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# Medical Director

The Millennium year 2000 was another very successful year for the Education and Research Centre. I would like to thank all of my colleagues who contributed so enthusiastically to this success. The consistent high quality research output from the ERC is increasingly recognised both nationally and internationally. The very high standard of applications for research positions within the ERC reflects our enhanced stature.

This year we celebrated our 10th Anniversary. This milestone was marked by our Annual Biomedical Symposium which highlighted the theme, "Hospital-Based Research: Advancing Patient Care". The keynote speaker for the occasion was Dr. Andrew Robertson, Director Conway Institute, UCD. The graduate students who presented some of their work during the symposium included Sinead Barry (Respiratory Medicine), Denise Drudy (Microbiology/Gastroenterology), Lucy Golden-Mason (Liver Immunology), Rosemary O'Hara (Rheumatology) and Caroline O'Shea (Tumour Biology). Poster prizes were won by Paddy Costello (Rheumatology), Caroline O'Shea (Tumour Biology) and Johnny Cahill (Cardiology).

The ERC is beginning to burst at the seams, another sign of its success. The need for additional space has become a priority. This year the hospital provided additional facilities in the new portabocabin village. This addition is very welcome and allows some of the research personnel to have space for reading and writing-up.



This is my last year as Director. I have greatly enjoyed my eight years in this post. There are many people I would like to thank for their help. The two that I must single out are Cliona O'Farrelly and Marie Lambe. I would like to wish my successor in this post every success.

**Professor Barry Bresnihan**

*Medical Director*

## Director Research Laboratories

The continued commitment of SVUH to developing a vibrant research community on campus reflects growing awareness of its essential contribution to continuous improved patient care in these times of change, development and discovery. The Research Laboratories play an important role facilitating the development of a thriving research community on campus. Three key issues marked progress of the Research Laboratories in 2000:

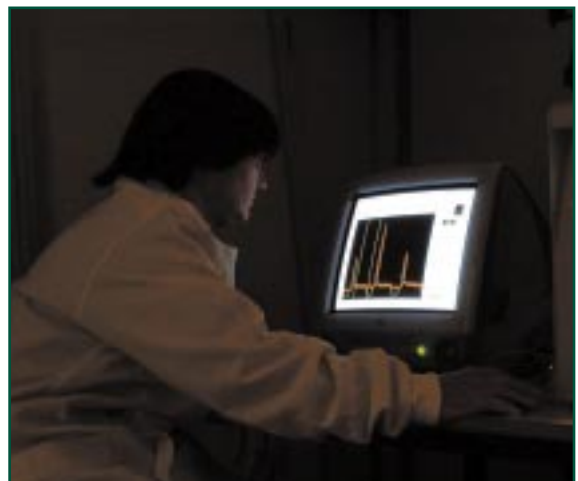
- a. successful collaborative grant applications.
- b. access to key core technologies on the Belfield Campus including gene array technology, confocal microscopy and transgenic animal facilities through the Core Conway Investigators attached to the ERC.
- c. continued pressure for space for clinical research activities.

Continued and additional funding from the Department of Agriculture has facilitated investment in the development of bioinformatics infrastructure in the Research Laboratories. Bioinformatics, (computer based analysis of genomic, transcriptomic and proteomic structure and content) will increasingly complement all biomedical research activities as the human and other genomes, transcriptomes and proteomes become available for general access.

The most vital issue currently facing the Research Laboratories, is that of space. In particular, the need to provide adequate facilities for current and future clinical research activities is becoming critical. Integrative physiology, involving collaborations with the cardiology team as well as within the respiratory and sleep apnoea groups requires additional facilities for patient based studies. The appointment to SVUH of Seamas Donnelly, Consultant Respiratory Physician and Doug Veale, Consultant Rheumatologist, both with extensive experience in clinical research, emphasises the need for clinical research wards, procedure rooms and support staff if SVUH is to further develop as a centre of excellent clinical and biomedical research.

### New Grants awarded during 2000 towards research in the ERC included:

- a. HRB Project Grant: £45,000. Leonie Young and TJ McKenna
- b. HRB Project Grant: £45,000. Joe Duffy
- c. HRB/Arthritis Council Grant: £119,000 Patrick Costello, Barry Bresnihan and Oliver Fitzgerald
- d. HRB/Arthritis Council Grant: £117,000 Evelyn Murphy, Barry Bresnihan and Oliver Fitzgerald
- e. HRB Project Grant: £40,000. Cliona O'Farrelly, John Hegarty and Tina Deignan
- f. Department of Agriculture: £500,000. Cliona O'Farrelly.
- g. HRB Equipment Grants
  - i. Microscope plus Fluorescence Filter Blocks): (Cliona O'Farrelly, Evelyn Murphy, Tina Deignan, Leonie Young, Diarmuid O'Donoghue, TJ McKenna, Barry Bresnihan) £39,119.30
  - ii. Fluoroskan plus Luminometric Microplate Reader: (Cliona O'Farrelly, Teasy Maguire, Evelyn Murphy, Joe Duffy ): £31,092.46.
  - iii. NO Analyser. (Paul McLoughlin, Clare O'Connor, Catherine Godson, Cliona O'Farrelly): £40,000



## New Members of Staff joining the Research Laboratories during 2000 Included:

Temporary Laboratory Coordinator: Carolyn Law, Ph.D

Bioinformatics Senior Research Fellow: Andrew Lloyd

Post-doctoral Research Fellow: Maria Benito

Conway Fellow: Margaret O'Brien

Enterprise Ireland Post-Doctoral Research Fellow: Joan O'Keeffe

Surgical Research Assistant: Deirdre Foley



### Graduate Students:

Sinead Barry

Susan Behan

Neil O'Brien

### Clinical Research Fellows:

John Cahill

Trevor Duffy

Susan Foley

Louise Kelly

Conor O'Brien

## Prizes and Awards

Barry Bresnihan: 1st Prize RAMI Awards for Medical Publications (Rheumatology Section)

Joe Duffy: First Prize RAMI Awards for Medical Publications (Surgical Section)

Martina Gogarty: Poster Prize, Irish Society of Rheumatology

Lucy Golden Mason: Best Poster at the Irish Society of Gastroenterology Millenium Meeting

Tina Deignan: Young Investigator Award at the American Association for Liver Disease

Leonie Young: O'Donovan Medal for Best Presentation at the Irish Endocrine Society Meeting.

## Degrees Awarded in 2000 to Researchers Based in the ERC:

**Ph.D.:** Brendan Byrne,  
Lorraine Flynn  
Kevin McCarthy

**M.Sc:** Rachel Cullen

## Publications

Over 40 publications from researchers associated with the Research Laboratories were published or accepted in peer-reviewed international journals in 2000.

## Cliona O'Farrelly Ph.D

*Director, Research Laboratories*

# Postgraduate Department

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 audience from St. Vincent's University Hospital and are a vital contact for all the NCHDs.

## Annual Hospital Study Day

The Annual Hospital Study Day continues to remain a very important day for the hospital staff and the general practitioners in the community. This year our Study Day was held on Saturday 2nd December 2000 and was extremely well attended. The format consisted of Poster Sessions on Musculoskeletal and Genito Urinary Disorders. There were also two Practical Workshops on Skin Lesions and Altered Bowel Habit.

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 7.45am	SHO Conference
Thursdays at 8.00am	Medical Conference
Fridays at 7.30am	Cardiology

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

## Intern Lunch-Time Report

The Tuesday Lunch-Time Report is organised by the Medical Tutor with the help of the Postgraduate Department. An Intern takes turn weekly to present a case on a lively current topic. The feedback from the Interns is that it is a very constructive lecture and attendance is now compulsory.

## International and National Meetings

In addition to the large number of in-house meetings, the Postgraduate Department helped organise the seventh Coloproctology Meeting. This year's topic was "New Perspectives in Colonic Cancer". The organising committee included Dr. D. Fennelly, Mr. J.M. Hyland, Dr. D.P. O'Donoghue and Dr. K. Sheahan. The meeting was considered to be the best ever with regard to attendance and interaction.

## G. P. Meetings

The monthly G. P. Meetings continue to be organised through the Postgraduate Office with Dr. Edmond O'Flaherty as convenor. As always a Consultant gives a talk on a topical subject that is relevant to the General Practitioner. These meetings continue to be an important source of contact between the hospital and the community.

## Clinical Science

The Clinical Science 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.

## The Student Summer Research 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 participating student submits a one page abstract on their Research Project and a panel of physicians and surgeons select the winner. The successful student receives a scholarship from the Hospital Board. This year the winner was Dermot Phelan whose project was entitled "Heparin and Pentosan Polysulphate inhibit Interleukin-8 ICAM-1 expression in a Human Colon Epithelial Cell Line". This was held on 16th November last.

### **"Get to Know You Function" for Incoming NCHDs**

This year we had a very successful and enjoyable welcoming lunch for incoming NCHDs on Monday 17th July which was attended by about 80 people including consultants, NCHDs, etc. The purpose of this event was to give NCHDs the relevant information about ongoing lectures/conferences and welcome them to the hospital. This is now an annual event.

### **Postgraduate Education Committee**

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

### **Medical and Surgical Booklets**

Medical and Surgical Booklets have been compiled and circulated twice yearly by the Postgraduate Department. These booklets contain valuable information re contacts in various departments, dates of tutorials and lecture programmes, useful telephone numbers etc.

### **Dr. Walter McNicholas**

*Co-ordinator of Postgraduate Education*

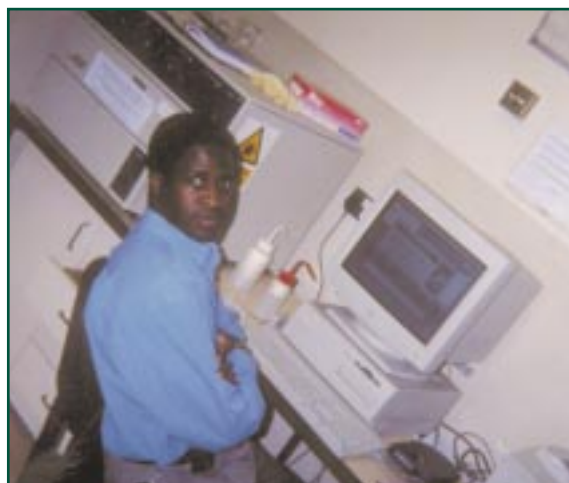
# Medical Library

The Library of St. Vincent's University Hospital caters for 500 undergraduates and 300 postgraduates from the various UCD schools - medical, nursing, diagnostic imaging, science, physiotherapy, occupational therapy, dietetics - all the elective courses attached to these, all hospital tutors and all hospital staff. It also provides services for local GPs and for personnel from SVPH.

## SERVICE ACTIVITIES

### I.T.

By far the most significant development in the area of IT in 2000 was the decision to appoint a full time Computing Services Officer in the Education & Research Centre through the Faculty of Medicine, UCD. Saul Lugoye was appointed late in the year to begin work in January 2001. His work here will be of enormous benefit not only to the Library but also to all staff members in the ERC and all who use the SVHERC server.



Another major achievement in 2000 was the purchasing of new computer and study desks in the Library. This modernized environment allows library users to study and conduct research in more comfortable and appropriate surroundings. It was achieved with the assistance of the Technical Services and Purchasing Departments.

UCD Computing Services donated 18 PCs to the library to upgrade the existing facilities and further enhance the IT services available to users.

Access to the Internet, email, and several document creating applications/databases continues. The Library also continues to provide computerised projection facilities in the lecture and conference rooms, which are complementary to the scanning and presentation options offered by the network, while we also provide scanning and zip drive facilities for Mac and PC.

The funding for these developments, as usual, came from a number of sources: from the UCD Faculty of Medicine, the Postgraduate Medical and Dental Board, the hospital consultants, and from the hospital management.

### Journals

Journal titles totalled 195. The library subscribed to 95 journals, with 95 journals taken on donation from consultants/departments/publishers. Continuing developments in electronic publishing are making journal articles more readily available on the Internet.

### Books

Book stock now amounts to over 5,000 copies; this includes 35 CD core textbooks.

### Databases

Databases subscribed to directly were the Cochrane Library and British Nursing Index. Medline, Cinahl and PsychLit were taken from the UCD network.

### Inter-Library Loans

During 1999 there were approximately 1,800 requests processed. 700 of these via UCD Medical Library, Earlsfort Terrace; and 1,100 requests exchanged within the Irish Healthcare Libraries Group.

### Council of International Hospitals

Librarian continued to coordinate requests for CIH reports on best demonstrated practices in the health care industry. Reports are issued free of charge, and are available online or in hard copy.

### Other Facilities

Tutorials, photocopying, current awareness, audio-visual resources.

The main library is open 5 days per week incl. lunchtime, 9.30am-5.30pm Monday and Friday, and 9.30am-9pm Tuesday-Thursday. The library study area is open on a 7 days-a-week, 24 hours-a-day basis, and is heavily used. There is limited computer access outside normal library hours.

The extension of the SVHERC network throughout the hospital campus allows 24 hour access from some departments to the network facilities.

