicians and researchers from leading national and international institutes to address major questions in the diseases that afflict the Irish population including rheumatoid arthritis, hepatitis C, cancer and diabetes. A common theme of the research programmes is the investigation of molecular mechanisms of inflammatory and malignant disease with a particular focus on gene expression and its regulation. Identification of specific changes in gene expression will lead to the development of novel diagnostic and prognostic applications, insight into failure of current therapeutic strategies as well as identification of new therapeutic targets for arthritis, liver disease and malignancy.

A strong feature of the ERC research is the collection, over many years, of tissue samples from well-defined cohorts of patients and from normal donors. The clinical data on these cohorts is collated and stored in databases, constituting a valuable research resource. The combination of these clinical data with state-of-the-art molecular techniques for the analysis of disease markers and mechanisms places the E.R.C. in a position to make singular, clinically relevant contributions to biomedical research that will have implications worldwide.



## E.R.C. Principal Investigators – 2003

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### Principal Investigators – 2003

Prof. Barry Bresnihan	Prof. John Crown
Dr. Derek Doherty	Professor Joe Duffy
Dr. Lynda Fenelon	Professor Oliver FitzGerald
Dr. Charles Gallagher	Mr. Justin Geoghegan
Prof. John Hegarty	Mr. Arnold Hill
Dr. Andrew Lloyd	Dr. Donald McCarthy
Dr. Ken McDonald	Mr. Gerry McEntee
Professor T.J. McKenna	Prof. Paul McLoughlin
Prof. Walter McNicholas	Mr. Hugh Mulcahy,
Dr. Evelyn Murphy	Prof. Diarmuid O'Donoghue
Prof. Cliona O'Farrelly	Prof. Niall O'Higgins
Dr. Jacintha O'Sullivan	Dr. Kieran Sheahan
Dr. Tom Smith	Prof. Oscar Traynor
Dr. James Tharappel	Dr. Leonie Young
Dr. Doug Veale	



## Research Laboratories - Personnel 2003

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<b>Laboratory Co-ordinator</b>	Michelle Ipadeola	
<b>Senior Scientists &amp; Post Doctoral Fellows</b>		
Jimmy Tharappel	Andrew Lloyd	Lucy Golden-Mason
Ursula Fearon	Margaret O'Brien	Marie Benito
Jacintha O'Sullivan	Vincent Leroy	
<b>Research Assistants</b>		
Susan Gaines	Martina Gogarty	Laura Greenan
Marie Elena Ruiz Zamora	Deirdre Foley	
<b>M.D</b>		
Trevor Markham	Ronan Mullen	Lorraine Power
Diarmuid Manning	Ronan Ryan	Conor O'Brien
Terence Rooney	Trevor Duffy	
<b>MCh.</b>		
Caitriona Canning	Raghu Varadarajan	
<b>MSc.</b>		
Shane O'Sullivan		
<b>Ph.D Students (Post Grads)</b>		
Rowan Higgs	Lydia Lynch	David Lynn
Patricia McGowan	Sinead Kelly	Neil O'Brien
Jane Culleton	Brid Ryan	Susan Behan
Jonathan Dean	Tony Kenna	Lucielle Kavanagh
Alison Beime		
<b>Under Graduate Students</b>		
Lillian Lau		
Ashling Hume	Ciara Mahon	Paul Cunningham
Ashling Mulcahy		



## Review by Director, Research Laboratories

Education and Research Centre

These continue to be challenging times for the provision of healthcare in Ireland. Yet never has it been more important to continue to invest in future healthcare. Investment in a major strategic review of research needs and policy in SVUH initiated in 2003 is indicative of the hospital's commitment in this area. SVUH researchers are optimistic that this report will provide the impetus for significant, focused development of research at SVUH

As one of Ireland's leading teaching hospitals and tertiary referral centres, SVUH has long recognised the need to foster a generation of tomorrow's solutions today. Complementary development with the Conway Institute at UCD now places SVUH in a unique position amongst Irish teaching hospitals to become a leading international player in the field of biomedical research.

Continuing investment in and support for Research at SVUH, often through the ERC Centre over the years has allowed several research groups at SVUH to flourish and develop international academic reputations. This emerging research capability reflects key areas of clinical expertise for which SVUH has a significant national reputation and is already making significant impact on patient care in:

- a. Arthritis
- b. Colon & Breast Cancer
- c. Liver Transplantation and Hepatitis C
- d. Endocrinology
- e. Pulmonary Dysfunction
  - i. Cystic fibrosis
  - ii. Sleep apnoea

Continued excellence was achieved during 2003 when over 70 papers were published in international, peer-reviewed journals by researchers attached to the ERC and grants worth over 6 million Euro were active. These grants support 43 researchers based in the Research Laboratories of whom 26 are registered for higher degrees (12 Ph.D; 8 MD; 1 MSc; 1 MCh), 5 are

research assistants, 5 are post-doctoral fellows and one, Michelle Ipadeola, is the Laboratory Co-ordinator. Collaborations with national and international institutes were strengthened in 2003 with several exchange visits, shared publications and invitations to speak. Training for medical and scientific graduate students was improved by the development of a Conway based Academic Programme for Graduate Students. SVUH research success during 2003 was reflected in the high level positions awarded to several ERC researchers by other institutes including the HRB, UCD and RCSI. However continued loss of experienced researchers from the Research Laboratories inevitably brings its own challenge to maintaining excellent academic and research standards.

If SVUH is to foster the research excellence already in place and continue to develop an international profile as a leading player in biomedical research and education, an integrated, focused strategic plan is now urgently required. Key to this plan must be the appointment of senior academic faculty and support staff. This plan should ideally complement the aspirations and missions of related entities - UCD, the Conway Institute, the Dublin Molecular Medicine Centre etc but must focus primarily on the mission of the hospital: to provide the best of healthcare for its patients, now and in the future.

Cliona O'Farrelly, Ph.D



## Research at the E.R.C

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The principal investigators at the E.R.C. include physicians and scientists whose collaboration is key to the developing profile of cutting edge biomedical research. National and international reputations have developed as evidenced by publications in international peer-reviewed journals, and by grants and awards.

E.R.C. Principal Investigators have raised several million Euro in research funds, from governmental and charitable sources. New facilities for laboratory and clinical research have been designed. On a regular basis, new equipment is purchased, technologies introduced, and research staff recruited – critical for continued development of the E.R.C. as a premier Biomedical Research Centre exploring key genetic, molecular, clinical and therapeutic features of some of the most important diseases suffered by adults in Ireland today.

### Research Groups

Research Group	Principal Investigator	Research Staff
<b>Bioinformatics</b>	Dr. Andrew Lloyd Prof. Cliona O'Farrelly	David Lynn
<b>Sleep</b>	Prof. Walter McNicholas	Dr. Silke Ryan Dr. Liam Doherty
<b>Endocrinology</b>	Prof. T.J. McKenna Dr. Leonie Young Dr. Tom Smith	Sinead Kelly Lucille Kavanagh
<b>Innate Immunity</b>	Prof. Cliona O'Farrelly Dr. James Tharappel Dr. Andrew Lloyd	Susan Gaines Colin Murtagh Rowan Higgs
<b>Liver Research/Hepatitis C</b>	Prof. Cliona O'Farrelly Prof. John Hegarty Dr. Derek Doherty Mr. Justin Geoghegan Mr. Oscar Traynor Mr. Gerry McEntee	Dr. Lucy Golden-Mason Susan Behan Tony Kenna Dr. Conor O'Brien Dr. Lorraine Power Dr. Diarmuid Manning Dr. Caitriona Canning Dr. Margaret O'Brien Dr. Vincent Leroy Alison Beime Dr. Raghu Varadarajan Marie Elena Ruiz-Zamora
<b>Haematology</b>	Prof. Cliona O'Farrelly Dr. Donald McCarthy	Dr. Lucy Golden-Mason Jonathan Dean
<b>Gastrointestinal Research &amp; Colon Cancer</b>	Prof. Cliona O'Farrelly Prof. Diarmuid O'Donoghue Dr. Kieran Sheahan Dr. Lucy Golden-Mason Dr. Jacintha O'Sullivan	Shane O'Sullivan Lydia Lynch
<b>Oncology</b>	Prof. Joe Duffy Prof. John Crown	Brigid Browne
<b>Respiratory/Comparative Physiology</b>	Dr. Charles Gallagher	Sinead Barry
<b>Rheumatology</b>	Prof. Oliver FitzGerald Prof. Barry Bresnihan Dr. Doug Veale Dr. Maria Benito Dr. Ursula Fearon Dr. Rosemary O'Hara	Dr. Ronan Mullan Dr. Wahlid-Al-Shehi Laura Greenan Dr. Trevor Duffy Dr. Terence Rooney Dr. Trevor Markham Martina Gogarty Alice McEvoy Jennifer Ralph
<b>Breast Cancer Research</b>	Prof. Joe Duffy Mr. Amie Hill Prof. John Crown Prof. Niall O'Higgins Mr. Enda McDermott	Neil O'Brien Brid Ryan Jane Culleton Brigid Browne Patricia McGowan



## Research Activities

Education and Research Centre

### Department of Surgery

#### Principal Investigators:

Mr. Arnold Hill, Prof. Joe Duffy, Mr. Enda McDermott,  
Prof. Niall O'Higgins, Dr. Leonie Young

#### Research team

*Yvonne Buggy*, Post-Doc.

Chromatin remodelling due to p160 protein in human breast cancer

*Sinead Kelly*, PhD student.

ACTH regulation of adrenocortical steroidogenesis

*Niamh Cosgrave*, PhD student.

Survivin regulation in human breast cancer

*Eddie Myers*, MD student.

Ets interacting proteins in human breast cancer

*Dara Kavanagh*, MCh student.

Steroid regulation of p160 proteins

*Ruth Pritchard*, MCh student.

Growth factor regulation of p160 proteins

*May Cleary*, MCh student.

Glucocorticoid receptor suppression of TGF-beta in human bone

*Julie Watson*, Research assistant.

#### Collaborators

*Marc Timmers* Laboratory for Physiological Chemistry, Utrecht University, The Netherlands.

*John Hassell*, Institute for Molecular Biology and Biotechnology, McMaster University, Hamilton, Ontario, Canada

#### Intracellular signalling and transcriptional regulation in human breast cancer

The clinical use of an antiestrogen for the treatment of breast cancer was first reported by Cole et al in 1971, who described the potential use of tamoxifen (ICI 46,474). Since then tamoxifen has become the most widely prescribed anti-cancer drug in the world. However, while most estrogen receptor (ER) positive patients will initially respond to tamoxifen, approximately one third relapse within a period of 18 months. While initial response rates are high among ER-positive tumours, most breast cancers that acquire tamoxifen resistance

do so while continuing to express functional ER. Despite extensive clinical use of tamoxifen several aspects of its mechanism of action and acquired resistance remain unclear.

The ER is encoded for by two genes, ER $\alpha$  and ER $\beta$ , both can function as transcription factors to modulate target gene expression. ER $\alpha$  and ER $\beta$  interact with a number of nuclear proteins in vitro. These 'co-activator/co-repressor' proteins interact directly with steroid receptors at their response element in the promoter region of target genes to enhance or inhibit transcription. Co-activators such as SRC-1 are thought to facilitate the activity of the ER whereas co-repressors such as SMRT maintain transcriptional silence. We have described a significant association between expression of co-activators SRC-1 and AIB1 in human breast cancer. At a molecular level we have observed distinct transcription factor-co-regulatory protein interactions and protein DNA interactions in endocrine sensitive cells compared to those that are resistant, in response to not only the steroid environment, but also growth factors. We feel that co-regulatory proteins are pivotal to the development of endocrine resistance and may ultimately be responsible for the development of steroid independent tumours.