### Future Developments

Plans for 2001 include upgrading the connection to the UCD network to allow for speedier transmission of data. As electronic publishing continues to develop some publishers are making their journal articles more readily available on the Internet and it is hoped that, with the support of UCD Library, 2001 will see an increase in online journal availability.

Lack of space in the Library, both for the collection and for the users, is an ongoing problem which will be addressed. The issue of security in the Library, particularly in the evenings, will also be explored. It is hoped to further develop the book collection to reflect the diverse study interests of all Hospital staff groups. Other housekeeping issues in the Library, such as the management of book loans and interlibrary loans, will also be addressed.

### Staffing

Seán Love - Librarian.

Part-time Library Assistant - Sarah Cahalane.

### Library-Sub Committee

This committee met once a month, chaired by Dr. D.P. O'Donoghue.

Its members included Mr. Pdraig Diggin (Surgery), Dr. John Boylan (Anaes), Ms. Regina Joye (School Nursing), Dr. Cliona O'Farrelly (ERC Research), Dr. Jackie Rendall (Med), and Dr. Amel Roche (Med Informatics).

The meetings have also been regularly attended by representatives from the hospital Computer Department, and UCD Computing Services.

The librarian would like to acknowledge and express his thanks for the tremendous support, encouragement, and ideas for library developments received from Dr. O'Donoghue and all the members of this committee. Finally, the librarian would like to acknowledge the hospital Senior Management Team's continued active support for library developments.

### Seán Love

*Librarian*

# Department of Preventive Medicine/Cardiology

*Bernadette Herity, Leslie Daly, Anna Clarke, Denise Comerford, Anne-Honan-Croke, Veronica O'Neill, Vivien Reid, Brenda Whiteside, Patricia Fitzpatrick, Anthony Staines, Frances Conlan*

## Service Developments/Activities

### Health Promoting Hospitals

St. Vincent's University Hospital takes a prominent position in the National Network of Health Promoting Hospitals (HPH). Denise Comerford is a member of the National Executive and the National Scientific Committee of the HPH. She has also been co-opted to the National Training Committee.



SVUH was invited by the National HPH Director to host the launch of the Minimum Standard Smoke Free Hospital Policy in May 2000 by the Minister for Health & Children, Mr. Micheal Martin. SVUH has signed up to the European Smoke Free Hospital Policy initiative. Denise Comerford represented SVUH at the launch of the Health Promotion Strategy 2001-2005 by the Minister for Health in May 2000.

The HPH is developing a training pack for use by HPH hospital co-ordinators to educate hospital staff on health promotion in the hospital setting. A short video will be included and SVUH was chosen for filming of health promotion activities in November 2000. Activities included were:

- A Cardiac Rehabilitation session
- A Transition Year Health Promotion Seminar on Cancer Awareness

- An Occupational Therapist working with an older lady in a kitchen setting
  - Still shots of Health Promotion Boards in SVUH
- Filming of Shopping Tours for cardiac patients facilitated by Vivien Reid will also be included.

### Health Promotion Training in SVUH

The Tutors in the School of Nursing invited Denise Comerford to talk to 1st, 2nd and 3rd year student nurses on the concepts, aims and responsibilities of SVUH in relation to a Health Promoting Hospital. Denise Comerford has also given presentations on the HPH to:

- Staff nurses at ward level as part of their ongoing Education Programmes
- Occupational Therapists
- Coronary Care and Accident & Emergency Nurses, as part of their Post Graduate Courses.

### Education and Training Days

Ten training days for health professionals were provided in 2000. These days are co-ordinated by this department in conjunction with colleagues within the hospital. Topics offered were:

- Inflammatory Bowel Disease with Grace McEvoy, Coloproctology Nurse Specialist and the team.
- Breast Disease with Mary Murray, Breast Care Nurse Specialist and the team.
- Interactive Listening Skills (2 days) with Brenda Whiteside and Denise Comerford, Department of Preventive Medicine/Health Promotion.
- Wound Care (2 days) with Helen Strapp, Ward Sister, St. Josephs.
- Palliative Care with the Palliative Care Team.
- Infection Control with Carmel Fallon, Infection Control Sister and the team.
- Cardio-Pulmonary Resuscitation (2 days) with Liz Tuohy, Nursing Support Staff Supervisor.

### Health Promotion Committee

Denise Comerford (Secretary) and Anna Clarke are members of the SVUH Health Promotion Committee. Denise Comerford co-ordinated SVUH's official Health Promoting Hospital Projects, which are available and updated annually on the HPH International Website ([www.ihph.ie](http://www.ihph.ie)).

### New Projects for 2000

- Introduction of a needleless system - Carmel Fallon, Infection Control Sister.
- An evaluation of staff health promoting activities within SVUH for year 2000 - Justine McGrane, Occupational Health Sister.
- Information sessions for outpatients referred to the Nutrition & Dietetic service for cholesterol lowering advice - Vivien Reid, Senior Dietitian.

### Continued Projects

- Missed Meals - Food for Thought - Kirstan Doherty, Department of Nutrition & Dietetics.
- An investigation into the development of back problems among health care students - Theresa Flynn, Physiotherapy Department.

Denise Comerford has been invited to talk on healthy lifestyle to patients in St. Camillus Ward as part of their ongoing series of weekly activities.

### Health Promotion for Staff

The Occupational Health Department and the Health Promotion Co-ordinator provided four Health Promotion Information Stands for staff in 2000. Topics were:

- Smoking
- Healthy Eating (in association with the Department of Nutrition & Dietetics)
- Cancer Awareness
- Alcohol Awareness

Denise Comerford co-ordinates the Healthwise Newsletter which is produced and distributed quarterly.



### Health Promotion Seminars for Transition Year Students

The programme of health promotion seminars for transition year students initiated in 1997 was provided again in 2000. These are held in the Education &

Research Centre, and were fully subscribed by students from the schools within the catchment area of the hospital. The feedback from teachers and students has been very positive.

Topics offered were:

- Cancer Prevention (in conjunction with Sr. T. King, Oncology Unit and Dr. D. Fennelly, Consultant Oncologist).
- Heart Health
- Smoking - Active and Passive



### Nutrition

In association with the Health Promotion Unit at the Department of Health & Children, Vivien Reid continues to organise seminars for dietitians working in community nutrition and primary care. In May a Group Counselling Skills for Dietitians training course was provided in the Education and Research Centre. The facilitator was Ms. Judy Gable, a dietitian specialising in counselling.

Vivien continues to be consulted on nutrition matters by various organisations. She is a member of the Council on Nutrition at the Irish Heart Foundation and a member of the editorial Board of Heartwise.

### Research

**Cardiac Rehabilitation** - Since May 2000, patients complete a Heart Health and Lifestyle Questionnaire when starting the Cardiac Rehabilitation Programme, at the end of the programme and at the end of one year. The aim is to document lifestyle changes during Cardiac Rehabilitation and assess how they are maintained over one year. Vivien Reid coordinates this study with the support of the multidisciplinary Cardiac Rehabilitation Team.

**Cholesterol Information Session** - A study was carried out from April to September 2000 to assess the feasibility of recruiting outpatients referred for cholesterol lowering advice to attend a one hour evening information session provided by a dietitian. A session

was provided once each month. These were well attended and proved to be popular with the patients.

This was a Health Promoting Hospitals project developed by Vivien Reid in cooperation with the Department of Nutrition & Dietetics. The Cholesterol Information Session is continuing as part of the outpatient dietetic service.

### Ongoing

Smoking Prevalence among Student Nurses - This is a follow-up study of three consecutive years' intake to the School of Nursing, which will be completed in 2001.

The St. Vincent's Hospital Heart Study - This is a study of long-term survival after a heart attack in patients recruited between 1965 and 1975. A 35-year follow up was completed in 2000.

### Cardiac Rehabilitation

The staff of the Department of Preventive Medicine and Health Promotion continue to support the well-established multidisciplinary team of cardiac rehabilitation.

### Stop Smoking Services

The department continues to offer smoking cessation services to hospital patients, staff and community. In 2000 the services included:

- Individual inpatient and outpatient consultations.
- A drop-in support session every Tuesday 1.00-2.00pm.
- Three 6-week stop smoking courses.

These services are available free of charge to staff members.

### Twenty-Four Hour Ambulatory Blood Pressure Monitoring

A twenty-four hour Ambulatory Blood Pressure Monitoring Service was provided for over 384 patients in 2000. This service takes referrals from out-patient clinics and GPs.

### Achievements

Ms. Comerford completed her Presidency of the Nurses Cardiovascular Association in May 2000. She was also appointed to the SVUH Mission Committee.

Dr. Fitzpatrick was appointed to the Department of Health & Children's Cystic Fibrosis Screening Programme Working Group 1999 - 2000 (Representative of Faculty of Public Health Medicine, RCPI) and to the Advisory Committee on North-South survey of MRSA in Ireland 1999-2000.

The 5th edition of Interpretation and Uses of Medical Statistics by Professor Leslie Daly and Professor Geoffrey Bourke was published in July 2000 by Blackwell Science.

### Future Plans

A major EU-Funded project on smoking-cessation intervention will commence in 2001. Funding for expansion of smoking-cessation services is being sought under the National Cardiovascular Strategy.

## Inflammation, Immunity and Infection

# Department of Rheumatology

Barry Bresnihan, Oliver FitzGerald, Evelyn Murphy, Patrick Costello, Maria Benito, David Kane, Eithne Murphy, Trevor Duffy, Shane Curran, Rosemary O'Hara, Alice McEvoy, Martina Gogarty, Leona Gallagher, Anne Madigan, Philomena Gallagher, Michelle Hickey

During 2000, we recruited two new post-doctoral scientists:

- a. Patrick Costello was awarded a Ph.D for his work on T cell receptor biology and remained with our group as a post-doctoral scientist.
- b. Maria Benito Ph.D was recruited from Madrid, Spain. Her work will focus on the role of cytokines in osteoarthritis.



Trevor Duffy joined the research team as a research fellow. Eithne Murphy completed her research project and rejoined the SpR scheme. She will submit her work for an MD degree. David Kane also completed his research project and moved to the SpR scheme in Glasgow. His work will be submitted for Ph.D Degree.

## Report progress in ongoing research projects during 2000

### 1. Signal Transduction in Rheumatic Disease

This work is led by Evelyn Murphy Ph.D. Recent advances have highlighted the efficacy of cytokine blocking strategies in the treatment of inflammatory arthritis, including rheumatoid arthritis (RA). However, not everyone responds to these treatments and it is clear that redundancy of cytokine actions necessitates combination therapy to interrupt positive feedback loops. The identification of signal transduction pathways involved in the pathogenesis of RA has sparked a search for novel therapeutic strategies. These intracellular signalling systems transduce extracellular signals from the cell surface to the nucleus, where they are integrated at the level of transcription factor activity. The aberrant functions of downstream transcription factors have been implicated as critical regulators of gene expression involved in chronic inflammation. Therefore specific signal transduction targets or transcription factor targets may interrupt the perpetuation mechanisms in RA and help re-establish homeostasis. We have evidence to support the conclusion that modulation of the nuclear transcription factor NURR1 by pro-inflammatory mediators is an important component of the inflammatory process in human arthritis. Our preliminary data demonstrates that NURR1 induction occurs downstream to TNF and IL-1 $\beta$  signalling and may therefore be an effective target for anti-cytokine therapy in inflammatory arthritis. The aim of our research is to gain further insight into the cytokine signalling pathways regulating NURR1 expression and to understand the regulatory targets of NURR1 transcriptional activity. These studies will provide important information on disease mechanism and pathways involved in the inflammatory process.

## 2. Role of T Cell Receptors in Arthritis

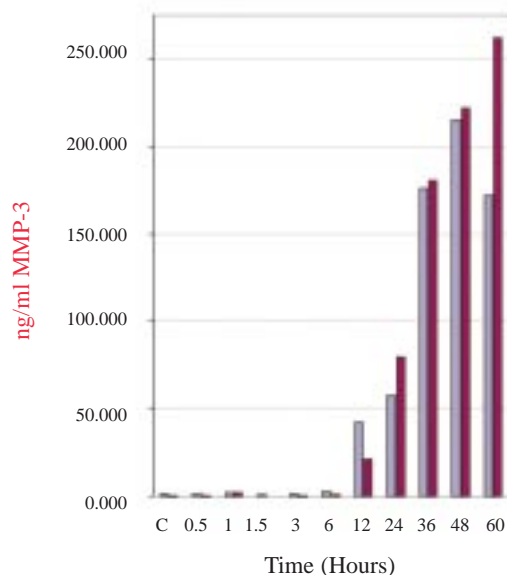
This work is led by Paddy Costello Ph.D and developed from an ongoing collaboration between Oliver FitzGerald and Robert Winchester, Columbia University, New York. In this work, it was observed that the CD8  $\beta$ T cell receptor repertoire in joint fluid in individuals with active psoriatic arthritis contained an average of 32 major oligoclonal expansions in many variable genes of the TCR  $\beta$  chain (BV) families, as shown by  $\beta$ -chain CDR3 length analysis. Interestingly, a small number of oligoclonal expansions were shared between simultaneous samples of joint fluid and blood; however, most expansions found in joint fluid were not identifiable in blood emphasizing the immunologic specificity of the clonal events of the inflamed joint at a given point of time. The CD4 T cell joint fluid repertoire contained fewer and smaller oligoclonal expansions also largely restricted to the joint, suggesting that CD4 T cells participate perhaps by interacting cognitively to generate the CD8 clones. The inferred amino acid sequence of a single CD8 oligoclonal expansion revealed that they usually are composed of one or few structurally related clones at the amino acid sequence level with  $\beta$ -chains that encode identical or highly homologous CDR3 motifs. These were not shared among patients. Moreover, several clones that encoded the same amino acid sequence were found to be structurally distinct at the nucleotide level, strongly implying clonal selection and expansion is operating at the level of specific TCR-peptide interactions. The findings support a model of psoriatic arthritis inflammation involving extensive and selective Ag, likely autoantigen, driven intra-articular CD4, and CD8 T cell clonal expansions.