### Tumour Biology Group

**Principal Investigator** Professor Joe Duffy

#### Researchers

Neil O'Brien, Brid Ryan, Brigid Browne, Jane Culleton,  
Patricia McGowan

#### Collaborators (Local)

Dr John Crown, Mr Arnold Hill, Mr Enda McDermott,  
Professor Niall O'Higgins.

#### Collaborators (International)

Drs Denis Slamon/Gottfried Konecny,  
University of California at Los Angeles;  
Dr Stan Krajewski, Burnham Institute, La Jolla;  
Prof Fred Sweep, Nijmegen; Prof Nils Brunner, Copenhagen,  
Prof Manfred Schmitt, Munich

### Research Focus

The overall aim of the Tumour Biology Group is to develop new molecular markers to aid the early diagnosis of breast cancer; help with prognosis and predict likely response or resistance to specific therapies.

Neil O'Brien's research is focusing on mammaglobin, a recently identified gene which appears to be expressed specifically in breast tissue. Neil has shown that expression of the mammaglobin gene is almost exclusively confined to breast tissue with higher levels in breast cancer than non-malignant breast tissue. Neil was also one of the first to show that mammaglobin exists as 2 distinct proteins in breast cancer. These different proteins appear to contain different amounts of carbohydrate. Despite considerable efforts, Neil was unable to identify factors that regulate mammaglobin expression in breast cancer cells. Based on its almost exclusive expression in breast tissue, mammaglobin is currently one of the most promising new markers in breast cancer.

In breast tumour cell, mammaglobin exists in a complex with another protein known as lipophilin B. Jane Culleton has shown that while lipophilin B is preferentially expressed in breast tissue, limited expression also occurs in other steroid-dependent tissues. In breast cancers however, a significant correlation was found between mammaglobin and lipophilin B suggesting co-ordinate regulation of these genes. Currently, Jane is investigating lipophilin B at protein level using Western blotting and immunohistochemistry.

Brid Ryan's work involves investigating survivin which is both an inhibitor of apoptosis (or cell death) and a regulator of cell division. Although not specific for breast tissue, survivin is one of the most pan tumour-specific genes identified to-date. Brid has shown that survivin is present in almost all breast cancers but is rarely detected in normal breast tissue. Surprisingly, levels of survivin in breast cancer do not appear to correlate with rates of apoptosis but do correlate with rates of proliferation. These findings suggest that the primary function of survivin in breast cancer may be to control proliferation rather than apoptosis.

Brigid Browne is researching the mode of action of the therapeutic antibody Herceptin as well as Taxanes in breast cancer cells grown in culture. Brid has shown that taxanes both inhibit proliferation and induce apoptosis in cell culture. During the year, Brigid spent some time working in the Laboratory of Prof Denis Slamon at the University of California, Los Angeles.

Patricia McGowan started a new project on the role of TACE (ADAM17) in September 2003. TACE is a multidomain protein possessing both a protease and an adhesion domain. It is thus

potentially involved in cancer progression. Patricia's early results suggests that the TACE protein exists in multiple molecular forms in breast cancer. The clinical significance of these different forms will now be investigated.

### Bioinformatics Group

#### Senior scientist

Andrew T. Lloyd PhD

#### Graduate student

David Lynn, M.Sc.

#### Research

The principal research project, funded by the Department of Agriculture, continues to investigate innate immunity in chickens. We have clustered more than 400,000 ESTs from chicken using two different techniques and found good concordance between the methods. Using these data, we have identified nine novel anti-microbial peptides in this genome and their existence has been confirmed by the molecular biology group of Professor C. O'Farrelly. One current project investigates the rates of sequence evolution in those genes involved in the control of the immune system. We have identified sites within mammalian defensin sequences that are undergoing positive selection. We have also completed a project investigating whether genes preferentially or exclusively expressed in human and mouse tissues are clustered in their genomes. This project compared the quality of the data available from EST, SAGE and Microarray studies.

#### Education and outreach

The Bioinformatics Group is now fully integrated into the daily work of the ERC. A number of collaborative projects are developing with other groups, notably the breast cancer research group of Professor M.J. Duffy.

In September 2003, we organised a third WWW-based post-graduate bioinformatics course under the auspices of the Dublin Molecular Medicine Centre (DMMC). This is currently the most comprehensive such course offered on a regular basis in Ireland. The course links and manual are available at <http://ercbinfol.ucd.ie/course2003.html>



**Invited talks by David Lynn:**

"An Introduction to Bioinformatics for Immunologists". Irish Society of Immunology, Scientific Meeting, Dublin. Sept 2003

"Bioinformatic Approach to the Discovery of Antimicrobial Peptides in the Chicken". Irish Society of Immunology, Scientific Meeting, Dublin. Sept 2003

"Bioinformatics and Veterinary Research - Antimicrobial Peptides in the Chicken". Veterinary College, UCD, Departmental Seminar. Oct 2003

**Posters presented by David Lynn**

"Bioinformatic Discovery and Initial Characterisation of Nine Novel Antimicrobial Peptides in the Chicken". 3rd Farm Animal Genomics workshop Royal Veterinary College, London. Sept 2003

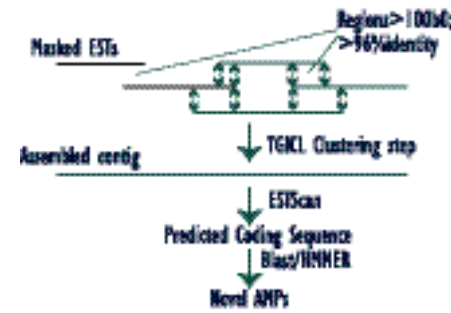
"Bioinformatic Discovery and Initial Characterisation of Nine Novel Antimicrobial Peptides in the Chicken". Conway Institute, Research Festival, UCD, Dublin. Sept 2003

**Innate Immunity Group**

**Team Leader** Professor Cliona O'Farrelly  
**Team Members** Dr. Andrew Lloyd,  
 Dr. James Tharappel,  
 David Lynn M.Sc.,  
 Susan Gaines M.Sc. and  
 Rowan Higgs B.Sc.

The Innate Immunity Group at St.Vincent's University Hospital uses a combined bioinformatics and molecular approach to searching for novel antimicrobial peptides (AMPs). AMPs are part of the innate immune system and primary line of defence in organisms against invading pathogens. These peptides are short proteins, about 30-50 amino acids that destroy a wide variety of microbes by disrupting their cell membranes.

Bioinformatics makes use of data from internet accessible databases of gene and protein sequences, computers and software to identify and characterise genes of interest. 420,000 chicken ESTs were downloaded from a database. ESTs were clustered using TIGR Gene Indices clustering tools (TGICL) that compare ESTs with each other to find those that share regions of similarity. Clustering generated 30,000 of these longer sequences of chicken DNA, known as contigs as they are made up from contiguous sequences (Figure).

**Figure- EST Clustering**

From the contigs, the amino acid sequence of the protein was predicted using ESTScan, a programme which detects and reconstructs potential coding regions. A second search using BLAST (Basic Local Alignment Search Tool) was then carried out using the predicted protein sequences, to look for homologous sequences in known AMPs.

Eleven novel AMPs have been discovered to date. Nine belong to the defensin family of AMPs. In collaboration with Dr. Grace Mulcahy of the Faculty of Veterinary Medicine UCD, we examined chicken tissue infected with a protozoan parasite for expression of these predicted genes by RT-PCR analysis. All predicted genes were shown to be expressed and were cloned and sequenced.

This combined bioinformatic and molecular biological strategy is also being exploited in a comparative immunogenomics analysis of the toll like pathway in humans, mice and chickens. This work is of particular relevance to our knowledge of the innate immune system and how it might be manipulated in infection and inflammation.

This work is funded by the Irish Department of Agriculture under Food Institutional Research Measure (FIRM).

Technical article/report published in Irish Scientist 2003 Yearbook

27th March 2003 – Presentation at workshop entitled 'Innate Enteric Immunity Mediated by Paneth Cell Alpha-Defensins' with Professor Andre Ouellette from University of California at St. Vincent's University Hospital

**Meetings Attended:**

Sept. 8th & 9th 2003 "Bioinformatic Discovery and Initial Characterisation of Nine Novel Antimicrobial Peptides in the Chicken". 3rd Farm Animal Genomics workshop Royal Veterinary College, London. – Poster presentation.

Sept. 11th & 12th 2003 "Bioinformatic Discovery and Initial Characterisation of Nine Novel Antimicrobial Peptides in the Chicken". Conway Institute, Research Festival, UCD, Dublin. – Poster presentation.

18th Sept. 2003 "An Introduction to Bioinformatics for Immunologists". Irish Society of Immunology, Scientific Meeting, Dublin. – Oral presentation by D. Lynn

18th Sept. 2003 "Bioinformatic Approach to the Discovery of Antimicrobial Peptides in the Chicken". Irish Society of Immunology, Scientific Meeting, Dublin. – Oral presentation by D. Lynn

15th Oct. 2003 "Bioinformatics and Veterinary Research - Antimicrobial Peptides in the Chicken". Veterinary College, UCD, Departmental Seminar. – Oral presentation by D. Lynn

4th Dec 2003 "Bioinformatic Discovery and Initial Characterisation of Nine Novel Antimicrobial Peptides in the Chicken". Annual Congress of the British Society for Immunology. – Poster presentation.

**Liver Research Group****Principal Investigators**

Prof. John Hegarty, Prof. Cliona O'Farrelly,  
 Mr. Justin Geoghegan, Mr. Oscar Traynor

**Research Staff**

Dr. Lucy Golden-Mason, Dr. Conor O'Brien,  
 Dr. Lorraine Power, Dr. Diarmuid Manning,  
 Dr. Caitriona Canning, Dr. Margaret O'Brien,  
 Dr. Vincent Leroy, Dr. Raghu Varadarajan,  
 Marie Elena Ruiz Zamora, Alison Beirne, Susan Behan,  
 Tony Kenna

**Basic Research**

The Liver research group was established in 1993 and is now concerned with several strands of research including transplantation, immune regulation mediated by cytokines in the liver, tumour immunology and Hepatitis C infection.

One area of research has focussed on the expression and function of CD1d and NKT cells in normal livers and tumours as NKT cells have been implicated in potent anti-tumour responses. We have shown altered pattern of CD1d expression, the ligand for NKT cells, and also phenotypic and functional differences in NKT cell in normal and tumor-bearing human livers. We have also explored the role of Interleukin 12 (IL-12) in the liver as this regulatory cytokine has a function central to the initiation and regulation of cellular immune responses. It has the capacity to regulate the differentiation of naive T cells into TH1 cells and stimulates the growth and function of T cells. We have shown that IL-12 is increased in tumour bearing human liver and expands CD8(+) and CD56(+) T cells in vitro but not in vivo.

We have also been interested in unconventional lymphocytes present in normal adult human liver. Relatively high levels of CD8(pos) T cells with a naive phenotype were found in liver

suggesting that naive CD8(pos) T cells may enter the liver without prior activation. In addition, an almost complete absence of TCR excision suggests that normal adult human liver is not a site for the development of conventional alphabeta T cells.

Raghu Varadarajan gave a talk entitled 'Activation of the Nitric Oxide Pathway in Early Ischaemia Reperfusion Injury Following Human Orthotopic Liver Transplantation' detailing his work on transplantation and reperfusion injury in the human liver, at the American Transplant Congress in Washington.

**Hepatitis C Research**

As part of our ongoing Hepatitis C Virus (HCV) research program we have been looking at various liver lymphocyte populations, cytokines and genetic determinants of viral persistence and chronic HCV infection. One focus of interest has been in expression of IFN $\alpha$ -stimulated genes (ISGs) which may play a key role in resolution of HCV-infection. We have shown that infection with HCV genotype 1b does not appear to inhibit the expression of ISGs compared with the uninfected study populations indicating that IFN $\alpha$ -stimulated gene responses are not impaired in PBMCs from HCV-infected patients. In addition, we have identified NK cells and monocytes as the cell populations most responsive to IFN .