## 3. Mechanisms of Serum Amyloid A Function in Human Inflammatory Arthritis

The study of serum amyloid A function has been a major focus of the Early Arthritis Unit research. Serum Amyloid A (SAA) is the circulating precursor of amyloid A protein, the fibrillar component of amyloid deposits. Acute phase SAA (A-SAA) is mainly produced by the liver under the influence of inflammatory-mediated cytokines, such as IL1 $\beta$  and TNF. Serum A-SAA increases dramatically during acute inflammation and may

reach levels 1000-fold greater than normal. The value of measuring serum A-SAA levels as a reliable surrogate marker of inflammation has been demonstrated in several diseases. It has been suggested that serum A-SAA levels may represent the most sensitive measurement of the acute phase reaction. We have demonstrated that serum A-SAA levels in 140 patients with various inflammatory joint disease correlate with other acute phase measurements such as C-reactive protein and the erythrocyte sedimentation rate. The magnitude of the A-SAA response was greatest and highest levels occurred in patients diagnosed with rheumatoid arthritis (RA). In RA, A-SAA levels provided the strongest correlation with clinical measurements of disease activity and changes in serum levels best reflected the clinical course. The biologic function of A-SAA is not known. However, a number of biologic effects have been described including several which are relevant to the understanding of inflammatory and tissue degrading mechanisms in human arthritis. It has been demonstrated that A-SAA induced adhesion and chemotaxis of human leukocytes and phagocytes and suggested that A-SAA may regulate the recruitment of these cells to inflammatory sites. Furthermore, A-SAA is a potent inducer of MMPs in the RA synovium and may play a critical role in the degradation of extracellular matrix in the rheumatoid joint. The effects of A-SAA on protease production are particularly interesting because in RA a sustained acute phase response has been strongly associated with progressive joint damage. Our recent observations support a local physiological role for A-SAA in inflamed synovium and suggest that the known association

Time course following IL-1 $\beta$  (10ng/ml) stimulation



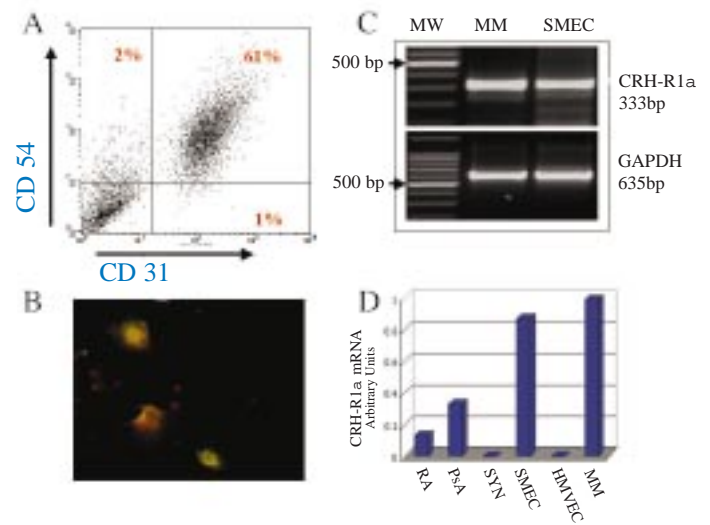
between the acute phase response and progressive joint damage may be a direct result of synovial-derived A-SAA effects on cartilage degradation.

#### 4. The Role of Vascular Endothelial Growth Factor (VEGF) and its Receptors in Inflammatory Arthritis

This work has been supervised by Evelyn Murphy Ph.D. The joint in rheumatoid arthritis is characterised by massive synovial proliferation and changes in synovial architecture resulting in inter-digitating folds of tissue, termed pannus. The formation of active inflamed pannus is thought to be central to erosive disease resulting in joint destruction. Angiogenesis, the formation of new blood vessels, is one of the earliest histopathologic findings in rheumatoid arthritis (RA) and appears to be required for pannus development. Until recently, the endothelium lining the blood vessels was thought to be a passive bystander in the inflammatory processes of RA. However, it is now recognised as playing an active and pivotal part in the recruitment of leukocytes to the inflamed synovium. Endothelial cells have become recognised as critical in a variety of pathophysiological processes including inflammation, angiogenesis and leukocyte trafficking. The cellular players, soluble factors and environmental conditions that are able to affect these events in rheumatic disease are only beginning to be explored. Vascular Endothelial Growth Factor (VEGF), also known as vascular permeability factor, is a specific mitogen for endothelial cells. Modulation of VEGF-receptor mediated signalling may be an important mechanism regulating inflammatory events in human arthritis. We propose that VEGF signalling, through its receptor, Flt-1 and Flt-1, may play a role in both vascular changes and pathologic mechanism associated with joint inflammation. Defining these mechanisms may result in a better understanding of RA pathogenesis and will likely have an impact on the care we give to patients.

#### Honors, Awards and Prizes

The Department was awarded a number of significant research grants, including Health Research Board, Wellcome Trust, European 5th Framework, Amgen. The Department continues to be represented at major international conferences including the British Society for Rheumatology, EULAR, and the American College for Rheumatology.



## Inflammation, Immunity and Infection

# Gastrointestinal Infection and Antimicrobial Strategies

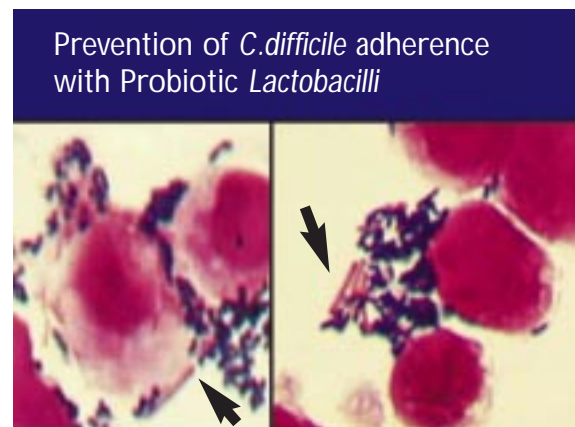
Damien Brady, Susan Gaines, Joseph McPartlin, Lynda Fenelon, Denise Drudy, Diarmuid O'Donoghue, Alan Baird, Mike Folan, Cliona O'Farrelly

Gastrointestinal infection is responsible for an astonishing incidence of morbidity and mortality in developed as well as developing countries. Emergence of antibiotic resistant organisms has stimulated major new research initiatives into finding novel ways of preventing and treating bacterial disease. A key step in initiating gastrointestinal infection is colonisation of the gut by the pathogen - a step which requires adherence of the infectious agent to its target. Our research group has developed a number of assays for investigating bacterial adherence to targets. We are using these assays to test novel strategies for preventing bacterial adherence.

### *Clostridium difficile* Adherence to Human Intestinal Epithelial Cells: Prevention with Probiotics

*Clostridium difficile* (*C. difficile*) is a common cause of diarrhoea in hospitalised patients. Bacterial adherence to gut epithelium is a likely prerequisite to toxin production and infection. Antimicrobial therapy results in loss of the normal colonic flora, allowing this organism to colonise and infect. Probiotics may restore the normal flora and could be used as an alternative therapy. For this study, we developed a novel method for testing adherence of fluorochrome-labelled *C. difficile* to intestinal epithelial cells (EC) isolated from biopsy specimens. Two Lactobacilli strains were labelled with a second fluorochrome to allow differentiation from *C. difficile*. As the host inflammatory response to *C. difficile* is characterised by marked neutrophil recruitment in the intestinal mucosa, the role of intestinal EC in initiating an inflammatory response was addressed by examining ICAM 1 expression in cells exposed to *C. difficile* and / or lactobacilli strains by flow cytometry. IL8 secretion was also measured by ELISA. Toxigenic and non toxigenic *C. difficile* adhered to colonic and small intestinal EC. Adherence was blocked using specific *C. difficile* antiserum. Both lactobacilli strains adhered to human colonic epithelial cell lines and competed with *C. difficile*, reducing the amount of adherent bacteria. Constitutive ICAM expression was upregulated on EC following

incubation with toxigenic and non-toxigenic *C. difficile* strains and lactobacilli strains. EC secretion of IL8 was greater after infection with toxigenic bacteria than non-toxigenic and was reduced following preincubation with lactobacilli strains. In conclusion, adherence of *C. difficile* to human intestinal epithelial cells can be usefully quantified using flow cytometry. *Clostridium difficile* adherence is significantly inhibited by probiotic lactobacilli which may therefore be useful for both the treatment of recurrent or relapsing *C. difficile* infection, or prevention of disease in high risk patient cohorts.

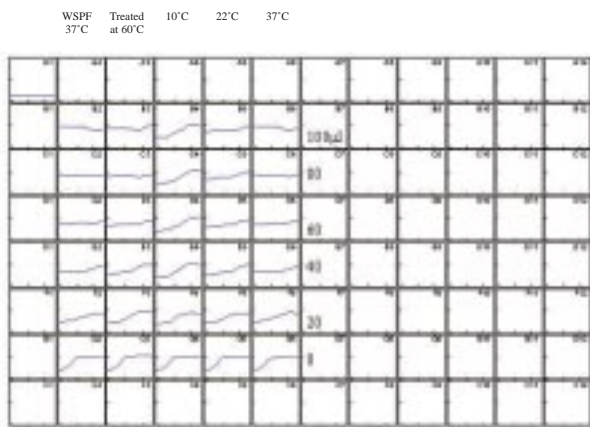
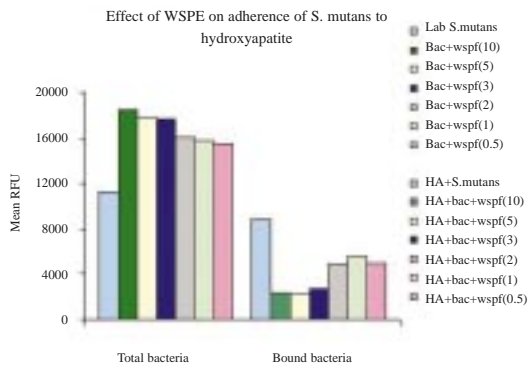


### *S. mutans* Adherence to Hydroxyapatite: a Model for Dental Caries

Dental caries is a widespread microbial infection of dental hard tissue. *S. mutans* adherence to the oral mucosa and tooth enamel is known to be the primary step in the pathogenesis of dental caries. During the past year, in collaboration with our Industrial partner (Mike Folan, Director of Westgate Biological), we have developed a model of streptococcal adherence enamel using hydroxyapatite and have examined the potential of milk and egg preparations to inhibit adherence of *S. mutans*. In this period, initial steps have been made to identify the preparations with the greatest levels of anti-*S. mutans* activity and also to develop formulations with broad range activity with the intention of developing novel dental healthcare products.

## Isolation and Characterisation of Avian Antimicrobial Factors

During the course of this study funded by the Dept. of Agriculture, we successfully identified novel antibacterial activity in hen egg yolk. Two types of activity were detected, namely inhibition of bacterial adherence to hydroxyapatite and growth inhibition. In the past year we have characterised these novel antibacterial activities in hen egg yolk and shown that they reside in the water soluble protein fraction of hen egg yolk. We have also shown that particularly high levels of anti-Streptococcal activity can be detected in the lipid fraction of egg yolk. Employing acetone extraction of egg yolk we were able to obtain a preparation which was 97% triglyceride and highly antibacterial to Streptococcal strains. The effect of these fatty acid rich fractions or non-immune yolk proteins on *S. mutans* has not yet been reported. The possibility that egg yolk may inhibit caries-inducing activity of oral Streptococci could have significant implications on the oral healthcare industry.



## Inflammation, Immunity and Infection

# Gastrointestinal Cancer Research

*Diarmuid O'Donoghue, David Fennelly, John Hyland, Kieran Sheahan, Cliona O'Farrelly, Joan O'Keefe*

There are 1785 new cases of colorectal cancer every year in Ireland. Apart from skin cancer, this is the single largest group of cancers. It has a high morbidity & mortality and a significant impact on the community and the health service. Our multidisciplinary group has a large database of patients with almost 2000 patients. All are well phenotyped clinically and pathologically. Numerous multidisciplinary and collaborative research projects are in progress.