A HRB HCV Programme Grant entitled 'Genetic and Functional Analyses of the Immune Response to Hepatitis C: Predictive Indicators of Response to Treatment and Disease Progression' was awarded to Cliona O'Farrelly in collaboration with Dermot Kelleher and Kingston Mills (TCD) and also Derek Doherty (NUI, Maynooth). This project builds on previous data from our group which showed that HCV stimulates IL10 production. We and others have also shown that NKT cells, a population of innate type T cells thought to play a central role in autoimmunity and viral immunity decrease as Hepatitis C progresses. We propose that immunogenetic analysis of key cytokines in tandem with functional studies of these molecules and analysis of patterns of response to IFN- treatment will provide unique insight into the pathogenesis of Hepatitis C and will identify clinically important sub groups of patients who will not respond to current treatment regimens and who will progress to severe liver disease. Early identification of these patient groups would have major implications for clinical decision-making and planning. It would also identify targets for new therapeutic strategies and focus attention on the development of modified treatment schedules for key sub-groups of patients.

An International conference entitled 'Hepatitis C – Past Present and Future' was organised by Dr Golden-Mason and Prof. O'Farrelly and held in Trinity College from 25th – 27th June 2003. This conference featured parallel programs for lay and specialist audiences and aimed to provide insight into living



with Hepatitis C and to make key aspects of the most recent developments in the management, treatment and research of Hepatitis C available to a lay audience. Invited speakers included experts from Europe and the US.

### Haematology Group

#### Principal Investigators

Dr. Donald McCarthy, Prof. Cliona O'Farrelly

#### Researchers

Jonathan Dean, Dr. Lucy Golden-Mason

### Immunology of Haematopoietic Malignancies

#### NKR+ Lymphoid Cells in Human Bone Marrow

The importance of the immune system, and T-cells and natural killer (NK) cells in particular, in combating cancers of various types has gained a lot of attention in the last few years. Recently, a more unusual population of cells, characterised by simultaneous cell-surface expression of protein marker molecules normally associated with either T-cells (such as CD3) or NK cells (such as CD56), has been described. These NK<sup>+</sup> T-cells are present at a number of sites in the human body, and analogous cells can be detected in the mouse. In both species, they have been associated with a range of important immune functions, including the eradication of cancerous cells.

Although the bone marrow is often only thought of in terms of the role it plays in generating new cells for the circulatory system, it also contains distinct groups of mature, functional immune cells, including NK cells and both NK<sup>+</sup>-expressing and non-expressing T-cells. The principle aim of this group's research has been to examine these cells, with particular emphasis on the NK<sup>+</sup> T-cells, characterising them in normal bone marrow, and in the marrow of patients currently suffering from, or in remission following, haematopoietic malignancies.

In addition, there is evidence from the investigation of mice, and from the human liver and gastrointestinal tract, which suggests that the specific immunological needs of some organs may be met by a pool of immune cells that, rather than maturing elsewhere in the body, as they are traditionally believed to do, arise and mature locally, within the organ itself. Therefore, our group is also exploring the possibility that human bone marrow may also represent such a site of "regional immunity", and that T-cells and / or NK cells are developing locally.

### Sleep Research Laboratory

The laboratory is under the direction of Prof. Walter McNicholas with Dr. Silke Ryan as Research Lecturer. Active collaborations are ongoing with Dr. Cormac Taylor in the

Conway Institute at UCD related to identifying the molecular signatures and cytokine production in obstructive sleep apnoea syndrome (OSAS) with a view to understanding the molecular mechanisms responsible for cardiovascular complications in the disorder. Other collaborations are ongoing with the Dept of Electronic Engineering at UCD related to identifying unique associations between cardiac rhythm and sleep apnoea with a view to developing simple diagnostic systems that could be used to assess the disorder in an outpatient setting. Enterprise Ireland has recently awarded a grant to our group in support of this research. Several clinical projects are also underway evaluating different approaches to nasal CPAP therapy in OSAS.

Research papers were presented by Dr. Liam Doherty, Research Registrar in the Sleep Laboratory and Ms Geraldine Lawless, Chief Pulmonary Technician at the annual meetings of the American Thoracic Society in Seattle in May 2003 and the European Respiratory Society in Vienna in September 2003.

### Centre for Colorectal Disease

#### Clinical & Scientific Team

Prof. Diarmuid O'Donoghue Dr. Kieran Sheahan  
Mr. John Hyland Dr. David Fennelly Dr. Hugh Mulcahy  
Dr. Dermot Leahy Dr. Jacintha O'Sullivan Mr. Eddie Fox  
Mr. Ciaran O'Riain Mr. Shane Sullivan Mr. Robert Geraghty  
Ms. Julie Gorman Ms. Denise Keegan Ms. Anne White

#### Centre for Colorectal Disease

Bowel diseases are responsible for considerable mortality and morbidity in the Irish population. Colorectal Cancer (CRC) is the most common malignancy affecting both males and females in Ireland today. Detection of early CRC is essential as early treatment has proved to be the most successful way to combat this disease. The Integrated Clinical Colorectal Unit is a multi-disciplinary team at St. Vincent's University Hospital, which includes colorectal surgeons, gastroenterologists, oncologists, pathologists, radiologists and specialist paramedical and nursing personnel who work closely with research scientists. This medical and scientific team are currently working on using different biological markers to help to identify people at most risk of CRC.

*Overall goal:* To achieve a more complete understanding of what factors fuel Colorectal Cancer development. One of these ongoing research studies is to determine if the use of different biomarkers can help distinguish people at highest risk of Colorectal Cancer. The above research will be of major importance to the Irish population and worldwide, resulting in the following: more effective treatments of the disease and early identification of people at highest risk to the disease to allow early medical intervention to prevent the development of the cancer.

Ongoing research studies (in 2003).

- Role of proteases in early CRC development and progression.
- Screen CRC specimens for the presence of microsatellite instability and expression of mismatch repair genes.
- Role of telomeres and chromosomal instability in promoting CRC development in Ulcerative Colitis.
- Pathological response following long course chemoradiotherapy for locally advanced rectal cancer.

#### Presentations

E.J.P.Fox,A.M.Lennon, D.T. Leahy, R.Geraghty, D. Keegan,H.E. Mulcahy, J.M.Hyland, D. Fennelly, D.P. O'Donoghue, K.Sheahan. *Epigenetic, immunohistochemical and microsatellite marker analysis of DNA mismatch repair defects in colorectal cancer.* Irish Association for Cancer Research Annual Meeting,Kilkenny, April,2003.

E.J.P.Fox,A.M.Lennon, D.T. Leahy, R.Geraghty, D. Keegan,H.E. Mulcahy, J.M.Hyland, D. Fennelly, D.P. O'Donoghue, K. Sheahan. *Clinico-pathological features in the identification of cases of familial colorectal cancer.* Irish Society of Gastroenterology Spring Meeting,Belfast,June, 2003.

E.J.P.Fox, D.T. Leahy, A.M.Lennon, R.Geraghty, D. Keegan ,A. White, H.E.Mulcahy, J.M. Hyland, D. Fennelly, D.P. O'Donoghue, K.Sheahan. *Consequences of gene promoter hypermethylation in colorectal cancer.* Irish Society of Gastroenterology Winter Meeting,Dublin,November, 2003.

Jacintha O'Sullivan - Oral Presentation:  
*Role of Telomere Dysfunction and oxidative stress in neoplastic progression in Ulcerative Colitis.* ERC Annual Symposium, Nov 2003.

### Rheumatology Department

**Consultant Staff** Professor Barry Bresnihan  
Professor Oliver FitzGerald Dr Douglas Veale

#### Post-Doctoral Scientists

Maria Benito Ursula Fearon

#### Graduate Students

Alice McEvoy Jennifer Ralph

#### Research Assistants

Martina Gogarty Laura Greenan

#### Clinical Research Fellows

Trevor Duffy Terence Rooney Ronan Mullen  
Trevor Markham Wahlid-Al-Shehi  
Ceara Walsh

### Research Activities

#### Rheumatoid Arthritis - Scientific Studies

Much of our research is related to aspects of cytokine biology in RA. Dr Terence Rooney measured synovial tissue expression

of interleukin-18 (IL-18) in patients with inflammatory arthritis in order to identify associations with serum levels, disease activity and response to treatment. It was observed that synovial tissue IL-18 expression correlated significantly with disease activity in inflammatory arthritis. After treatment tissue levels changed in parallel with changes in acute phase response, and with changes in serum levels of IL-18. These observations support a role for IL-18 in the pathophysiology of inflammatory arthritis.

Dr Rooney also undertook an evaluation of the effects of combination therapy with IL-1 receptor antagonist and a soluble TNF $\alpha$  receptor on disease activity, physical function, synovial tissue inflammation and radiographic progression in RA. The preliminary results demonstrated positive clinical, functional and radiographic responses to combination therapy. The treatment responses were reflected by changes in selected markers of synovial pathophysiology.

Dr Eithne Murphy completed studies of periarticular and axial bone loss in patients with early RA. Her primary goal was to investigate the relationship between disease activity, serum biological mediators of inflammation and joint destruction, and periarticular and axial bone loss in patients with inflammatory arthritis. Persistent disease activity was associated with increased periarticular bone loss in the hands in rheumatoid arthritis and axial bone loss in seronegative arthritis. The association between TIMP-1 levels and periarticular bone loss suggests that dysregulated metalloproteinase homeostasis may be an important factor in the pathophysiology. Dr Murphy also demonstrated that baseline synovial sublining macrophage infiltration and IL-1 expression were associated with local periarticular bone loss during the first year. These studies were extended by Terence Rooney who demonstrated that periarticular bone loss in the hands occurred before radiographic change was detectable in RA. Measurement of periarticular BMD in the hands by DXA may identify patients with progressive destructive RA with greater sensitivity than conventional radiographic evaluation.

Dr Ursula Fearon evaluated aspects of angiogenesis. One aim of her work was to examine the expression and functional role of Ang2 in inflammatory cells. Her studies demonstrated increased Ang2 expression in inflamed SM and skin, especially in ECs and SFs. Ang2 increased ECs tubule formation and matrix turnover in SM explant, EC and SF cultures, suggesting it plays a dual role. In the EC it is critical for angiogenesis and advancement of the new blood vessel through the SM by matrix turnover; and in the SFs at the site of erosion, where the lining layer invades and destroys cartilage and bone. These results suggest Ang2 is an important factor for angiogenesis and joint erosion in inflammation.

Dr Trevor Duffy's studies included the novel observation of preferential expression of profibrotic mRNA in OA and AS,

supporting a role for TGF $\beta$  family members, their receptor BMPRII and CTGF in disease processes, such as the development of enthesophytes and osteophytes. Reduction in TGF $\beta$  expression following treatment with methotrexate suggests the possibility of therapeutic modulation of these cytokines. The presence of members of the TGF $\beta$  family in all forms of arthritis suggests they may play a role in synovial proliferation.

#### Clinical Studies

Dr Trevor Duffy evaluated arthroscopic measures of change in synovial tissue. The aim of this study was to maximise the potential of arthroscopy by developing a scoring system that would allow interobserver comparison, correlation with microscopy, correlation with clinical diagnosis and severity, and be sensitive to change. The appearance of vascularity and proliferation contributed independently to the macroscopic severity of synovitis. In combination, they provided a new scoring system for static images of macroscopic synovitis obtained at arthroscopy. The system displayed good reliability and validity.