These include:

Molecular analysis of colorectal cancer: its role in detecting familial cancer & predicting response to chemotherapy (*Dr AM Lennon, Dr D Leahy, Dr W Gallagher & Prof A Greene*)

Molecular analysis of dysplasia in ulcerative colitis (*in collaboration with Prof F. Shanahan, UCC*)

Analysis of fibulin-1 expression in colorectal cancer (*in collaboration with Dr W Gallagher, UCD*)

Detailed clinical & pathological analysis of neoadjuvant chemoradiotherapy treatment in rectal cancer (*Drs A Brannigan, S Connolly & D Treanor*)

Assessment of peritoneal involvement in colorectal cancer (*Dr AM Lennon*)

Investigation of Ets transcription factors in colorectal cancer (*Robert Geraghty, Drs T Maguire & Dr C Farrelly*)

Dendritic cell infiltration & cancer-specific death rates in colorectal cancer (*Dr Conor Delaney, Dr J Quinlan, Catherine Geoghegan*)

NK T cells in colorectal cancer (*Dr Joan O'Keefe, Dr. Derek G Doherty, Margaret O'Brien, Dr C O'Farrelly*)

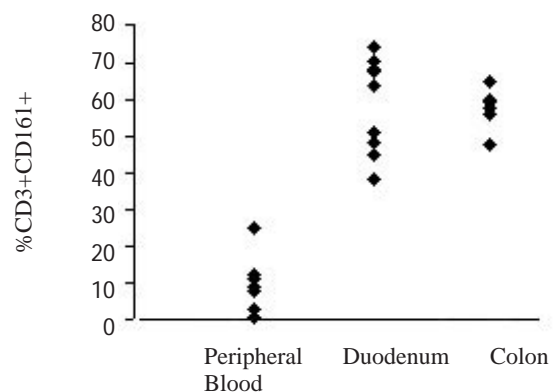
Fas ligand expression in colorectal cancer (*in collaboration with Dr K Sheahan, Dr E Kay & Dr F Murray, RCSI*)

### Natural Killer T Cells in Adult Human Intestine: an Important Anti-Tumour Defence Mechanism?

Natural killer T cells (NKT) are a heterogeneous population of T lymphocytes that display phenotypic and functional characteristics of both classical T lymphocytes

and natural killer cells. They have been found in large proportions in the human liver and are thought to have an important role in tumour surveillance. In recent studies, we have identified significant proportions of these NKT cells which express CD161 in human small and large intestine, markedly contrasting with results from the peripheral blood. *In vitro* stimulation with phorbol-esters and ionomycin induces the CD161+ NKT cells from both the duodenum and colon to produce inflammatory cytokines, interferon gamma and tumour necrosis factor alpha. The significance of these findings is unknown but their high frequency in the intestine suggests a unique anti metastatic role. As part of the present proposed research it is planned to investigate further the phenotypic, signalling and functional features of the intestinal CD161+ NKT cells.

Several studies now suggest that NKT cells are the major effector cells in the rejection of tumours and in the inhibition of experimental tumour metastases. Specific changes in these characteristics in human colon may be associated with the development of colon cancer. Preliminary studies have shown changes in the numbers of NKT cells in the tumour tissue from patients with colonic cancer compared with normal control tissue. In further studies, we propose to characterise the potential anti-malignant role of CD161+ NKT cells by examining the cytokine elaboration and cytotoxic activity in colon cancer. Specific changes in the numbers, cytokine products or functional properties in human colon may have important novel implications in the development of colon cancer.



## Inflammation, Immunity and Infection

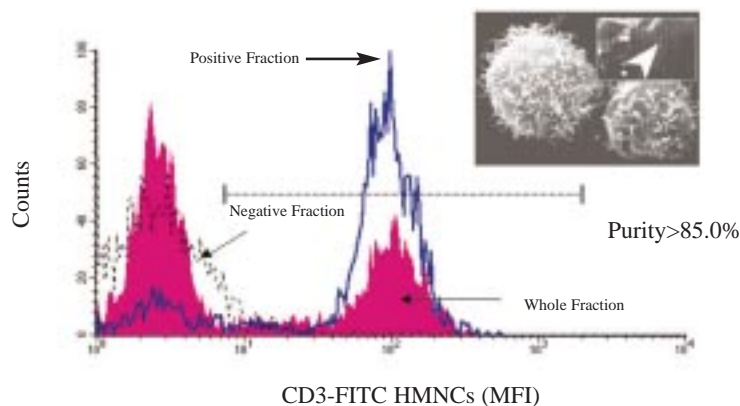
### Liver Research

Derek Doherty, Lucy Golden-Mason, Anne Farrell, Raghu Varadarajan, Tony Kenna, Susan Behan, Margaret O'Brien, Anna Kelly, Conor O'Brien, Gerry McEntee, Oscar Traynor, Justin Geoghegan, Niamh Nolan, William Hall, John Hegarty, Cliona O'Farrelly

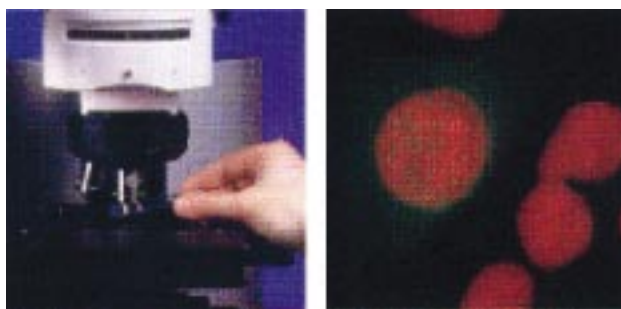
The National Liver Transplant Unit based at SVUH has transplanted more than 150 patients and has figures that compare with some of the best centres in the UK and Europe. The research programme initiated in 1993 to complement the clinical programme continues to develop. Clinical and science graduates of the programme are now in positions in leading hepatology and biotechnology centres, new technologies are being introduced and collaborations established. Work produced by the group has made significant contributions to the new field of liver immunology which is now emerging as a functional bridge between innate and adaptive immune systems. Basic research in hepatic immunology has been critical for the development of an exciting and productive programme in Hepatitis C research at SVUH.

#### Liver Stem Cells

Lucy Golden-Mason, John Hegarty, Cliona O'Farrelly  
The capacity of the liver to regenerate has long been recognised. Several lines of evidence suggest that the adult human liver harbours epithelial stem cells which can give rise to either hepatocytes or biliary epithelium. Our early studies demonstrated the presence of functional stem cells, with the capacity to form erythroid and multiple monocytic/granulocytic colonies *in vitro*. Studies in mice suggest that one important physiological role of hepatic stem cells is to give rise to immunoregulatory cells which play an important role in the prevention of infection and hepatic metastases and are involved in the generation of tolerance.



Immunophenotyping studies carried out by the liver group have provided evidence to support the existence of a similar haematopoietic pathway in the normal adult human liver. The publication of recent reports, which indicate that in man, bone marrow-derived stem cells can differentiate into hepatic epithelium, has generated the intriguing possibility that hepatic cells of epithelial and blood lineages may arise from a common stem cell. However, the bone-marrow stem cell compartment comprises a heterogeneous population of cells at different stages of maturation, which may contain separate haematopoietic, stromal and epithelial stem cell populations. We are now investigating whether the hepatic stem cell compartment comprises separate haematopoietic and epithelial precursors. This study is being carried out in collaboration with Prof. Alastair Strain and Dr. Heather Crosby of the University of Birmingham and has been funded in part by the HRB Research Visits Scheme. The demonstration of stem cells in the adult liver raises exciting possibilities for the future. Intervention in the normal development pathways of adult stem cells has the potential to provide us with a natural, safe, tool to tailor the immune system to be more effective in the elimination of disease, induction of peripheral tolerance and stimulation of tissue regeneration. Defining whether a common stem cell gives rise to both epithelial and haematopoietic lineages has important implications for the design of therapeutic strategies which exploit the innate-regulatory and regenerative properties of the liver.



## Mechanisms Contributing to Short Term Graft Outcome Following Orthotopic Liver Transplantation : the Role of Nitric Oxide and Nitric Oxide Related Apoptosis

Raghu Varadarajan, Gerry McEntee, Oscar Traynor, Justin Geoghegan, John Hegarty, Paul McLoughlin, Cliona O'Farrelly

It has been shown that nitric oxide can play a major role in tissue damage following ischaemic insult. We propose that nitric oxide mediates injury during cold ischaemia and reperfusion in donor livers and that nitric oxide related apoptosis mediates organ damage during human liver transplantation. Thus by including antioxidants in the preservation fluid we may be able to protect against ischaemic damage. We are using the new NO analyser obtained through a successful HRB Equipment Grant application led by Prof. Paul McLoughlin to measure nitric oxide and metabolite levels in human donor liver before and after cold ischaemia. We are making similar measurements after reperfusion and propose to correlate the findings with acute cellular rejection and short term graft outcome.

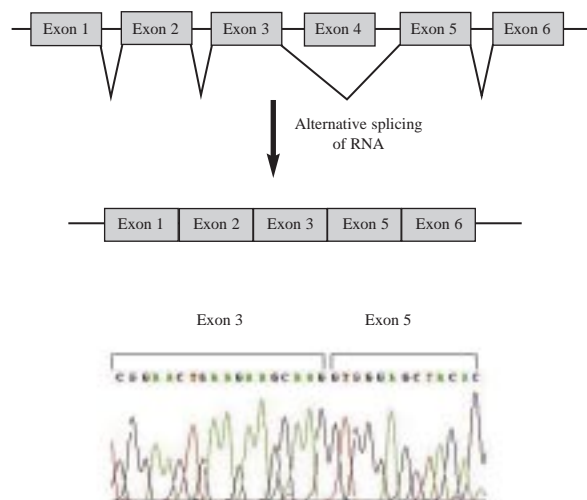
## CD1d Expression in Liver

Margaret O'Brien, Derek Doherty, John Hegarty, Cliona O'Farrelly

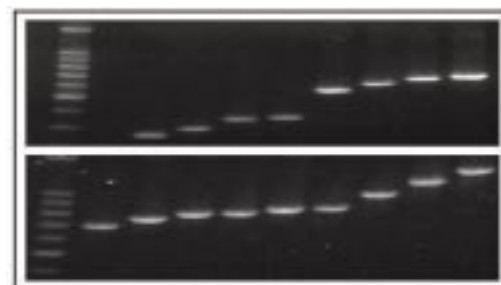
The human CD1 family, located on chromosome 1q22-23, is a family of nonpolymorphic cell surface glycoproteins. There are five distinct members - CD1a-e that are conserved in different mammalian species. These molecules are closely related to MHC class I genes having a similar intron-exon structure and are able to associate with  $\beta$ 2-microglobulin. The binding of lipid antigen to CD1 molecules and subsequent recognition by T cells suggests that CD1 proteins represent a third lineage of antigen presenting molecules, capable of presenting non-peptide lipid and glycolipid antigens to T

cells. In particular, CD1d can bind a synthetic glycolipid  $\alpha$ -Gal-Cer.

We have examined CD1d expression at the level of mRNA in normal and tumour bearing liver tissue. Complex alternative splicing of the gene, generating multiple isoforms, was observed. Some of these isoforms lack exons for the extracellular ligand binding domains ( $\alpha$ 1 and  $\alpha$ 2), the  $\beta$ 2-microglobulin binding domain ( $\alpha$ 3), the transmembrane region (Tm) or the cytoplasmic tail (C).



Although the function of these isoforms is not yet known, it is likely that loss of key domains involved in ligand binding/presentation would dramatically alter the three dimensional structure and stability of these molecules. In future work, the tissue distribution of these isoforms will be determined. In addition binding/presentation of antigen, signalling through the cytoplasmic tail and stability of alternative transcripts will be examined.



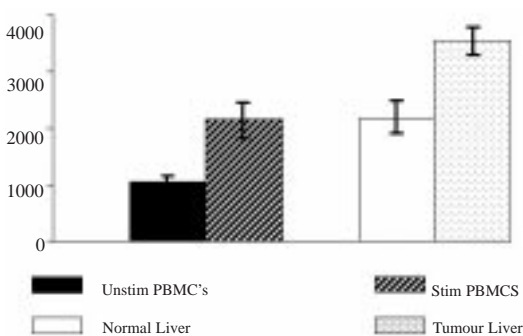
Alternative spliced transcripts of CD1d  
Transcripts were amplified by RT-PCR and cloned into the pCB2 1-TOPO vector from Invitrogen. Vector inserts were amplified using M13 primers, and separated on 1% agarose gel

## Hepatic Cytokine Microenvironment

Anna Kelly, John Hegarty, Cliona O'Farrelly, Derek Doherty

Previous studies carried out by the liver group have shown that the adult human liver contains a unique lymphocyte repertoire. The liver is dominated by the presence of innate lymphocytes, natural killer (NK) and natural killer T (NKT) cells, which have important anti-metastatic properties. It is not known what properties influence the unique functional and phenotypic characteristics of hepatic lymphocyte populations. It is likely that locally produced cytokines promote the survival and expansion of cells involved in tumour immunity. Interleukins (IL)-12, 7 and 15 have all been implicated in promoting tumour-specific killing activity. The levels of these cytokines have been investigated in both the normal and tumour bearing liver. IL-12 was significantly increased in tumour bearing compared to normal liver, whereas IL-7 and IL-15 were not. Our studies have also shown that IL-12 expands NKT cells, known to have important antimetastatic functions in mice. The high level of IL-12, IL-7 and IL-15 in normal liver is suggestive of a distinct hepatic cytokine microenvironment. The raised level of IL-12 in tumour bearing liver suggests that locally produced cytokines are important in the host antitumour response. These findings have implications for future therapeutic manipulation.

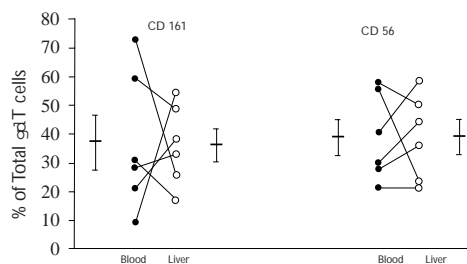
IL-12 levels in Liver and Peripheral Blood Mononuclear cells (PBMC's)



## The Role of Hepatic Lymphocytes in Innate Immunity

Tony Kenna, John Hegarty, Cliona O'Farrelly, Derek Doherty

Because of its unique location and enormous blood supply, the adult human liver is exposed to a very large and diverse antigenic load. The immune response in the liver must be capable of recognising and responding appropriately to a range of antigens including bacteria, viruses, toxins, tumour cells and harmless self- or dietary antigens. Aggressive immune responses must be directed against pathogens and malignant cells, while self- and dietary antigens must be tolerised. Consequently, the liver must be a site of specialised and tightly regulated immune responses. However the mechanisms by which the local hepatic immune system distinguishes between different types of danger and selectively activates the appropriate effector functions are poorly understood.



Previous studies from our group have shown that the liver contains large numbers of lymphocytes involved in the early stages of defence. These cells, which we have collectively termed 'innate lymphocytes', include Natural Killer cells, Natural Killer T (NKT) cells and  $\gamma\delta$  T cells. Innate lymphocytes have been shown to produce a range of cytokines including IFN- $\gamma$  and IL-4 which promote cytotoxicity by T cells and antibody production by B cells, respectively. They are therefore able to regulate the activity of other cellular subsets and to potentially affect the outcome of an immune response. Innate lymphocytes are also thought to recognise a much broader range of antigens than conventional lymphocytes. It is our belief, therefore, that these cells may act as a first line of the adaptive defences against pathogens and tumours and as such as a bridge between the innate and adaptive immune systems. At present we are examining the phenotype and effector functions of hepatic  $\gamma\delta$  T cells and NKT cells with a view to identifying the key regulators of the adaptive immune response to tumour cells and pathogens.

## Hepatic Natural T cells in Chronic Hepatitis C Virus Infection

Michael Curry, Derek Doherty, Tina Deignan, Suzanne Norris, MA Morsy, Gerry McEntee, Oscar Traynor, John Hegarty, Cliona O'Farrelly

Liver damage in chronic hepatitis C virus (HCV) infection is characterised by the presence of large numbers of lymphocytes which may be the result of an infiltration of peripheral blood lymphocytes or an expansion of resident populations. Resident liver lymphocytes include distinct subpopulations of T cells, natural killer (NK) cells and natural T (NT) cells, the majority of which produce inflammatory (Th1) cytokines and are capable of cytotoxicity. It is not known which populations of lymphocytes contribute to liver damage in HCV infection. We therefore have compared the liver repertoires and their cytokine secretion profiles in patients with end-stage HCV cirrhosis with those from normal healthy donors. Lymphocytes were isolated from wedge liver biopsies from individuals undergoing liver transplantation for end stage HCV cirrhosis and 7 normal donors. The proportions of liver lymphocytes expressing conventional T cell phenotypes were increased in end-stage HCV cirrhosis compared to controls while the proportions of NT cells were decreased. The proportions of NK cells were unchanged. The increase in T cells was mainly associated with an expansion of CD4+ T cells. Analysis of cytokine production by individual subpopulations indicated that the majority of the CD4+ T cells that are expanded in HCV cirrhosis can produce the inflammatory cytokines IFN $\gamma$ , TNF $\alpha$  and/or IL-2, while only a minority produce the antiinflammatory (Th2) cytokines IL-4, IL-5 and/or IL-10. These data suggest that the effector cells that contribute to liver cirrhosis in chronic HCV infection include abTCR+, CD4+ Th1 effector cells. The reductions in the proportions of hepatic NT and gdTCR+ cells early inducers of Th2 immune responses, may favour the expansion of these inflammatory T cell subpopulations.

## Hepatitis C Viral Load Quantification

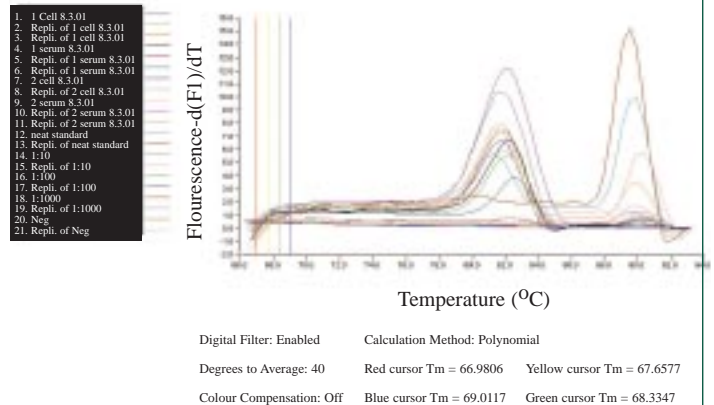
Susan Behan, Lucy Golden-Mason, Margaret O'Brien, John Hegarty, Cliona O'Farrelly

A significant proportion of patients infected with Hepatitis C do not show a sustained response to treatment with interferon. This may be because the virus remains sequestered during treatment and is capable of rapid replication and reinfection as soon as treatment is

terminated. It is possible that certain types of lymphocytes act as reservoirs of viral infection leading to resistance to interferon treatment. The aim of this project is to quantify the Hepatitis C viral load in serum and in lymphoid sub-populations from the peripheral blood and liver of infected patients. Real Time RT-PCR on the Light Cycler will be used to quantify viral load in CD5+ and CD5- B cell, and ((- and ((- TCR+ T cells. Levels of HCV will then be monitored inpatients undergoing combination therapy to identify potential reservoirs of the virus. Identification of HCV reservoirs may allow for development of more effective methods of monitoring and evaluation of treatment as well as the design of more effective therapies. Current work is focused on optimising Real Time RT-PCR conditions for measuring HCV RNA in anti-D patients found to be HCV positive by conventional PCR.

### LightCycler Manual Tm Estimation Report

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Run Version: 3.39 Analysis Version: 3.1.102



## Appointments

The appointment of Conway Fellow, Margaret O'Brien from Jean Dausset's laboratory in Paris has made a significant contribution to the groups.

## Prizes and Invitations

Lucy Golden-Mason won first prize at the ISG Millenium meeting for her work on 'Lymphocyte Differentiation in Adult human Liver'.

Cliona O'Farrelly was invited to talk at the American Association of Liver Diseases on 'Human Liver Lymphocytes'

Cliona O'Farrelly and Derek Doherty were invited to write a review on Liver Lymphocytes for Immunological Reviews

## Tumour Biology

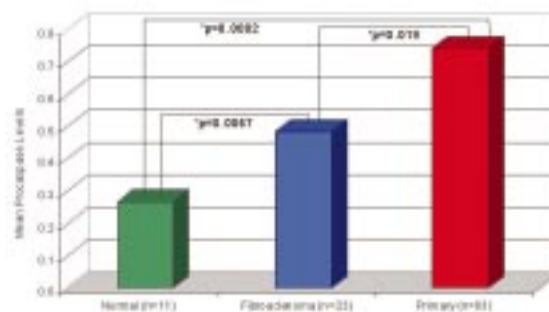
# Breast Cancer

Norma O'Donovan, Caroline O'Shea, Yvonne Buggy, Rachel Cullen, Neil O'Brien, John Crown, Arnold Hill, Enda McDermott, Niall O'Higgins, Joe Duffy

### Caspases in Breast Cancer

Norma O'Donovan, John Crown, Joe Duffy

It is now widely believed that most chemotherapeutic drugs induce tumour regression by causing apoptotic cell death. The principle mediators of apoptosis are a family of cysteine aspartate proteases, known as caspases. They are synthesised as inactive proenzymes requiring proteolytic processing in cells undergoing apoptosis. Caspase 3 is a terminal effector of apoptosis and degrades substrates such as DNA repair enzymes and structural components of the cell resulting in DNA fragmentation and cell death. We measured caspase 3 expression in primary breast carcinomas, fibroadenomas and normal breast tissue samples by Western Blot analysis. All samples tested were positive for procaspase 3, however the active enzyme was only detected in 49.4% of primary carcinomas, 43.5% of fibroadenomas and 18.2% of normal breast tissues. Although all samples tested expressed procaspase 3, levels were higher in carcinomas compared with either fibroadenomas ( $p=0.019$ ) or normal breast tissues ( $p=0.0002$ ). We found no significant difference in levels of active caspase 3 between primary breast carcinomas, fibroadenomas and normal breast tissues. The apoptotic index was also measured in primary breast carcinomas, fibroadenomas and normal breast tissue samples using a Cell Death Detection ELISA. The apoptotic index did not differ significantly between primary breast carcinomas and fibroadenomas but was significantly lower in normal breast tissues than in fibroadenomas ( $p=0.0294$ ). Furthermore, there was a strong correlation between the apoptotic index and the level of active caspase 3 in the primary breast carcinomas ( $p=0.0003$ ). Our results indicate that the apoptotic index is higher in primary breast carcinomas and fibroadenomas than in



Mean levels of Procaspase 3 in normal breast tissue, fibroadenomas and primary breast carcinomas determined by densitometry analysis of Western blots. Procaspase 3 levels are expressed relative to  $\beta$ -actin.

normal breast tissues. Also since caspase 3 levels correlated with the apoptotic index it may be a measure of ongoing apoptosis and thus a potential marker for predicting response to cytotoxic drugs.

### Estrogen Receptor - $\beta$ Role in Breast Cancer

Rachel Cullen, Brigid Browne, Belinda Byrne, Arnold Hill, Enda McDermott, Niall O'Higgins

The estrogen receptor (ER) is the prototype predictive marker in oncology, being widely used to select tamoxifen sensitivity in patients with both early and advanced breast cancer. Recently, a new form of ER known as ER $\beta$  was identified, the original ER is now designated ER $\alpha$ . As ER $\beta$  can bind both estrogens and tamoxifen, it is a potential adjunct to ER $\alpha$  in selecting sensitivity to endocrine therapy in patients with breast cancer. In this study, ER $\alpha$  and ER $\beta$  were measured at mRNA level using RT-PCR in 181 breast carcinomas and 33 fibroadenomas. ER $\alpha$  was detected in 21/33 (64%) of the fibroadenomas and in 121/181 (67%) of the carcinomas ( $p$ , NS). ER $\beta$  however, was present more frequently in the fibroadenomas (70%) compared to the carcinomas (43%) ( $p=0.007$ ). In the carcinomas, ER $\beta$  was present in a greater proportion of samples positive for

ER $\alpha$  mRNA than those lacking this receptor form. ER $\alpha$  but not ER $\beta$  was significantly associated with ER protein as determined by both ELISA and immunohistochemistry. ER $\alpha$  mRNA was also positively correlated with progesterone receptors (PR) but ER $\beta$  showed an inverse relationship with PR. We conclude that the existing ER protein assays appear to be mostly detecting ER $\alpha$ . However, as ER $\beta$  binds tamoxifen and is expressed in a proportion of breast cancers, it may be an adjunct to ER $\alpha$  for predicting anti-estrogen sensitivity/resistance in breast cancer.

## Regulation of Expression of ADAMs in Breast Cancer Cell Lines

Caroline O'Shea, Joe Duffy

The ADAMs (A Disintegrin And Metalloprotease) are a group of membrane-bound glycoproteins that are comprised of multiple modules, including a metalloprotease domain, an adhesion domain, a cysteine-rich region and an EGF-like repeat. Because these glycoproteins contain both protease and adhesion domains, they are potentially important in cancer invasion and metastasis. Previously, we studied the distribution of different ADAMs in breast cancer extracts. The purpose of this study was to evaluate the regulation of expression of ADAM-9, 10, 11 and 15 by the tumour promoter, phorbol 12-myristate 13-acetate (PMA). Expression was studied at both mRNA and protein level using 2 different breast cancer cell line, ie, MDA-MB-231 and MCF-7. Expression of ADAM-9, 10, 11 & 15 was induced in a dose and time dependent manner when MDA-MB-231 cells were treated with PMA. The stimulatory effect of PMA was seen within 1 hr, peaked at 6 hrs, and declined thereafter (up to 24 hrs). Except for ADAM-11 which declined after PMA treatment, similar results were obtained using MCF-7 cells. In general, identical results were obtained at both mRNA and protein levels.