Dr David Kane also compared acute phase response markers, erythrocyte sedimentation rate, C-reactive protein and serum amyloid A, and serum levels of COMP as indices of inflammatory joint disease and as biologic markers of radiologic joint damage in 100 patients with early arthritis. The study demonstrated that SAA was the most sensitive acute phase marker in PsA, the ESR had the highest degree of correlation with clinical joint scores and CRP correlated with radiologic outcome. COMP levels correlated with the acute phase response and with development of erosions in early PsA.

Therapeutic studies in PsA demonstrated that TNF $\beta$  blockade produced a dramatic clinical response in skin and joints paralleled by a reduction in the inflammatory cell infiltrate and angiogenic growth factors VEG-F and ANG2, critical mediators of angiogenesis.

Dr Maria Benito evaluated the effects of methotrexate treatment on aspects of apoptosis in PsA. This study demonstrated that methotrexate induces apoptosis in PsA through a decrease of Bcl-2, without changing bax protein levels. It suggested that the excess of bax free induces enhanced cytochrome c efflux the mitochondria, and the activation of the effector caspase-3.

Dr Noralee Kennedy assessed cost effectiveness of inpatient and outpatient multidisciplinary team care for patients with rheumatoid arthritis. Her studies suggested that inpatient rehabilitation appears to produce more effective treatment than outpatient rehabilitation and costs are considerably higher in the inpatient group. The average cost per DAS28 unit reduction was lower in the outpatient group.

#### Psoriatic Arthritis - Scientific Studies

Dr David Kane completed a study that evaluated cytokine expression in synovial tissue from patients with Psoriatic Arthritis. The study suggested that IL15 and IL18 likely play an important pro-inflammatory role in PsA via enhanced T cell recruitment/activation, macrophage activation, neutrophil activation and angiogenesis.

Dr Trevor Markham has completed a clinical and scientific study funded through an HRB fellowship to examine Psoriasis before and after treatment with anti-TNF therapy. This has led to a number of abstracts presented at The Conway institute, opening day, the American, British and Irish Dermatology meetings.

Dr Ronan Mullan, was the Pfizer Research Fellow in Rheumatology, undertaking laboratory studies of the role of SAA in cell adhesion, migration and angiogenesis. He was awarded best oral paper at the Irish Society for Immunology and a second year fellow award by the American College of Rheumatology.

Patricia Minnock was appointed Advanced Nurse Practitioner in September 2003.

Dr David Kane was appointed Senior Lecturer at University of Newcastle.

Dr Trevor Duffy secured the position of Research Fellow at the University Hospital Geneva.

### Respiratory Medicine and Cystic Fibrosis

#### Overview

The research programme focuses on the mechanisms, treatment and prevention of disability in adults with cystic fibrosis and other respiratory diseases. There has been a major emphasis on mechanisms and treatment of skeletal muscle dysfunction and systemic inflammation in cystic fibrosis, especially during acute exacerbations.

#### Research Projects during 2003

The research team included Dr: Sinead Barry, Mr: Donal O'Callaghan and Dr: Charles Gallagher.

Dr: S. Barry's research examined the effects of strength training on exercise capacity in Cystic Fibrosis. The results from this study demonstrated that improvements in muscle strength translate into increased aerobic fitness and real quality of life improvements for patients with CF. Her research has also examined the mechanisms of skeletal myopathy in adults with cystic fibrosis. Her ongoing research has examined the mechanisms of gender differences in prognosis in adults with cystic fibrosis. Her research results were presented at the American Thoracic Society Meeting.

Mr. Donal O'Callaghan completed his Masters thesis, which examined bronchodilator responsiveness in adults with cystic fibrosis. His work examined the mechanisms and predictors of nebuliser induced and inhaler induced bronchodilatation. The two methods of bronchodilator administration were equally effective. He was awarded a Masters Degree in 2003.

Dr. Sinead Barry presented her research at the American Thoracic Society Meeting in Seattle.

#### Presentations

Gender Differences in the Response to Inhaled CO<sub>2</sub> during Constant Work-load Exercise in Healthy Untrained Subjects. Harty H R, Kilbride E, Fitzsimons A, Gallagher C G, McLoughlin P. Presented at the American Thoracic Society, Seattle, 2003.

Determinants of Change in Exercise Capacity over Time in Cystic Fibrosis. Barry S C, Gallagher C G. Presented at the American Thoracic Society, Seattle, 2003.

A Novel Macrophage Migration Inhibitory Factor (MIF) Functional Polymorphism and Clinical Prognosis in Cystic Fibrosis (CF). Plant B J, Gallagher C G, Phelan P, Baugh J A, Plummer S, FitzGerald M X, Bucala R, Morgan K, Donnelly S C. Presented at the American Thoracic Society, Seattle, 2003.

### Endocrinology & Diabetes Mellitus

#### Personnel

##### Consultants

Professor T J McKenna,  
Dr Malachi McKenna, Dr Donal O'Shea  
Lecturer Department of Medicine, University College Dublin:  
Dr James Gibney.

##### Specialist Registrars

Dr Diarmuid Smith, Dr Kevin Moore.

##### Research Registrars

Dr Twani Tuthill, Dr Tom Cawood.

##### Principal Biochemist

Dr. Thomas Smith

##### Research-Graduate Students

Sinead Kelly, Lucille Kavanagh.

##### Endocrine and Diabetes Research Nurse

Ciara O'Dwyer

#### Projects

##### Macroprolactin:

This year saw the publication of the second of our papers on macroprolactinaemia in the journal *Clinical Chemistry (US)* which attracted an editorial. The paper and editorial highlighted that approximately 10% of prolactin measurements worldwide may be misleading. The innocent phenomenon of macroprolactinemia may be interpreted as providing a diagnosis for infertility mainly in women. The papers which have appeared in

the leading US clinical endocrinology and laboratory journals, highlight the message that frequent misdiagnosis, unnecessary investigation and inappropriate treatment may be prevented when elevated prolactin levels are submitted to additional relatively simple testing to identify the presence of macroprolactin.

While gel filtration chromatography (GFC) is the "gold standard" for quantifying levels of bioactive macroprolactin and bioactive monomeric prolactin in sera, the cost and labour intensive nature of this procedure precludes its use in all except research laboratories. We have undertaken an extensive examination of the specificity and clinical utility of methods for removing macroprolactin from serum prior to immunoassay. This involved pre-treatment of sera from patients with macroprolactinaemia with a variety of reagents and procedures including: polyethylene glycol, ultrafiltration, adsorption with protein G Sepharose, protein A Sepharose or anti-human IgG agarose. Results obtained with polyethylene glycol and protein G were closest to those obtained with the reference GFC method suggesting that either of these procedures represent practical alternatives to the more costly and labour intensive chromatographic procedure.

Ms Lucille Kavanagh, post-graduate student, continued her investigations to elucidate the structure, bioactivity and aetiology of macroprolactin. Lucille's work has focused on assessing the nature of macroprolactin and its relationship to the autoimmunity status of patients exhibiting this condition. Experiments to dissociate the macroprolactin complex into its constituents, monomeric prolactin and an IgG antibody, have been successful and she is now assessing the ability of the purified autoantibody to reassociate with both native and recombinant prolactin.

There is a general consensus that the macroprolactin complex possesses little if any bioactivity *in vivo*. However, there is conflict in the published literature in relation to the bioactivity of macroprolactin *in vitro*. Interpretation of *in vitro* experiments is complicated by contamination of tested macroprolactinaemic sera with monomeric prolactin, dimeric prolactin and growth hormone, all of which react positively with the existing bioassay. In an effort to clarify the situation Lucille has established and validated an in-vitro bioassay utilising an Nb2 lymphoma cell line. She has prepared macroprolactin preparations that are free of both monomeric and dimeric prolactin and also growth hormone and is about to assess their bioactivity *in vitro*.

Autoimmune conditions such as systemic lupus erythematosus and rheumatoid arthritis have been previously linked with increased circulating CD5 positive B lymphocyte levels. In an effort to assess the autoimmune profile of patients with macroprolactinaemia, whole blood, stained for the cell surface markers CD19, CD5 and CD 45, was subjected to flow cytometric analysis to determine the levels of circulating B lymphocytes

expressing such markers. Blood was also obtained from patients with true hyperprolactinaemia and normal individuals to serve as controls. Our preliminary results indicate that macroprolactinaemic patients exhibit significantly elevated CD5<sup>+</sup> B lymphocyte levels with respect to both hyperprolactinaemic patients and normoprolactinaemic controls. These findings are consistent with our current working hypothesis that macroprolactinaemia is associated with increased humoral autoimmunity in such individuals.

#### Control of Adrenal Steroid Production:

Leonie Young and Sinead Kelly have pursued their on-going research into the control of adrenal steroidogenesis using a human adrenal tumour cell line. The adrenal cortex produces aldosterone, cortisol and adrenal androgens in response to secretagogues including ACTH and angiotensin II. ACTH is the master secretagogue and modulates both cortisol and adrenal androgen production. They have already investigated the differential response of morphologically distinct cells of the human adrenal to these classic secretagogues. It has been demonstrated that purified adrenocortical cells are capable of producing a range of steroids, but that the relative production of cortisol, androgen and aldosterone differs. Adrenal steroids are produced by a complex series of enzymatic steps. Differential regulation is achieved by expression of key steroidogenic enzymes in particular 21-hydroxylase and 17-hydroxylase for regulation of cortisol and adrenal androgen production. The induction of these enzymes requires *de novo* protein synthesis. The expression of these enzymes at both the transcriptional level and translational level have been examined and shown to be differentially modulated by the secretagogues. Steroid enzyme regulation by classic and novel transcription factors such as SF-1 and Nur77 is of particular interest. These transcription factors are known to be involved in the modulation of steroidogenic enzymes in the adrenal cortex. They have already demonstrated that angiotensin II can signal through Nur77 to regulate steroid enzymes relevant to cortisol production and thereby regulate differential cortisol and adrenal androgens production. Recently coregulatory proteins have been implicated in the modulation of nuclear receptor transcriptional activity. Ongoing investigations examine whether ACTH and angiotensin II differentially recruit these coregulators resulting in divergent production of adrenal steroid production. This work will allow greater understanding of the physiological functioning of the adrenal cortex and may give fundamental insight into common basic disorders such as hypertension and infertility.

#### Weight Management in Type 2 Diabetes:

Obesity and weight gain are central to the development of diabetes mellitus and pose major impediments to its successful management. Dr Twani Tuthill in her MD project has

retrospectively reviewed the profile of weight change in patients attending the Diabetes Service. Reviewing over 1,000 patients for an average of 5 years, Dr Tuthill noted that a mean weight loss of approximately 4kgs was achieved in the first year. Over the succeeding years there was a gradual return towards baseline. The weight loss achieved was superior to that reported internationally. Patients on diet alone were more successful in losing weight. Analysis of the data suggested that deterioration in diabetes control lead to changes in treatment, i.e. the addition of pharmaceutical agents. Weight gain accompanied the introduction of sulphonylureas and insulin but not metformin. Deteriorating glycaemic control was not dependent on weight gain. In a prospective study the impact of an intensified weight reduction programme for diabetic patients unsuccessful in losing weight following conventional treatment, was also studied by Dr Tuthill. In collaboration with a dietician, exercise therapist and psychologist, weight reduction was achieved in the majority of patients. This intensive form of treatment is successful and deserves extended application to a larger cohort of patients for a longer period.

#### Bone Related Research:

A number of ongoing projects are undertaken in collaboration with Barbara Murray, Principal Biochemist, Metabolism Laboratory. These include:

- Identification of sub-clinical breast cancer bone metastases.*  
Evaluation of bone biomarker levels to provide early evidence of bone metastases in patients with breast cancer with normal bone scans. At the time of diagnosis bone scanning is routinely performed. This test is repeated after one and two years. A comprehensive array of bone turnover biomarkers are measured in serum and urine obtained at diagnosis pre-surgery and after one and two years. It is hoped to detect a characteristic pattern of bone biomarkers which will identify the presence of bone metastases prior to a point they are detectable by scanning. This project is undertaken in collaboration with the Department of Surgery and the Department of Nuclear Medicine.
- Indices of Bone Remodeling and Turnover.*  
Interpretation of bone turnover biomarkers is complex. Current research





## Postgraduate Department

Education and Research Centre

examines the possibility of producing indices of bone turnover and bone remodeling balance using specific pairs of markers for bone resorption and bone formation expressed as T-scores. It is likely that such indices will be disease specific eg. osteoporosis, osteomalacia, Paget's disease, hyperparathyroidism. In this way it will be possible to provide the clinician with a numerical index indicating whether there is a positive or negative bone remodeling balance and the extent of which bone formation or resorption is occurring. Similarly it will be possible to supply a single number indicating whether the rate of bone turnover is raised, normal or suppressed.

- c) *Thyroid related bone disease.* Investigations to date have indicated that hyperthyroidism is associated with increased bone turnover; reduced bone formation; and that successful treatment is associated with correction of these disorders. Ongoing studies investigate the impact of sub-clinical thyroid disorders on bone turnover and remodelling.
- d) *Bone metabolism in patients with anorexia nervosa.* Bone turnover markers are analyzed in patients who present with severe anorexia nervosa. Current studies investigate the impact of successful weight gain on bone turnover and remodeling.

### *Radioactive Iodine Treatment of Thyrotoxicosis:*

Radioiodine is an established treatment for thyrotoxicosis. The principle disadvantage is the frequent occurrence of under-activity of thyroid gland following treatment. Dr Husafa Adamali and Dr James Gibney have reviewed results from a 10 year period to examine the outcome of treatment in patients with diffuse toxic goitre and patients with toxic nodular goitre. In addition they have examined the possibility that in patients with

toxic nodular goitre the frequency of the development of hypothyroidism is directly related to the level of serum thyroid stimulating hormone (TSH). Their investigations to date have disclosed that while under-activity of the thyroid gland occurs in >50% of patients treated with diffuse toxic goitre, the recurrence is <20% to those with toxic nodular goitre. In addition, the studies tend to confirm the hypothesis that elevations in serum TSH levels prior to radioactive iodine administration of toxic nodular goitre, predispose to subsequent hypothyroidism

### *Thyroid Ophthalmopathy:*

Dr Tom Cawood has undertaken a Ph.D. project focused on the role of cytokines in thyroid associated ophthalmopathy and is exploring potential new therapeutic strategies for this challenging condition. He has recently been awarded a 3 year research grant from the Irish Research Council for Science Engineering and Technology. He also worked on a number of other projects including "cystic fibrosis-related diabetes mellitus" and "the effects of bisphosphonates on bone mineral density in cystic fibrosis".

### **Presentations**

The 22nd Joint Meeting of the British Endocrine Societies, Glasgow, UK 24-26 March 2003

The 85th Annual Endocrine Society Meeting, Philadelphia, June 19th – 22nd 2003

Irish Endocrine Society 28th Annual Meeting, Armagh, 7th and 8th November 2003

The Postgraduate Department once again had a very successful and busy year. The meetings organised at postgraduate level for the hospital staff still continue to attract a large attendance from St. Vincent's University Hospital and are a vital contact for all the NCHDs.

### **Annual Hospital Study Day**

The Hospital Annual G. P. Study Day remains a very important event for the hospital staff and the general practitioners in the community. This year our Study Day was held on Saturday 8th November and was exceptionally well attended. The format consisted of Poster Sessions as follows:

### **Open Access to Cardiovascular Examinations – Initial results**

Dr. Charles McCreery

### **Haemochromatosis**

Dr. P.A. McCormick

### **Update on Obesity Management**

Mr. Justin Geoghegan

### **The Dilemma of Suicide in Modern Ireland**

Prof. Kevin Malone

There were also two Practical Workshops:

### **New Approaches to the Management of C.O.P.D.**

Dr. Tim McDonnell

Dr. Donal McCafferty

### **Management of Complications following Prostate Surgery**

Mr. Gerard Lennon

Dr. Cathy Cullen

At 6.30pm there was a lecture by Ms. Margaret O'Donnell, Consultant Plastic and Reconstruction Surgeon, entitled "What use is Plastic Surgery to a G. P.?"

Later in the evening a reception and dinner was held in the hospital restaurant and the consensus was that this was a huge success both with regard to attendance and atmosphere.

### **Medical and Surgical Meetings**

The Postgraduate Lunch Time Meetings include:

Respiratory	Gastroenterology	Neurology
Nephrology	Palliative Care	Endocrinology
Colorectal	Surgical Audit	

There are also early morning meetings as follows:

Tuesdays at 8.00am	SHO Conference
Thursdays at 8.00am	Medical Conference
Fridays at 7.30am	Cardiology Conference

All of the above meetings are organised by the Postgraduate Department. Lunch or breakfast is provided.

### **Intern Lunch Time Seminars**

Monday Lunch Time Seminars for Interns consist of Clinical Skills Sessions and Data Interpretation.

The Tuesday Lunch Time Seminar is organised by the Medical Intern Tutor in conjunction with the Postgraduate Department. Each week an Intern presents a case to the class with a discussion on same afterwards.

Thursday Lunch Time Lectures are on matters relating to all aspects of Surgery and are given by Consultant Surgeons within the hospital.

Friday Lunch Time Seminars for the Interns are presented by guest speakers and include Career Guidance, Risk Management, Stress Management and a wide variety of other topics.

Due to demand it was decided to introduce further lectures for Interns on Wednesdays at lunch time which commenced in January 2003.

### **MRCPI Membership Tutorials**

A structured series of Membership Tutorials which run throughout the year are held on Mondays and Thursdays, usually at lunch time. These tutorials are patient orientated and focus on physical examination and interpretation of physical signs. There are also SHO/Registrar tutorials held every Tuesday morning at 8.00am.

#### Clinical Science Course

The above course is also organised by the Postgraduate Department in conjunction with the Royal College of Physicians of Ireland. These meetings are aimed at candidates preparing to sit Part II of the MRCPi Examination. The course is run from this office bi-annually, ending before the June and November examinations. The course continues to run smoothly and the standard of teaching is excellent covering such specialties as Rheumatology, Geriatrics, Haematology/Oncology, Gastroenterology, Endocrinology, Cardiology, Nephrology, Dermatology, Respiratory and Neurology.

#### International and National Meetings

In addition to the large number of in-house meetings, the Postgraduate Department helped organise the 10th Colorectal Study Day which was held on Friday 5th September 2003. This year's programme was as follows:

#### Cox II Inhibitors in Prevention and Treatment of Colorectal Neoplasia

Dr. Frank Murray

#### Contemporary Algorithms for Patients with Colorectal Cancer

Dr. Hugh Mulcahy

#### Pathological Reporting in the Molecular Age

Dr. Kieran Sheahan

#### Development of an Advanced Laparoscopic Programme

Prof. Kevin Conlon

#### Laparoscopic Colorectal Cancer Surgery – the Leuven Experience

Prof. Andre D'Hoore

The State of the Art Lecture was given by Prof. Bruce Minsky on "Adjuvant Therapy of Rectal Cancer"

The organising committee included Dr. D. Fennelly, Mr. J.M. Hyland, Prof. D.P. O'Donoghue, Dr. H. Mulcahy and Dr. K. Sheahan. The meeting was extremely well attended and interaction was excellent.

A dinner was held afterwards in the Conrad Hotel and was attended by fifty guests.

#### "Get to Know Your Function" for Incoming NCHDs

Once again this year we had a very successful and enjoyable welcoming lunch for incoming NCHDs on Monday 7th July. This event is an opportunity to give NCHDs the relevant information about ongoing lectures/conferences and welcome them to the hospital. This is now an annual event.

#### The Student Summer Project

This continues to be an important part of the hospital's academic year. The aim of the Project for the student is to develop an interest in research so that he/she will continue to develop this interest at postgraduate level. The judging panel of physicians and surgeons select the students to present a formal evening presentation based on the original abstract submitted. This year the winner was Cillian Clancy whose project was entitled "Construction of a Macrophage Migration Inhibitory Factor Mammalian Over-Expression Vector". Along with the prestige of winning this award the student also receives a monetary amount. The presentations were held on Wednesday 26th November 2003.

#### The Library

The Library is located on the first floor of the Education & Research Centre and is open to all staff of St Vincent's University Hospital Group. Its collection includes books, journals and audiovisual material covering all disciplines. Some journals are available online and many more are available via the UCD Library website.

There are 17 PCs in the Library providing access to several databases including Medline, the Cochrane Library and Web of Science. Advanced training on these products is available free of charge by appointment only. Internet, document-creating, printing, scanning and multimedia projection facilities are also available.

#### Postgraduate Education Committee

This committee is now well established and meets biannually to discuss postgraduate education in the hospital. Its aim being to enhance the education environment of postgraduate doctors at St. Vincent's University Hospital.

#### Pharmaceutical Representatives

The link for the pharmaceutical companies here in St. Vincent's University Hospital is the Postgraduate Department. The companies sponsor the Medical and Surgical Lunch and Breakfast Meetings and in turn the medical representative meets the consultants and NCHDs to discuss their products. This is an important link for both the doctors and medical representatives.

#### Postgraduate Medical Training Booklet

A Medical Booklet is now being compiled and circulated bi-annually by the Postgraduate Department. It contains valuable information re contacts in various departments, dates of tutorials and lecture programmes, useful telephone numbers etc.

Prof. Walter McNicholas  
*Co-ordinator of Postgraduate Education*

Ms. Betty McArdle  
*Administration Postgraduate Department*



## Academic Activities

Education and Research Centre

### Annual Biomedical Research Symposium 2003

#### "Common Molecular Mechanisms in Inflammation & Malignancy"

The E.R.C. Biomedical Research Symposium has emerged as a leading event in the calendar of Irish research activities with a reputation for addressing important topics in a lively stimulating environment. The aim of the biomedical Research Symposium is to explore basic and clinical research topics of relevance to all biomedical researchers, but which particularly reflect the research interests and clinical strengths of St. Vincent's University Hospital.

The Annual Research Symposium was held on Friday 21st November 2003 in the E.R.C. and was a joint meeting with the Conway Institute in U.C.D. The keynote speakers were Prof. Fionula Brennan of the Kennedy Institute in London and Prof. Jim Johnston of Queens University Belfast. The welcome address was given by Prof. Hugh Brady Dept Medicine UCD and incoming U.C.D. President

The focus on the immune mechanisms in inflammation and malignancy was a topic of relevance to several S.V.U.H. Principle Investigators and many members of the Conway Institute.

#### Session I:

##### Cytokines and Cytokine Therapies in Inflammatory and Malignant Conditions

Chair: Oliver FitzGerald & Gaye Cunnane

##### Cytokines and anti-cytokine biologicals in autoimmunity: present and future.

Fionula Brennan, Kennedy Institute, London

##### Identification of Naf1/ABIN-1 among TNF-alpha-induced expressed genes in human synoviocytes using oligonucleotide microarrays.

Joanne Gallagher, Conway Institute, UCD Dublin

##### Cytokine patterns in inflamed, infected and malignant liver tissue.

Lucy Golden Mason, S.V.U.H.

#### Session II:

##### Early Activation of Inflammation and Tumour Related Genes: Detection, Quantification and Characterisation.

Chair: Luke O'Neill & Arnold Hill

Cytokine Signalling and Disease. Jim Johnston, QUB

##### Gene Expression Profiling in Cancer: Mechanistic Insights and Biomarker Discovery.

Liam Gallagher, Conway Institute, UCD Dublin

##### Bioinformatic Microarray Analyses: Proceed with Caution

John O'Brien, RCSI

#### Session III:

##### Reactive Oxygen Species: Key Regulators of Inflammatory and Malignant Pathogenesis.

Chair: Catherine Godson & Walter McNicholas

##### Oxygen sensing mechanisms in epithelial cells.

Cornac Taylor, Conway Institute, UCD Dublin

##### ROS and IL-2 mediated apoptosis.

Deirdre Toomey, RCSI, Dublin

##### Telomere Dysfunction and Oxidative Stress: important modulators controlling the initiation and development of colorectal cancer.