In addition, processed forms of ADAM-9 & 10 protein were detected in the culture media of PMA-treated MDA-MB-231 and MCF-7 cells. Increasing levels of these forms in the media coincided with declining protein levels in the cell lysates. This suggests that potentially active cleaved ADAMs are shed by the MDA-MB-231 and MCF-7 breast cancer cell lines.

In conclusion, these ADAMs are rapidly and transiently increased with kinetics common to immediate early genes. The induction of ADAM-9, 10, 11 & 15 by PMA suggests a role for the protein kinase C (PKC) pathway in the regulation of their gene expression.

## Ets-1 AND Ets-2 Transcription Factors In Human Breast Cancer

Yvonne Buggy, Joe Duffy, Enda McDermott, Arnold Hill, Niall O'Higgins, Teresa Maguire

Ets-1 and Ets-2 are members of the Ets family of transcription factors known to regulate the expression of a number of genes involved in remodelling of the extracellular matrix. Both Ets-1 and Ets-2 can induce the expression of proteases such as uPA and MMP's. The aim of this study was to examine Ets-1 and Ets-2 mRNA levels in a large series of primary breast carcinomas and to compare them to levels found in normal breast and fibroadenoma tissue. Ets levels were also correlated with proteases commonly increased in human malignancy (uPA, MMP-2, MMP-9).

	Ets-1		Ets-2	
	% Pos	Mean*	%Pos	Mean*
Normal (n=39)	54	0.141	49	0.087
Fibroadenoma (n=31)	65	0.310	55	0.173
Primary (n = 147)	69	0.286	70	0.375

\*Mean Levels (Arbitrary Units) following densitometry

Ets-1 levels were increased significantly in the carcinomas compared to the normal group ( $p=0.039$ ). Ets-2 was expressed more frequently in the carcinoma group ( $p=0.021$ ) and mean levels were statistically higher than those in the normal ( $p=0.0001$ ) and the fibroadenoma groups ( $p=0.013$ ). Neither Ets-1 nor Ets-2 correlated with tumour size, nodal status or tumour grade. Ets-1, however, correlated inversely with ER status ( $p=0.0075$ ,  $r=0.22$ ) and Ets-2 correlated inversely with both ER ( $p=0.0001$ ,  $r=0.34$ ) and PR status ( $p=0.0225$ ,  $r=0.22$ ). Furthermore, both Ets-1 ( $p=0.0051$ ;  $r=0.29$ ) and Ets-2 ( $p=0.034$ ,  $r=0.22$ ) correlated positively with MMP-2 mRNA levels. No correlation existed between Ets factors and MMP-9 or uPA. The impact of Ets-1 and Ets-2 on disease-free interval and overall survival is currently being assessed.

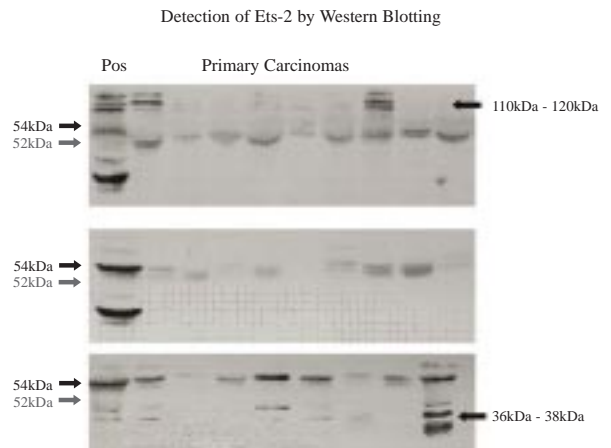
Increased levels of Ets-1 and -2, their ability to induce MMP production and the recent discovery that Ets-2 can inhibit apoptosis, suggests that they may be contributing to the metastatic phenotype observed in breast cancer.

## Higher Degrees

Rachel Cullen was awarded a MSc for her work on estrogen receptor-  $\beta$  in breast cancer.

## Awards

The Royal Academy of Medicine in Ireland award for the best publication in Surgery was won by a paper jointly written by members of the Nuclear Medicine and Surgery Departments. The winning paper was entitled: Preoperative CA 15-3 Concentrations Predict Outcome of Patients with Breast Carcinoma. The paper was published in *Cancer* (1998;83:2521), the authors being: Sheering SG, Sherry F, McDermott E, O'Higgins NJ and Duffy MJ.

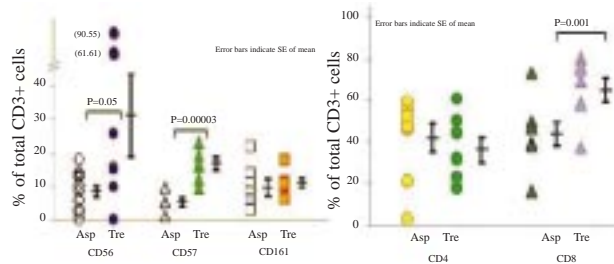


## Tumour Biology

# Haematological Malignancies: A Role for Bone Marrow NT Cells

Donald McCarthy, Lucy Golden-Mason, Jonathan Dean, Cliona O'Farrelly

Natural T cells (NT cells) are a sub-population of T-lymphocytes that can be characterised by the co-expression of the T-cell surface marker CD3 with one, or more, Natural Killer Cell markers. These cells are thought to be important in protecting against malignancy and include the human homologue of murine NK1.1+ T-cells. In murine liver and bone marrow, NK1.1+ T-cells represent up to 50% of the T-lymphocytes present and our own group has observed similar proportions of NT cells in human liver. Initially, we discovered NT cells in human bone marrow aspirates at levels much lower than expected. Therefore, we began investigation of cells extracted from solid trephine biopsies. Having developed a technique to extract the cells, we performed phenotypic examination, as for the aspirates. We have found NT cells, and CD8+ T-cells, in significantly larger proportions in solid human bone marrow than in liquid aspirates. More NT cells in the bone marrow produce the cytokines IFN- $\gamma$  IL-4 and Granzyme B in response to short-term stimulation than T-cells not expressing NK markers. We also have evidence that the activation pathways of NT cells from the periphery (and, perhaps, the bone marrow) differ from those in conventional T-cells. Coupled with a statistically larger frequency of CD8+ cytotoxic T-cells (which may or may not also be expressing NK cell markers), these results indicate that there is a mixed population of cells, some with cytotoxic capabilities, resident in human bone marrow. The presence of such cells - capable of rapid activation and subsequent target cell killing-may highlight a role in surveillance against nascent malignancies.



## Metabolism and Physiology

# Department of Endocrinology

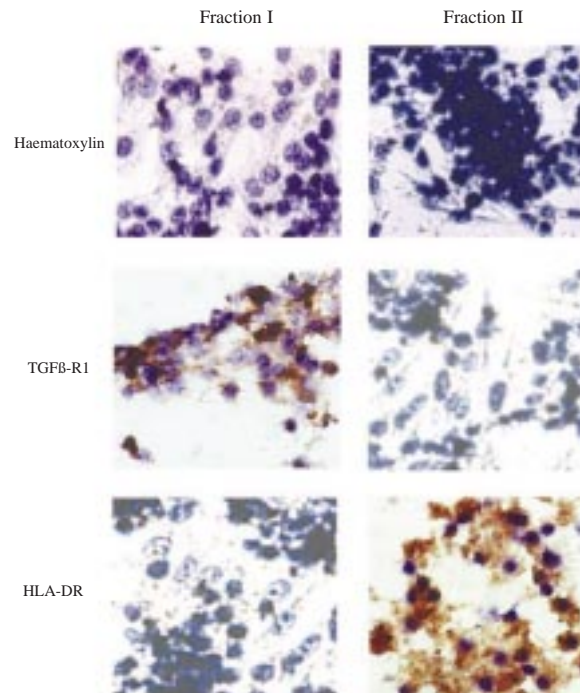
Leonie Young, Geraldine Murphy, Sinead Kelly, Abdulwahab Sulieman, Aoife O'Keefe, S K Cunningham, Thomas Smith, T J McKenna

### Control of Adrenal Steroidogenesis

The adrenal cortex produces aldosterone, cortisol and adrenal androgens in response to secretagogues including ACTH and angiotensin II. This work has investigated the differential response of morphologically distinct cells of the human adrenal to these classic secretagogues. Leonie Young, Geraldine Murphy and most recently Sinead Kelly have demonstrated that purified adrenocortical cells are capable of producing a wide range of steroids, but that the relative production of cortisol, androgen and aldosterone differs. Relative differences in the expression of key steroidogenic enzymes in different zones of the human cortex and following stimulation in a human adrenal tumour cell line, is currently under investigation. Enzyme regulation by classic and novel transcription factors is of particular interest. This work will allow greater understanding of the physiological functioning of the adrenal cortex and will give fundamental insight into common disorders such as hypertension and infertility.

### Significance of Macroprolactin

A significant proportion of subjects noted to have hyperprolactinaemia on further evaluation are found to have a bio-inactive prolactin autoantibody complex termed macroprolactin. Macroprolactin is detected by most prolactin immunoassays and commonly leads to misdiagnosis of hyperprolactinaemia. In conjunction with the Irish External Quality Assessment Scheme macroprolactinaemic sera were distributed to Laboratories throughout the country to assess their effects on prolactin measurements. Depending on the analytical method used, prolactin levels varied from relatively normal to grossly elevated. Such findings are of critical importance given that macroprolactin is present in 20% of the hyperprolactinaemic population. Patients in whom a diagnosis of hyperprolactinaemia is accounted for by macroprolactinaemia may a) be given a misleading diagnosis, b) undergo inappropriate imaging of the



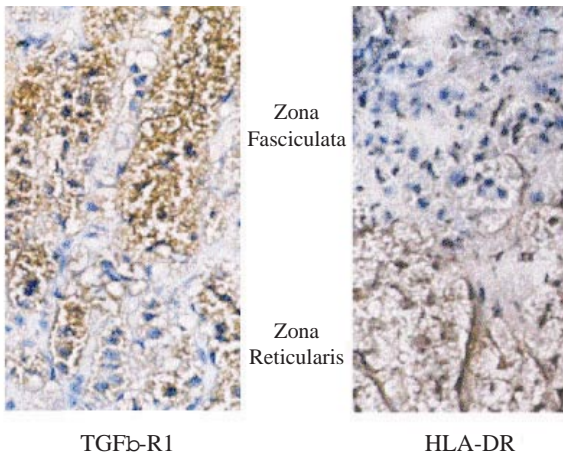
pituitary gland, with CT or MRI scanning and c) be prescribed unnecessary drug treatment. Inappropriate investigation and unnecessary treatment occur in approximately 70% of patients with macroprolactinaemia if this clinical entity is not recognised. The clinical significance of macroprolactinaemia is being investigated further by Dr. Abdulwahab Sulieman.

Production of an auto-antibody against the hormone prolactin suggests the occurrence of an auto-immune phenomenon in such individuals. However, when we compared common markers of auto-immunity such as anti-nuclear or anti-thyroid autoantibodies, we did not find generalised activation of the humoral immune system. Clinical review similarly failed to identify increased levels of autoimmune disease in macroprolactinaemic individuals over their hyperprolactinaemic counterparts. In contrast we have demonstrated a significant increase in CD5 positive B cells in macroprolactinaemic subjects compared to true hyperprolactinaemic or normoprolactinaemic control subjects. Attempts to directly quantify anti-prolactin

auto-antibody levels in sera using ELISA and immunoblotting approaches are currently being developed.

### Assessments of Tests for Secondary Adrenal Insufficiency

Investigations have confirmed the hypothesis that to establish a diagnosis of secondary adrenal insufficiency it is necessary to have a test which evaluates the entire hypothalamic-pituitary-adrenal axis such as the overnight metyraprone test, widely used in our Clinical Endocrinology practice. Investigations using ACTH stimulation of the adrenal gland alone either in conventional or in low doses as recently recommended, are associated with unacceptably high false positive and false negative results depending upon the plasma cortisol cut-off points utilised.



### Evaluation of Different Replacements Regimes for Adrenal Insufficiency

These studies identified significant differences in insulin sensitivity and bone turnover using three different schedules of glucocorticoid replacement including hydrocortisone 15 and 20 mg per day and dexamethasone 0.1mg/15kg body weight.

Dexamethasone had the least favourable effects. Hypoglycaemia utilised to evaluate insulin sensitivity consistently caused suppression of the parathyroid hormone levels in the blood.