Jacinta O'Sullivan, SVUH

#### Session IV:

##### Poster Discussion:

Leader: Steve Simpson, SCIENCE

#### Session V:

##### Developing a Road Map for Future Biomedical Research in Inflammation and Malignancy in Ireland

Chair Dr. Pierre Meulien,

Dublin Molecular Medicine Centre, Dublin;

Panel: Prof. Luke O'Neill, T.C.D.; Prof.

Fionula Brennan, Kennedy Institute, London;

Prof. Stephen Pennington, U.C.D. & Dr. Doug Veale SVUH

The proceedings were followed by a Tour and Dinner at Wyeth's Grange Castle Campus in Clondalkin, Co. Dublin.



## Lecture Series 2003

Education and Research Centre

### Research Methods Course

**Location** Education & Research Centre, S.V.U.H.  
**Dates** 9th January – 20th March 2003  
**Instructors** Prof. Cliona O'Farrelly  
 Mr. Hugh Mulcahy  
 Dr. Kieran Sheahan  
 Mr. Michael Casey  
 Ms. Niamh Lucey  
 Mr. Stephen Skehan  
 Mr. Jonathan Dean  
 Ms. Yvonne Buggy

This was a course for M.D., Ph.D, MCh and MSc students

### Advanced Immunobiology Course

**Location** Seminar Room, Education & Research Centre, S.V.U.H.  
**Dates** 29th January – 26th February 2003

This course built on what was covered in the Introductory Immunobiology Course provided for undergraduates in Spring 2002.

**Course Director** Prof. Cliona O'Farrelly  
**Instructors** Prof. Alex Whelan  
 Dr. Lucy Golden-Mason

### Science Writing Workshop

**By** Steve Simpson, Immunology Editor, SCIENCE Magazine  
**Venue** Education & Research Centre  
**Date** Thursday 20th November 3-5 pm  
**Title** 'Getting your science into Science: perspectives and advice on scientific publishing'

### Bioinformatics Course (graduate course)

**Venue** U.C.D.  
**Date** 1st-5th September  
**Instructors** Andrew Lloyd  
 David Lynn

### Biochemistry/Immunology (4th Year course)

**Venue** Trinity College  
**Date** 5th & 12th November  
**Instructor** Cliona O'Farrelly  
**Subject** Regional Immunity



## Research Seminars E.R.C. Journal Club 2003

Education and Research Centre

### Held in the Education & Research Centre during 2003

Friday 14th March:

Prof. A. Robin Poole, PhD DSc, Joint Diseases Laboratory, Shriners Hospital for Children, Depts. Surgery & Medicine, McGill University, Montreal, Quebec

**Title:** "Matrix Metalloproteinases and collagen metabolism in inflammation"

Thurs 27th March:

Prof. Andre Ouellette, University of California

**Title:** "Innate enteric immunity mediated by paneth cell alpha-defensins"

Friday 11th April:

Dr. John Seery, S.V.U.H.

**Title:** "The skin immune system and systemic autoimmunity"

Monday 12th May:

Prof. Peter Rabinovitch, Fred Hutchinson Cancer Centre & University of Washington, Seattle, Washington, U.S.A.

**Title:** "Genomic instability and cancer risk in Ulcerative Colitis and Barrett's oesophagus"

Friday 6th June:

Prof. Bert W. O'Malley, M.D. Baylor College of Medicine, Dept. of Molecular & Cellular Biology, Houston, Texas, U.S.A.

**Title:** "Steroid Hormone Receptors and Coactivators: Mechanisms and Biological Applications"

Prof. Brian Harvey, R.C.S.I. Beaumont Hospital

**Title:** "Physiological implications of rapid response to aldosterone and estrogen".

Dr. Leonie Young, Dept. Surgery U.C.D.

**Title:** "Estrogen receptor response to endocrine treatment in human breast cancer"

Dr. Alice McEvoy, Veterinary Physiology and Biochemistry Dept., U.C.D.

**Title:** "The NURR subfamily of transcription factors in inflammation – friend or foe?"

### E.R.C. Journal Club 2003

**Schedule** Thurs mornings 9.00-10.00am  
**Venue** Seminar Room, E.R.C.



## Prestigious Invitations to E.R.C. Researchers

Education and Research Centre

### Prof. Cliona O'Farrelly

Appointed a member of the National Hepatitis C Database Scientific & Technical Committee

Re-appointed member of the Consultative Council on Hepatitis C 2003-2006 by Michael Martin, T.D. Minister for Health & Children.

"Natural T Cells in the Liver" Annual Congress of the British Society for Immunology, Harrogate, U.K. Dec 2003

Irish Society of Gastroenterology Annual Meeting Nov 2003

Workshop on National Code of Practice for Management of Intellectual Property, Forfas/Irish Council for Science Technology & Innovation, Dublin 14th Oct 2003

"Hepatic Stem Cells – Potential for the Future" Falk Symposium No. 135 "Immunological Diseases of Liver and Gut" Prague, Sept. 12-13th 2003

Evaluator for the European Commission Descartes Prize for Excellent Transnational Collaborative Research Panel "Life Science" Brussels June 2003

Irish Skeptics Society June 2003

"New antimicrobial peptides: A chicken and egg story" Moyné Institute T.C.D. 50th Anniversary March 2003

"Hunting genomes for new anti-microbial peptides: a chicken & egg story" Conway Institute Centre for Integrative Biology Symposium, U.C.D. February 2003

Irish Society of Immunology Public Lecture RDS May 2003

Hepatitis C International Conference 25th – 27th June 2003 Trinity College, Dublin

Irish Society of Immunology Annual Conference September 2003

### Prof. Joe Duffy

Association of Clinical Biochemist (UK) Focus Meeting, Manchester "Evidence for the use of tumor markers".

XXXI International Society for Oncodevelopmental Biology and Medicine (ISOBM); Edinburgh. "uPA and PAI-1: validated prognostic markers in breast cancer".

Continuing Education Meeting in Clinical Biochemistry: Windermere (UK). "Prostate cancer: to screen or not screen?".

Association of Clinical Biochemists Ireland, Annual Conference: Dublin. "Tumor markers, current and future uses".

Professor Joe Duffy was invited to Chair the National Academy of Clinical Biochemistry Panel to establish New Guidelines for the Clinical Use of Markers in Breast Cancer

### Prof. Walter McNicholas

Invited lecturer at the annual meeting of the Japanese Respiratory Society in March 2003 in Fukuoka, Japan,

Invited lecturer at the annual meeting of the European Respiratory Society in September 2003 in Vienna

Invited lecturer at the annual meeting of the Indian Chest Society in November 2003 in Coimbatore, India

Invited lecturer at the annual meeting of the Hellenic Thoracic Society in December 2003 in Athens.

He was also an invited lecturer at the World Congress on Sleep Apnoea held in July 2003 in Helsinki.

### Prof. Barry Bresnihan

Invited speaker at the Australian Rheumatology Association

Invited speaker at the Workshop for use of new technologies in genomics, genetics and proteomics in Stockholm, and the Targeted Therapies Meeting.

Visiting Professor at Kansas University.

Professor Bresnihan co-chairs the European Synovitis Study Group.

Chairman of the Subcommittee for Academic Support, Arthritis Research Campaign (UK).

Chairman of the Arthritis Foundation of Ireland and was a member of the Oliver Bird Programme Selection Committee, Nuffield Foundation.

Professor Bresnihan served on the Editorial Board for the Journal of Rheumatology, Annals of the Rheumatic Diseases, and Joint Bone and Spine.

### Prof. Oliver FitzGerald

Invited speaker on Spondyloarthropathy at the Belgian Congress of Rheumatology.

Invited speaker on Psoriatic Arthritis at the Bodnar Institute, Oxford.

Invited speaker on Psoriatic Arthritis Update at Glasgow Royal Infirmary.

He was an external examiner for Trinity College Final Medical, Queen's University Belfast PhD thesis and Oxford PhD thesis.

Prof FitzGerald was Chairman of St Vincent's University Hospital Medical Board, a Member of the St Vincent's Healthcare Group Board, a Council Member on the Arthritis Foundation of Ireland, and Interim Director Education and Research Centre.

He was also a member on the Editorial Board for Rheumatology and Current Rheumatology.

### Dr. Charles Gallagher

Invited speaker at the American Thoracic Society Annual Meeting in Seattle and the European Respiratory Society Annual Meeting in Vienna. He was author of the American Thoracic Society Position Paper "Indications and Performance of Cardiopulmonary Exercise Testing".

### Dr. Doug Veale

Dr Veale held the position of Medical Director, Rheumatology Unit at Our Lady's Hospice, Harold's Cross.

He is the chairman of Arthritis Action Ireland and the Pain Academy, a member of the European Arthritis Action Group and a Council member of the Irish Society for Rheumatology.

He is an editor for the web-based learning vehicle, E-Medicine. He was an invited speaker at the American College of Rheumatology, Florida, the Swedish Physicians Society, Stockholm and the Irish Society of Immunology.

He was external examiner for two MD theses at Imperial College, London and The University of Sheffield.

### Dr. Kieran Sheahan

Register of Medical Specialties 2003

Treasurer, Irish Society of Surgical Pathology 2003

Invited speaker at Colorectal Study Day, Education & Research Centre, Sept 2003.

"Pathological Reporting of Colorectal Cancer in the New Molecular Era"



## Honours, Awards & Prizes 2003

Education and Research Centre

**Dr. Cliona O'Farrelly** was appointed Adjunct Professor in the Faculty of Medicine, U.C.D.

**Dr. Joe Duffy** was appointed Adjunct Professor in Faculty of Medicine U.C.D.

**Prof. Walter McNicholas** became President of the European Respiratory Society in September 2003.

### **Dr. Lucy Golden-Mason**

Best Oral Presentation at Irish Society of Gastroenterology Winter Meeting 2003

### **Dr. Anna Kelly**

Best Poster Presentation at Irish Society of Gastroenterology Winter Meeting 2003

### **Dr. Margaret O'Brien**

Best Poster presentation St.Vincent's Biomedical Symposium Nov. 2003

### **Dr Ronan Mullan**

Best oral paper at the Irish Society for Immunology.

**Dr Tom Cawood** has travelled to the Mayo Clinic this year as part of his Ph.D. training, having been awarded a Travelling Fellowship, awarded by the Royal College of Physicians and Surgeons, Glasgow. Dr Cawood will be starting the Specialist Registrar Scheme in Endocrinology in July 2004.

### **Degrees awarded**

Susan Gaines	awarded M.Sc.
Caroline O'Shea	awarded PhD
Alice McEvoy	awarded PhD
Yvonne Buggy	awarded PhD

### **Thesis submitted:**

#### **Tony Kenna**

Title: *Characterisation of CD1-restricted T cells in Adult Human Liver*

#### **Mike Curry**

Title: *CD5+ B cells in Hepatitis C Infection*

#### **Raghu Varadarajan**

Title: *Activation of the nitric oxide pathway in early ischaemia reperfusion injury following human orthotopic liver transplantation*



## Publications

Education and Research Centre

### **Published or Accepted for Publication in International Peer Reviewed Journals 2003**

Ali M, Veale DJ, Reece RJ, Quinn M, Henshaw K, Zanders ED, Markham AF, Emery P, Isaacs JD. Overexpression of transcripts containing LINE-1 in the synovia of patients with rheumatoid arthritis. **Ann Rheum Dis.**2003 Jul;62(7):663-6.