## Metabolism and Physiology

# Departments of Medicine & Physiology

*MX FitzGerald, Paul McLoughlin, C Ryan, John Moynihan, J Laffey, Jean-Marc Hyvlin, Natalie Hopkins, Susan Foley, Kathy Howell, Alasdair Thin*

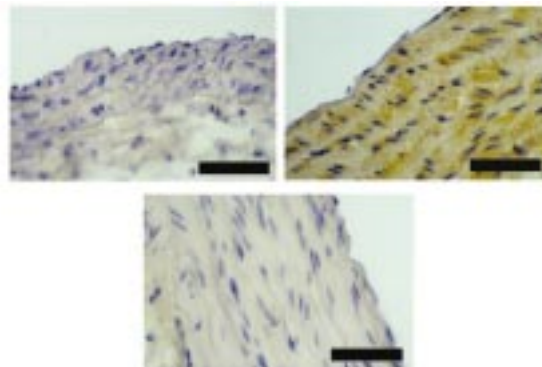
### Nitric Oxide in Chronic Inflammatory Lung Disease

The lung disease caused by cystic fibrosis is characterised by persistent infection leading to a chronic inflammatory response and progressive lung damage. The gas nitric oxide is produced in large amounts in inflamed tissues and it may have an important role in regulating the inflammatory response and protecting the lungs against invading microorganisms. Recently, it has been suggested, based on work "in the test tube" that the production of this gas is impaired in cystic fibrosis because a key enzyme in its production, inducible nitric oxide synthase, is not present. The resultant deficiency may allow chronic lung infection to become established. Recent findings from this project include:

That in patients with cystic fibrosis there is evidence that the low NO production can be further reduced by the anti-inflammatory action of corticosteroids. This suggests that inducible nitric oxide synthase is present in this disease but that its activity may be reduced (Clodagh Ryan, Alasdair Thin, John Moynihan).

That in other chronic infective lung conditions NO production may be reduced suggesting that this is not a finding specific to cystic fibrosis (Natalie Hopkins, Elaine Cadogan, Clodagh Ryan).

The findings suggest that low NO production is a feature of chronic lung inflammation of any cause that increasing its production may provide a useful therapeutic strategy in the future.



### Exercise Performance in Cystic Fibrosis

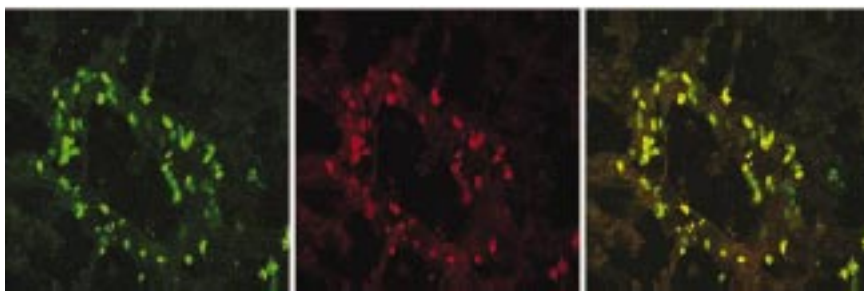
*Alasdair Thin*

One of the most serious consequences of cystic fibrosis is that it causes lung damage, which leads to a reduction in exercise capacity. Reduced exercise capacity is associated with a poorer long-term prognosis and there is evidence that exercise training improves quality of life and prognosis in these patients. Alasdair Thin, in a collaborative study with Charles Gallagher, Rosemarie Freaney, Jonathan Dodd and Sinead Barry, has demonstrated that an abnormal pattern of ventilation contributes significantly to impaired carbon dioxide excretion through the lungs in this condition.

### New Research Projects

#### Role of RhoA in Vascular Remodeling and Angiogenesis in the Lung

Alteration of the structure of blood vessels (vascular remodeling) is an important component of many diseases of the lung. We have recently found that growth of new blood vessels (angiogenesis) also occurs in chronically inflamed lungs (Natalie Hopkins). Jean-Marc Hyvelin has joined the group to investigate the role of the RhoA pathway in this process.



### **Investigation of the Protective Effects of Hypercapnic Acidosis in Sepsis-Induced Acute Lung Injury**

In a collaborative project with the Department of Anaesthesia and Intensive Care, John Laffey has joined the group to investigate the potential role of elevated carbon dioxide concentrations in protecting the lungs against damage in the presence of serious infections.

### **Higher Degrees Awarded**

Dr. N Hopkins was conferred (PhD)

Dr. Elaine Cadogan was conferred (PhD)

## Metabolism and Physiology

# Respiratory Medicine and Cystic Fibrosis

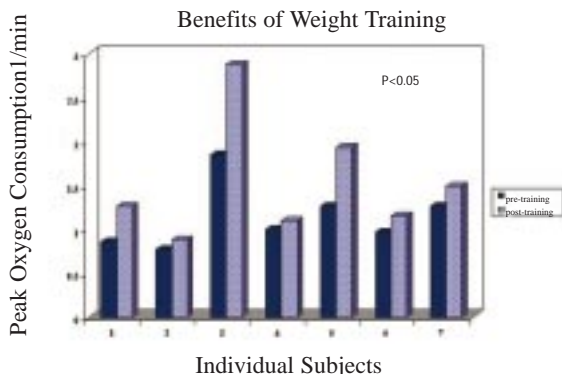
Charles Gallagher, Sinead Barry, Jonathan Dodd, Donal O'Callaghan

### Research Projects During 2000

#### Quality of Life and Muscle Function and Exercise Capacity in Cystic Fibrosis

Sinead Barry, Charles Gallagher

Sinead Barry's research focuses in particular on rehabilitation in Cystic Fibrosis patients. Sinead's work looks at the mechanisms and treatment of impaired quality of life in adults with Cystic Fibrosis. Her initial studies showed that measurement of quality of life is reproducible and sensitive to change in patients with Cystic Fibrosis. In order to assess the benefits of different exercise interventions reproducible assessment tools are required. Sinead has spent some time examining the reliability and usefulness of some frequently used clinical methods of measuring exercise capacity, muscle function and quality of life. Sinead has demonstrated that a significant relationship exists between long-term use of corticosteroids and muscle function in Cystic Fibrosis patients. She has also demonstrated the association between reduced peripheral muscle strength, exercise capacity and quality of life in CF patients. Her most recent work has focused on the benefits associated with peripheral muscle strength training. Sinead has found that improvements in exercise capacity, peripheral and respiratory muscle strength and quality of life are associated with increasing peripheral muscle strength. Her work is funded by scholarships from the Health Research Board and the National Rehabilitation Board.

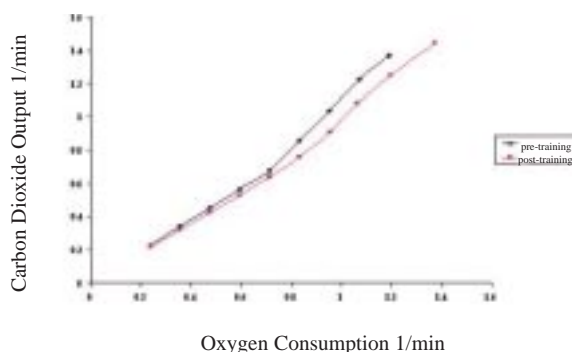


#### Respiratory Adaptations to Exercise in Patients with Mild Cystic Fibrosis

Jonathan Dodd, Sinead Barry, Charles Gallagher

We have already demonstrated that exercise is limited in patients with moderate to severe cystic fibrosis. Respiratory factors appear to play a very prominent limiting role which we have demonstrated using the technique of dead space loading. Jonathan Dodd studied the factors limiting exercise performance in patients with mild cystic fibrosis. He found that contrary to current conceptions, not all our patients with mild disease were limited by respiratory factors and some demonstrated a similar exercise capacity to those of normal subjects.

Changes in Exercise responses as a result of Weight Training



#### The Effects of Inhaled B2 Agonists on Exercise in Patients with Cystic Fibrosis

Jonathan Dodd, Sinead Barry, Charles Gallagher

There is little information on the effects of bronchodilators on exercise in patients with cystic fibrosis. Jonathan Dodd tested the effect of an inhaled B2 agonist, salbutamol, on maximal exercise capacity, breathing pattern and sense of dyspnoea in adult patients with cystic fibrosis in a randomized, double blind, placebo controlled crossover study. These results show that B2 agonists do not impair maximal exercise performance in adults with cystic fibrosis and work synergistically with exercise to improve lung function parameters. This paper is currently being prepared for submission for journal.

## Effect of Verbal Stimulation on Exercise Performance in Patients with Lung Disease

*Jonathan Dodd, Sinead Barry, Aidan Moran, Charles Gallagher*  
It has been shown in normal volunteers and patients with COPD that external stimuli can significantly influence the degree of perceived exertion during exercise. This in turn translates into higher total exercise times and improved external work performance. In this paper Jonathan Dodd found that verbal motivation did stimulate improved exercise capacity. The mechanisms underlying this are psychological as no change was found in VO<sub>2</sub> max. This study has important implications in using cycle ergometry in this patient group.

## An Evaluation of Pulsed Dose Oxygen Delivery in Patients with Cystic Fibrosis

*Donal O' Callaghan, Sinead Barry, Charles Gallagher*  
Donal O' Callaghan is a final year Physiotherapy student in UCD Donal's work looks at the effectiveness of Pulsed Dose Oxygen Delivery (PDOD) when compared with continuous flow oxygen and air, in the maintenance of arterial oxygen saturation and heart rate, and the effects on exercise tolerance, during a modified shuttle

walk test. Donal has demonstrated that the PDOD system is as effective as continuous flow oxygen in maintaining arterial oxygen saturation, both interventions are more effective than air in terms of increasing exercise tolerance, and maintaining oxygen saturation.

## Honours, Awards and Grants

Health Research Board of Ireland PhD Scholarship  
Cystic Fibrosis Research Grant 2000-2003 (Cystic Fibrosis Association of Ireland)

## Academic Programme

# Biomedical Research Seminars

February 25th, 2000

**Dr. Patrick Costello**

(Department of Biochemistry, Education & Research Centre, SVUH)

"T Cells in Psoriatic Arthritis."

March 3rd, 2000

**Dr. Susan McDonnell**

(Dublin City University)

"Matrix Metalloproteinases: Tumour-Stromal Interactions."

March 10th, 2000

**Professor Lionel Fry**

(Imperial College, London)

"The Genetics of Psoriasis."

March 24th, 2000

**Professor John Dalton**

(School of Biotechnology, Dublin City University)

"Cathepsin L Proteinases of Parasitic Helminths."

## Lecture Series

### Introduction to Immunobiology

Introduction to the Organs, Cells and Molecules of the Immune System.

*Dr. Cliona O Farrelly*

Innate and Adaptive Immune Systems.

*Dr. Joan O' Keffe*

T Lymphocytes: Genetics, Phenotype and Function.

*Dr. Patrick Costello*

B Lymphocytes: Immunoglobulin Diversity, Function and the Humoral Immune Response.

*Lucy Golden-Mason*

Structure of Antigen Presenting Molecules, the Major Histocompatibility Complex and Immunogenetics.

*Dr. Margaret O'Brien*

Immune Response to Bacterial Infection.

*Dr. Laura Madrigal-Estebas*

Immune response to Viral Infection.

*Dr. Joan O' Keffe*

Failure of Host Defence Mechanisms: Autoimmunity, Hypersensitivity and "the Immune Response as a Double Edged Sword".

*Dr. Patrick Costello*

Control and Manipulation of the Immune Response.

*Dr. Evelyn Murphy*

Laboratory Based Immunological Techniques.

*Dr. Cliona O'Farrelly*

# 10<sup>th</sup> Anniversary of ERC/Seventh Annual Biomedical Research Symposium

The Education & Research Centre (ERC), St. Vincent's University Hospital (SVUH), was opened in 1990. It is emerging as one of the nations leading biomedical research institutions, with research interests that reflect the clinical strengths of the hospital. Post-graduate training of researchers from medical and scientific backgrounds contributes significantly to its developing profile. In ten years, 31 post-graduate degrees have been awarded to researchers, including 17 Ph.Ds. Over 250 original papers have been published in international peer-reviewed medical and scientific journals. In collaboration with leading national and international groups, SVUH researchers use molecular and cellular approaches to study inflammation, infection, immune dysfunction and metastatic processes in human disease. Continued developments in these areas will have significant impact on the improved future care of St. Vincent's University Hospital patients.

## Hospital-Based Research: Advancing Patient Care

### SVUH Graduate Student Research Presentations I

**Chair:** Professor Muiris FitzGerald  
(Professor of Medicine, UCD/SVUH)

#### Sinead Barry

*"Muscle dysfunction and exercise intolerance in cystic fibrosis: a novel approach to treatment."*

#### Denise Drudy

*"Clostridium difficile adherence to intestinal epithelium: prevention with probiotics."*

#### Lucy Golden-Mason

*"Haematopoietic stem cells in adult human liver: a source of local T lymphocyte differentiation?"*

### SVUH Graduate Student Research Presentations II

**Chair:** Dr. Ruth Barrington  
(Chief Executive Officer, HRB)

#### Rosemary O'Hara

*"Biological effects of acute phase proteins: the regulation of serum Amyloid A receptor gene expression in human synovium."*

#### Caroline O'Shea

*"The ADAMS family of membrane proteins: a sinister role in breast cancer."*

#### Guest Lecture

#### Dr. Andrew Robertson

(Director, Conway Institute, UCD)

*"From basics to bedside: the role of a hospital-based research programme."*

Gala Dinner, O'Reilly Hall

## Degrees Awarded to ERC Personnel in 2000

Name	Degree Awarded	Year
Brendan Byrne	Ph.D	2000
Rachel Cullen	MS.c	2000
Lorraine Flynn	Ph.D	2000
Kevin McCarthy	Ph.D	2000

## Principal Investigators-

### Education & Research Centre

Barry Bresnihan M.D.  
 Donald McCarthy  
 John Crown  
 Gerry McEntee M.Ch.  
 Joe Duffy Ph.D  
 T.J.McKenna M.D.  
 Lynda Fenelon  
 Paul McLoughlin M.D.  
 M.X. FitzGerald M.D.  
 Walter McNicholas M.D.  
 Oliver FitzGerald M.D.  
 Diarmuid O'Donoghue M.D.  
 Charles Gallagher M.D.  
 Cliona O'Farrelly Ph.D  
 Justin Geoghegan M.Ch.  
 Kieran Sheahan M.D.  
 John Hegarty M.D.  
 Oscar Traynor M.Ch.  
 Arnie Hill M.D.