Axford JS, Cunnane G, Fitzgerald O, Bland JM, Bresnihan B, Frears ER. Rheumatic disease differentiation using immunoglobulin G sugar printing by high density electrophoresis. **J Rheumatol.**2003 Dec;30(12):2540-6.

Bairead E, Harmon DL, Curtis AM, Kelly Y, O'Leary C, Gardner M, Leahy DT, Vaughan P, Keegan D, O'Morain C, O'Donoghue D, Shanahan F, Parfrey NA, Quane KA. Association of NOD2 with Crohn's disease in a homogenous Irish population. **Eur J Hum Genet.**2003 Mar;11(3):237-44.

Balding J, Kane D, Livingstone W, Mynett-Johnson L, Bresnihan B, Smith O, Fitzgerald O. Cytokine gene polymorphisms: association with psoriatic arthritis susceptibility and severity. **Arthritis Rheum.**2003 May;48(5):1408-13.

Barry S. C., Gallagher C. G. *Corticosteroids and skeletal muscle function in Cystic Fibrosis.* **J Appl Physiol** 95: 1379-1384, 2003.

D. Brady, N. Lowe, S. Gaines L. Fenelon, J. McPartlin, C. O'Farrelly. Inhibition of S. Mutans Growth by Hen Egg Derived Fatty Acids **J Food Science** 2003 Vol.68(4)1433-1437

J. Carton, L Madrigal Estebas, B. Byrne, D.P. O'Donoghue, C. O'Farrelly. Persistently Low Numbers of CD4hiCD8lo (Double Positive) small intestinal T lymphocytes in coeliac disease. **Eur J Gastroenterol Hepatol** 2003

Chailleux E, Laaban JP, Veale D. Prognostic value of nutritional depletion in patients with COPD treated by long-term oxygen therapy: data from the ANTADIR observatory. **Chest.**2003 May;123(5):1460-6.

MP Curry, L Golden-Mason, DG Doherty, S Norris, M Duffy, N Nolan, W Hall, J E Hegarty, C O'Farrelly. Expansion of Innate CD5pos B Cells Expressing High Levels of CD81 in HCV Infected Liver. **J Hepatol** 2003; 38:642-650 PMID 12713876

Doherty LS, Kiely JL, Lawless G, McNicholas WT. Impact of nasal continuous positive airway pressure therapy on the quality of life of partners of patients with sleep apnea syndrome. **Chest** 2003; 124:2209-2214. PMID:14665502

Doherty LS, Kiely JL, Deggan PC, Nolan GM, McCabe S, Ennis S, Green AJ, McNicholas WT. A family with congenital central hypoventilation syndrome. **European Respiratory Journal** 2003; 21 (suppl):391s.

Doherty LS, Nolan P, McNicholas WT. Topical upper airway anaesthesia increases pharyngeal resistance in Stage I sleep in normal humans. **Am J Respir Crit Care Med** 2003; 167 (suppl):599.

Duffy MJ, van Dalen A, Haglund L, Klapdor R, Lamerz R, Nilsson O, Sturgeon C, Topolcan O. Clinical Utility of biochemical markers in colorectal cancer: European Group on Tumour Markers (EGTM) Guidelines. **Eur J Cancer** 2003;39:718.

Duffy MJ, Lynn DJ, Lloyd AT, O'Shea CM. The ADAMs family of proteins: from basic studies to potential clinical applications. **Thromb Haemost.**2003 Apr;89(4):622-31. PMID:12669115

Duffy T, Belton O, Bresnihan B, Fitzgerald O, Fitzgerald D. Inhibition of PGE2 production by nimesulide compared with diclofenac in the acutely inflamed joint of patients with arthritis. **Drugs.**2003;63 Suppl 1:31-6.

Fearon U, Griosios K, Fraser A, Reece R, Emery P, Jones PF, Veale DJ. Angiopoietins, growth factors, and vascular morphology in early arthritis. **J Rheumatol.**2003 Feb;30(2):260-8.

Fitzgerald S, Lyons R, Ryan J, Hall W, Gallagher C G. *Botulism as a cause of respiratory failure in injecting drug users.* **Irish Journal of Medical Science** 2003; 172:143-144.

Foell D, Kane D, Bresnihan B, Vogl T, Nacken W, Sorg C, Fitzgerald O, Roth J. Expression of the pro-inflammatory protein S100A12 (EN-RAGE) in rheumatoid and psoriatic arthritis. **Rheumatology (Oxford).**2003 Nov;42(11):1383-9.

Fortune DG, Richards HL, Kirby B, McElhone K, Markham T, Rogers S, Main CJ, Griffiths CE. Psychological distress impairs

clearance of psoriasis in patients treated with photochemotherapy. **Arch Dermatol.**2003 Jun;139(6):752-6.

Fraser A, Fearon U, Billingham RC, Ionescu M, Reece R, Barwick T, Emery P, Poole AR, Veale DJ. Turnover of type II collagen and aggrecan in cartilage matrix at the onset of inflammatory arthritis in humans: relationship to mediators of systemic and local inflammation. **Arthritis Rheum.**2003 Nov;48(11):3085-95.

S.Gaines, T.C. James, M.Folan, A.W. Baird, C. O'Farrelly A novel spectrofluorometric microassay for (*Streptococcus mutans*) Adherence to Hydroxylapatite **J Microbiological Methods** 2003 54:315-323.PMID 12842478

Gallagher J, Howlin J, McCarthy C, Murphy EP, Bresnihan B, FitzGerald O, Godson C, Brady HR, Martin F. Identification of Naf1/ABIN-1 among TNF-alpha-induced expressed genes in human synoviocytes using oligonucleotide microarrays. **FEBS Lett.**2003 Sep 11;551(1-3):8-12.

M.Garland, D. Doherty, L.Golden-Mason, P.Fitzpatrick, N. Walsh, C. O'Farrelly, Stress-related hormonal suppression of natural killer activity does not show menstrual cycle variations: implications for timing of surgery for breast cancer **Anticancer Res.**2003 May-Jun;23(3B):2531-5 PMID 12894537

Greene LM, Twal WO, Duffy MJ, McDermott E, Hill AD, O'Higgins N, McCann A, Dervan PA, Argraves WS, Gallagher W. Elevated expression and altered processing of fibulin-1 protein in human breast cancer. **Br J Cancer** 2003;88:871.

Haston JL, FitzGerald O, Kane D, Smith KD. The influence of alpha1-acid glycoprotein on collagenase-3 activity in early rheumatoid arthritis. **Biomed Chromatogr.** 2003 Sep;17(6):361-4.

Hegarty NJ, Young LS, O'Neill AJ, Watson RW, Fitzpatrick JM. Endothelin in unilateral ureteral obstruction: vascular and cellular effects. **J Urol.**2003 Feb;169(2):740-4.

Huminiecki L, Lloyd AT, Wolfe KH. Congruence of tissue expression profiles from Gene Expression Atlas, SAGEmap and TissueInfo databases. **BMC Genomics.**2003 Jul 29;4(1):31. PMID: 12885301

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Kane D, Barnes L, FitzGerald O. Topical corticosteroid treatment: systemic side-effects. **Br J Dermatol.** 2003 Aug;149(2):417.

Kane D, FitzGerald O. Re: The role of ultrasonography in the diagnosis and management of idiopathic plantar fasciitis. **Rheumatology (Oxford).**2003 Mar;42(3):486.

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study of clinical subsets in an inception cohort of early psoriatic peripheral arthritis--'DIP or not DIP revisited'. **Rheumatology (Oxford).**2003 Dec;42(12):1469-76.

Kane D, Roth J, Frosch M, Vogl T, Bresnihan B, FitzGerald O. Increased perivascular synovial membrane expression of myeloid-related proteins in psoriatic arthritis. **Arthritis Rheum.** 2003 Jun;48(6):1676-85.

T. Kenna, L. Golden-Mason, I. Steven, A. Porcelli, Y. Koezuka, John E. Hegarty, C. O'Farrelly, Derek G. Doherty. Selective depletion of V $\alpha$ 24V $\beta$ 11<sup>+</sup>T cell receptor-positive NKT cells in the livers of patients with hepatic malignancy. **J Immunol** 2003 Aug 15;171(4):1775-9 PMID 12902477

T. Kenna, L. Golden-Mason, SA Porcelli, Y. Koezuka, J. E. Hegarty, C. O'Farrelly, DG Doherty NKT cells from normal and tumor-bearing human livers are phenotypically and functionally distinct from murine NKT cells. **J Immunol.**2003 Aug 15;171(4):1775-9.PMID 12902477

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V Leiden PJ, Hayden M, O'Brien B, Collins C, O'Farrelly K, Murphy Inherited thrombotic tendency in a pedigree with antithrombin La roche (N405K) and factor **Clin Lab Haematol.** 2003 Jun;25(3):191-3 PMID 12755798

Lennon AM, Mulcahy HE, Hyland JMP, Lowry C, White A, Fennelly D, Murphy JJ, O'Donoghue DP, & Sheahan K. Peritoneal involvement in Stage II Colon Cancer **Am J Clin Path** 2003; 119:108-113.

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Martial FP, Dunleavy M, Jones JFX, Nolan P, O'Regan RG, McNicholas WT, Bradford A. Activity of dorsal medullary respiratory neurons in awake rats. **Advances in Experimental Medicine and Biology** 2003;536:445-53. PMID:14635698

Minnock P, FitzGerald O, Bresnihan B. Women with established rheumatoid arthritis perceive pain as the predominant impairment of health status. **Rheumatology (Oxford).**2003 Aug;42(8):995-1000.Epub 2003 Apr 16.

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Moloney E D, Clayton N, Mukherjee D K, Gallagher C G, Egan J J. The shuttle walk exercise test in idiopathic pulmonary fibrosis. **Resp Med** 2003; 97: 682-687.

Murphy E, Freaney R, Bresnihan B, McKenna M, FitzGerald O. Increased bone resorption and failure to respond to antiresorptive therapy in progressive dystrophic calcification. **Calcif Tissue Int.**2003 Nov;73(5):433-40.

McLaughlin AM, McNicholas WT. Sarcoidosis presenting as upper extremity venous thrombosis. **Thorax.**2003 Jun;58(6):552.PMID:12775877

Nolan GM, Doherty LS, Goodman PG, McNicholas WT. Comparison of autoadjusting and fixed positive airway pressure therapy in patients with mild to moderate obstructive sleep apnoea syndrome. **EJ Respiratory Journal** 2003; 21 (suppl): 95s

O'Donovan N, Crown J, Stunell H, Hill A, McDermott E, O'Higgins N, Duffy MJ. Caspase 3 in breast cancer. **Clin Cancer Res** 2003;9:783-742.

O'Shea C, McKie N, Buggy Y, Duggan C, Hill ADK, McDermott E, O'Higgins N, Duffy MJ. Expression of ADAM-9 mRNA and protein in human breast cancer. **Int J Cancer** 2003;105:754.

Ryan S, McNicholas W.T., O'Regan R, Nolan P. Upper airway muscle paralysis reduces the reflex upper airway motor response to negative transmural pressure in the rat. **Journal of Applied Physiology** 2003 Apr; 94(4):1307-16.PMID:12496136

Ryan S, McNicholas WT, O'Regan RG, Nolan P. Intralaryngeal neuroanatomy of the recurrent laryngeal nerve of the rabbit. **Journal of Anatomy** 2003 May;202(5):421-30.PMID: 12739619

Ryan S, McNicholas WT, Nolan P. Muscle relaxation reduces upper airway motor activity in the rat. **Am J Respir Crit Care Med** 2003; 167 (suppl):601.

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Sheehan KM, O'Donovan DG, Fitzmaurice G, O'Grady A, O'Donoghue DP, Sheahan K, Byrne MF, Conroy RM, Kay EW, Murray FE. Prognostic relevance of Fas (APO-1/CD95) ligand in human colorectal cancer. **Eur J Gastroenterol Hepatol** 2003;15:375-80

F. Smith, L.Golden-Mason, T. Deignan, S.Norris, N.Nolan, O.Traynor, G.McEntee, J.Hegarty, C.O'Farrelly Localisation of T and B Lymphocytes in Histologically Normal Adult Human Donor Liver **J.Hepato-Gastro** 2003; Sep-Oct:50(53):1311-5 PMID 14571725

Suliman AM, Smith TP, Gibney J and McKenna TJ. Frequent Misdiagnosis and Mismanagement of Hyperprolactinemic Patients before the Introduction of Macroprolactin Screening: Application of a New Strict Laboratory Definition of Macroprolactinemia. **Clin Chem** 2003;49(9) 1504-9.

Suliman AM, Freaney R, Smith TP, McBrinn Y, Murray B, McKenna TJ. The Impact of Different Glucocorticoid Replacement schedules on Bone Turnover and Insulin Sensitivity in Patients with Adrenal Insufficiency. **Clin Endocrinol (Oxf)** 2003 59(3): 380-87.

Veale D, De Haro L, Lambrou C. Cosmetic rhinoplasty in body dysmorphic disorder. **Br J Plast Surg.**2003 Sep;56(6):546-51.

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Young LS, Murphy G, Kelly SN, Smith TP, Cunningham SK, Joseph McKenna T. Differential production of adrenal steroids by purified cells of the human adrenal cortex is relative rather than absolute. **Eur J Endocrinol.**2003 Jan;148(1):139-45.



## Chapters in Books

Education and Research Centre

Bresnihan B:Management of rheumatoid arthritis:synovitis  
In: **Textbook of Rheumatology**, third edition.Edited by  
Hochberg MC, Silman AJ,Smolen JS,Weinblatt ME,Weisman  
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McNicholas WT. Impact of Sleep on Ventilation and Gas  
Exchange in Chronic **Lung Disease**. Monaldi Archives of Chest  
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101..

McNicholas WT. Impact of sleep on acute exacerbations of  
COPD. In: **Acute exacerbations of COPD**; edited by N.  
Anthonisen and N.Siafakas.Marcel Dekker, New York.2003:317  
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more to do. **Sleep Medicine Reviews** 2003 Feb;7(1):3-7.  
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Diseases.In: **Textbook of Dermatology**, Seventh Edition.Edited  
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## Invited Reviews

Education and Research Centre

Bresnihan B, Cunnane G. Infection complications associated  
with the use of biologic agents. **Rheum Dis Clin North Am**.  
2003 Feb;29(1):185-202.

Bresnihan B, Cobby M. Clinical and radiological effects of  
anakinra in patients with rheumatoid arthritis. **Rheumatology**  
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Bresnihan B. Are synovial biopsies of diagnostic value?  
**Arthritis Res Ther**. 2003;5(6):271-8.

Cunnane G,Doran M,Bresnihan B. Infections and biological  
therapy in rheumatoid arthritis. **Best Pract Res Clin Rheumatol**.  
2003 Apr;17(2):345-63.

Lynn, D. Lloyd,A.O'Farrelly C. Bioinformatics:implications for  
medical research and clinical practice. **Clin Invest Med**. 2003  
Apr;26(2):70-4 PMID 12722839

Mullan RH,Bresnihan B. Disease-modifying anti-rheumatic drug  
therapy and structural damage in early rheumatoid arthritis.  
**Clin Exp Rheumatol**.2003 Sep-Oct;21(5 Suppl 31):S158-64.

Valentini G,Silman AJ, Veale D. Assessment of disease activity.  
**Clin Exp Rheumatol**.2003;21(3 Suppl 29):S39-41.



## Grants Active 2003

Education and Research Centre

P.I.	Name of Study	Source of Grant	Fund Amount	Start Date	Finish Date
Dr. Evelyn Murphy	Pathobiologic function of - Corticotropin Releasing Hormone	HRB Research Funding	€110,000	2001	2004
Dr. Evelyn Murphy	Signal Transduction in inflammatory arthritis	HRB Research Project Grant	€150,000	2000	2003
Dr. Derek Doherty	The functional significance of diversity in human natural killer cell receptors	Enterprise Ireland Project Grant	€154,044	2000	2004
Dr. Derek Doherty	The role of intrahepatic gd T cells in immunity against hepatitis C virus	HRB Project Grant	€164,126	2001	2004
Dr. Derek Doherty	Activation and regulation of human NKT cells	Enterprise Ireland Project Grant	€72,616	2000	2003
Prof.Joe Duffy/ Brid Ryan (IRCSET)	Studies on survivin in breast cancer	Irish Research Council for Science, Engineering and Technology	€38,000	2002	2004
Prof.Joe Duffy	Role of ADAM17(TACE) in breast cancer	Health Research Board	€107,600	2003	2006
Prof.Joe Duffy	Mamaglobin as a marker for breast cancer	Irish Cancer Society	€52,000	2003	2004
Prof.Joe Duffy/ Prof. John Crown	Mode of action of the therapeutic antibody Herceptin in breast cancer.	St.Vincent's University Hospital Medical Oncology Fund	€100,000	2001	2004
Prof.Joe Duffy/ Jane Culleton (IRSET)	Studies on lipophilin B in breast cancer	Irish Research Council for Science, Engineering and Technology	€57,000	2002	2005
Prof.Joe Duffy/ Dr.W. Gallagher (Pharmacology Dept, UCD)	Use of microarray and proteomics to identify genes involved in breast cancer metastasis	Irish Cancer Society	€84,000	2003	2004

P.I.	Name of Study	Source of Grant	Fund Amount	Start Date	Finish Date
Dr. Leonie Young/ Mr.Arnold Hill	Molecular mechanisms of survivin regulation in breast cancer	Cancer Research Ireland	€97,700	2002	2005
Dr. Leonie Young/ Mr.Arnold Hill/	Chromatin remodelling in estrogen receptor target genes in breast cancer.	St.Lukes Institute of Cancer Research	€100,000	2003	2005
Dr. Leonie Young/ Mr.Arnold Hill	Role of co-regulatory proteins in estrogen receptor function in breast cancer	Presidents Award, University College Dublin	€10,000	2002	2003
Dr. Leonie Young/ Prof.T.J.McKenna	ACTH regulation of adrenal steroidogenesis	Health Research Board	€60,000	2000	2003
Dr. Leonie Young/ Mr.Arnold Hill	Estrogen receptor co-regulatory proteins in tamoxifen resistant breast cancer	Royal College of Surgeons in Ireland	€49,700	2002	2003
Prof.Cliona O'Farrelly		Westgate Biological Ltd.	€12,000	2002	2005
Dr. Margaret O'Brien (Prof.Cliona O'Farrelly)	Alternative splicing of CD1d: Generation of novel antigen presenting molecules	HRB Research Fellowship	€157,500	2002	2005
Dr. Conor O'Brien (Prof.Cliona O'Farrelly)	Cytokine Gene Polymorphisms and their association with the outcome of Hepatitis C viral infection	HRB Clinical Research Training	€89,500	2002	2005
Dr. Lucy Golden Mason/ Prof.Cliona O'Farrelly/ Prof.John Hegarty	Adult Hepatic Stem Cells	Health Research Board Post Doctoral Research Fellowship	€148,000	2001	2004
Prof.Cliona O'Farrelly/ Prof.John Hegarty	Hepatitis C Viral Load Quantification in Lymphocyte Sub-Populations and Correlation with CD81 Expression: Implications for Treatment and Prognosis	Health Research Board Postgraduate Student Scholarship	€54,700	2001	2003
Prof.Cliona O'Farrelly/ Dr. Lucy Golden-Mason	Adult Stem Cells:Development of cells in the human intestine	HRB Research Project Grant	€120,600	2001	2004
Prof.Cliona O'Farrelly/ Dr. Lucy Golden-Mason	Liver Immunology/Hepatic Lymphocyte Analysis	HRB Project Grant	€82,000		
Prof.Cliona O'Farrelly/ Prof.Dermot Kelleher/ Prof.Kingston Mills/ Dr. Derek Doherty	Characterisation Hepatitis C Induced Immunological Subversion and its Implications for Treatment Response	HRB Programme Grant	€552,000	2003	2006

## Grants Active 2003

P.I.	Name of Study	Source of Grant	Fund Amount	Start Date	Finish Date
Prof.Cliona O'Farrelly/ Prof.Colm O'Herlihy/ Dr. Lucy Golden-Mason	Cytokine Milieu,Natural Killer Receptor Positive Cells, Haematopoietic Progenitors in Human Endometrium	Enterprise Ireland Basic Research Grant Programme	€149,293	2003	2006
Prof.Cliona O'Farrelly	A combined bioinformatic, molecular and biochemical approach to the identification and analysis of antimicrobial peptides in Hen Eggs	Dept.Agriculture FIRM Grant	€671,437	2001	2005
Dr.Tom Smith/ Prof.T.J.McKenna	Structure and Etiology of Macrolactin	Health Research Board	€110,000	2002	2005
Prof.W. McNicholas/ Dr.A. Bradford/ Dr.P. Nolan	Pathophysiology of obstructive sleep apnoea	European Union	€280,000	2000	2003
Prof.W. McNicholas/ Dr. Philip Nolan	Pathophysiology of sleep apnoea	Health Research Board	€105,000	2000	2003
Prof.W. McNicholas/ Dr. Geraldine Connolly/ Dr. Peter McKenna	Sleep disordered breathing in pre-eclampsia	Friends of the Rotunda Hospital	€25,000	2001	2003
Prof.W. McNicholas	Sleep studies in COPD	Glaxo Smith Kline	€105,000	2001	2004
Prof.Diarmuid O'Donoghue/Alan Baird	Colonic Adhesion and Inflammation	Health Research Board	€74,000	2001	2003
Dr. Kieran Sheahan/ Prof.Diarmuid O'Donoghue	Familial Colorectal Cancer	Health Research Board	€150,000	2001	2004
David Gibbons	Predicting Response to Neo-Adjuvant Therapy in Rectal Cancer Using Multiple Biomarkers	St.Luke's Institute for Cancer Research	€90,000	2002	2004
Prof B. Bresnihan	Role of cytokines and growth factors in cartilage destruction in osteoarthritis	EU Fifth Framework Programme Research Grant	€190,460	2000	2003
Prof B. Bresnihan	Synovial pannus evaluation and Cytokine-targeted therapy in Rheumatoid arthritis	Amgen	€655,208	2001	2004
Prof O. FitzGerald	Kineret in psoriasis and psoriatic arthritis: a single center, open label pilot study	Amgen	€90,000	2002	2004

P.I.	Name of Study	Source of Grant	Fund Amount	Start Date	Finish Date
Dr. D.Veale	Angiogenic growth factors in Psoriasis before and after treatment with Anti TNF Therapy	Health Research Board	€129,640	2002	2004
Prof. O. FitzGerald	North/South Grant	Health Research Board	€15,655	2002	2003
Prof. O. FitzGerald	The profibrotic potential of ankylosing spondylitis synovial membrane	Health Research Board	€100,000	2001	2003
Prof. O. FitzGerald	T cell receptor analysis in seronegative Arthritis:evidence for persistence of oligoclonal T cells in remission tissue	Health Research Board	€117,000	2000	2003
Dr. D.Veale	The role of cytokine regulation of RA and the effect of TNF therapy	Pfizer	€155,000	2001	2003
Dr. D.Veale	Etanercept in psoriasis and psoriatic arthritis: a single center open label pilot study	Wyeth	€112,000	2002	2004
Dr. C. Gallagher	Continuous positive airways pressure (CPAP),Intrinsic PEEP and exercise tolerance in cystic fibrosis	CF Association of Ireland	€46,472	2000	2003