## Publications in International Peer-Reviewed Journals - 2000

### Research Papers

Bresnihan B, Tak PP, Emery P, Klareskog P, Breedveld F  
*Synovial biopsy in arthritis research: five years of concerted European collaboration.*

**Ann Rheum Dis 2000;59:506-510**

Chauhan A, Sridhar G, Clemens R, Krishan B, Marciniuk DD, Gallagher CG  
*Role of respiratory function in exercise limitation in chronic heart failure.*

**Chest 2001 (in press)**

Costello PJ, Winchester RJ, Curran SA, Peterson KS, Kane DJ, Bresnihan B, FitzGerald OM  
*Psoriatic arthritis joint fluids are characterized by CD8 and CD4 T Cell clonal expansions that appear antigen driven.*

**J Immunol 2001 (in press)**

Cullen R, Maguire T, Diggin P, Hill A, McDermott E, O'Higgins N, Duffy MJ  
*Detection of estrogen receptor-beta mRNA in breast cancer using RT-PCR.*

**Int J Biol Markers 2000;15:114**

Cunnane G, Madigan A, Murphy E, FitzGerald O, Bresnihan B  
*The effects of treatment with interleukin-1 receptor antagonist on the inflamed synovial membrane in rheumatoid arthritis.*

**Rheumatology 2001 (in press)**

Curry M, Golden-Mason L, Nolan N, Parfrey N, Hegarty J, O'Farrelly C  
*Increased primordial B cells in the peripheral blood may be protective in chronic Hepatitis C virus infection.*

**J Hepatol 2000;32:121-125**

Curry M, Norris S, Golden-Mason L, Doherty D, Deignan T, Collins C, Traynor O, McEntee G, Hegarty J, O'Farrelly C

*Isolation of lymphocytes from normal adult human liver suitable for phenotypic and functional characterisation.*

**J Immunol Methods 2000;242:21-31**

Deignan T, Kelly J, Alwan A, O'Farrelly C  
*Comparative analysis of methods of purification of egg yolk immunoglobulin.*

**Food and Agricultural Immun 2000;12:77-85**

Deignan T, Alwan A, Kelly J, McNair J, Warren T, O'Farrelly C  
*Serum haptoglobin: an objective indicator of experimentally-induced Salmonella infection in calves.*

**Vet Sci Res 2000;69:153-158**

Deignan T, Alwan A, Malone L, Kelly J, O'Farrelly C  
*Hen egg yolk prevents a bacterial adherence: a novel function of a familiar food.*

**J Food Science 2001 (in press)**

Drudy D, Fenelon L, O'Donoghue DP, O'Farrelly C  
*Clostridium difficile adherence to human Intestinal Epithelial cells.*

**J Gen Micro 2001 (in press)**

Duffy MJ, Maguire T, Hill A, McDermott E, O'Higgins N  
*Metalloproteinases: role in breast carcinogenesis, invasion and metastasis.*

**Breast Cancer Res 2000;2:252**

Duffy MJ, Shering S, Sherry F, McDermott E, O'Higgins N  
*CA 15-3: a prognostic marker in breast cancer.*

**Int J Biol Markers 2000;15:330**

Fitzpatrick PE, Salmon RL, Hunter PR, Roberts RJ, Palmer SR  
*Factors for carriage of epidemic and nonepidemic strains of Neisseria meningitidis.*

**Emerg Inf Dis 2000;6:65-69**

Flynn L, Byrne B, Carton J, Kelehan P, O'Herlihy C, O'Farrelly C  
*Menstrual cycle dependent fluctuations in NK and T-lymphocyte subsets from non-pregnant human endometrium.*

**Amer J Reproductive Immun 2000;43:209-217**

Garland M, Hickey D, Corvin A, Golden J, Fitzpatrick P, Cunningham S, Walsh N

*Total serum cholesterol in relation to psychological correlates in parasuicide.*

**Br J Psych 2000;177:77-83**

Genant H, Jiang Y, Watt I, Cobby M, Bresnihan B, Aitchison R, McCabe D  
*Radiologic progression and correlation of Genant and Larsen scoring methods in a multi-centre, double-blind, dose-ranging, randomised and placebo controlled study of recombinant human interleukin-1 receptor antagonist in patients with rheumatoid arthritis.*

**Ann Rheum Dis 2000;59:152**

Golden-Mason L, Curry M, Nolan N, Traynor O, McEntee G, Kelly J, Hegarty J, O'Farrelly C  
*Differential expression of lymphoid and myeloid markers on differentiating haematopoietic stem cells in normal and tumor-bearing adult human liver.*  
**Hepatology** 2000;**31**:1251-1256

Golden-Mason L, Kelly A, Curry M, McEntee G, Traynor O, Kelly J, Hegarty J, O'Farrelly C  
*Expression of interleukin 7 (IL-7) mRNA and protein in normal adult human liver: implications for extrathymic T-cell development liver.*  
**Cytokine** 2001 (in press)

Hayes C, Fitzpatrick P, Daly L, Buttiner J  
*Screening mammography re-evaluated.*  
**Lancet** 2000;**355**:749

Holohan TW, Humphreys CP, Johnson H, Casey PB, Tracey JA, Laffoy M, Clarke AT  
*Sources of information for acute poisoning in accident and emergency departments in Dublin, Ireland.*  
**J Toxicol Clin Toxicol** 2000;**38**:29-36

Hopkins N, Cadogan E, Giles S, McLoughlin P  
*Chronic airway infection leads to angiogenesis in the pulmonary circulation.*  
**J Applied Physiol** 2001 (in press)

Jiang Y, Genant H, Watt I, Cobby M, Bresnihan B, Aitchison R, McCabe D  
*A multi-centre, double-blind, dose-ranging, randomised, placebo-controlled study of recombinant human interleukin-1 receptor antagonist in patients with rheumatoid arthritis: radiology progression and correlation of Geneant and Larsen scores.*  
**Arthritis Rheum** 2000;**43**:1001-1009

Kokaly W, McKenna TJ  
*Relapse of hirsutism following long-term successful treatment with oestrogen Progestogen combination.*  
**Clin Endocrinol** 2000;**52**:379-382

Krishnan B, Zintel T, McParland C, Gallagher C  
*Evolution of inspiratory and expiratory muscle pressures during endurance exercise.*  
**J Appl Physiol** 2000;**88**:234-245

Linnane SJ, Thin AG, Keatings VM, Moynihan JB, McLoughlin P, FitzGerald MX  
*Glucocorticoid treatment reduces exhaled nitric oxide in cystic fibrosis patients.*  
**Eur Resp J** 2001 (in press)

Lynch F, Sweeney M, O'Regan RG, McLoughlin R  
*Hypercapnia-induced contraction in isolated pulmonary arteries is endothelium-dependent.*  
**Resp Physiol** 2000;**121**:65-74

Murphy E, McEvoy A, Conneely OM, Bresnihan B, FitzGerald O  
*Involvement of the nuclear orphan receptor NURR1 in the regulation of Corticotropin Releasing Hormone expression and actions in human inflammatory arthritis.*  
**Arthritis Rheum** 2001 (in press)

Murphy E, Bresnihan B, FitzGerald O  
*Validated measurement of periarticular bone mineral density at the knee joint by dual energy x-ray absorptimetry.*  
**Ann Rheum Dis** 2001 (in press)

Nourse C, Byrne C, Murphy H, Kaufmann ME, Clarke A, Butler K  
*Eradication of vancomycin resistant Enterococcus Faecium from a paediatric oncology unit and prevalence of colonisation in hospitalised and community based children.*  
**Epidemiol Infect** 2000;**123**:53-59

Ooi H, Cadogan E, Sweeney M, Howell K, O'Regan RG, McLoughlin P  
*Chronic hypercapnia inhibits hypoxic pulmonary vascular remodeling.*  
**Amer J Physiol** 2000;**278**:331-338

O'Connor S, McLoughlin P, Gallagher CG, Harty HR  
*Ventilatory response to incremental and constant-workload exercise in the presence of a thoracic restriction.*  
**J Applied Physiol** 2000;**89**:2179-2186

O'Hara R, Murphy EP, Whitehead AS, FitzGerald O, Bresnihan B  
*Acute-phase serum amyloid A production by rheumatoid arthritis synovial tissue.*  
**Arthritis Res** 2000;**2**:142-144

Remacle A, McCarthy K, Noel A, Maguire T, O'Higgins N, Foidart JM, Duffy MJ  
*High levels of TIMP-2 correlate with adverse prognosis in breast cancer.*  
**Int J Cancer** 2000;**89**:118

Suleiman AM, Al-Saber F, Hayes F, Fiad T, Culliton M, Cunningham S, McKenna TJ  
*Hyperprolactinaemia: Analysis of presentation, diagnosis and treatment in the endocrine services of a general hospital.*  
**Ir Med J** 2000;**93**:74-76

Tak PP, Bresnihan B  
*The pathogenesis and prevention of joint damage in rheumatoid arthritis. Advances from synovial biopsy and tissue analysis.*  
**Arthritis Rheum** 2000;**43**:2619-2633

## International Meetings

Professor Barry Bresnihan was an invited speaker at the BSR, EULAR and ACR.

Dr Joe Duffy was an invited speaker at Pathology 2000 Conference, Birmingham, Symposium on Proteases in Health and Disease, Strasbourg, Symposium on Prostate Cancer, London, Roche Diagnostics Users Meeting, Manchester.

Dr Oliver FitzGerald was an invited speaker at an International Symposium on Enthesiopathy, Berlin and the 2nd International Congress on Spondyloarthritis, Gent.

Anne Madigan was an invited speaker at an Amgen symposium, Lucerne, Switzerland.

Dr. Cliona O'Farrelly was an invited speaker at the AASLD Meeting in Dallas, October 2000.

# Grants Active in 2000

P.I.	Name of Study	Source of Grant	FundAmount	Start Date	Finish Date
Prof. Barry Bresnihan/ Dr. Oliver FitzGerald	Early Arthritis Unit	HRB	£375,000	1996	2001
Dr. Evelyn Murphy	Role and regulation of corticotropin releasing hormone in human inflammatory arthritis.	HRB	£40,000	1998	2001
Dr. Oliver FitzGerald	Molecular bases of HLA Class I association and of T cell repertoires in psoriatic arthritis.	Wellcome Trust	£18,000	1998	2001
Prof. Barry Bresnihan	Role of cytokines and growth factors in cartilage destruction in osteoarthritis.	EU Fifth Framework Programme Research Grant	£150,000	2000	2003
Prof. Barry Bresnihan	Synovial pannus evaluation and cytokine-targeted therapy in rheumatoid arthritis (spectra).	Amgen	£500,000	2000	2005
Dr. Patrick Costello	T cell receptor repertoire analysis in seronegative arthritis;evidence for persistence of oligoclonal T cells in remission tissue.	HRB	£117,000	2000	2003
Dr. Evelyn Murphy	Transcriptional events in inflammatory arthritis.	HRB	£117,000	2000	2003
Norelee Kennedy	NDA postgraduate research scholarship	National Disability Authority	£4,000	2000	2001
Dr. Joe Duffy	Anti-apoptotic gene, survivin in breast cancer.	Irish Cancer Society		2000	
Prof. Barry Bresnihan/ Dr. Oliver FitzGerald	Investigation into the production and regulation of ASAA in synovial membrane.	HRB Unit Grant Early Arthritis	£225,000	1997	2002
Dr. Ken McDonald	Comparision of a multi-disciplinary approach to heart failure with routine therapy.	Irish Heart Foundation & Servier Laboratories	£86,000	1998	2000
Dr. Ken McDonald	Assessment of general practitioner practice patterns in heart failure.	Smith Kline Beecham	£5,000	1999	2000
Dr. Ken McDonald	Development of a multi-disciplinary heart failure programme.	Parke Davis Pharmaceuticals	£10,000	1999	2000
Dr. Ken McDonald	Development of a multi-disciplinary heart failure programme.	Zeneca Pharmaceuticals	£10,000	1999	2000
Dr. Derek Doherty	CD1 restricted T cells in the human liver.	HRB Project Grant	£45,000	1999	2002
Dr. Lynda Fenelon/ Dr. Cliona O'Farrelly	Flow cytometric technique for Streptococcus mutans adherence to hydroxyapatite beads.	HRB Project Grant	£24,000	1999	2001
Dr. Cliona O'Farrelly/ Dr.Diarmuid O'Donoghue	Lymphoepithelial interactions in the gastrointestinal tract.	Basic Research Grant, Enterprise Ireland	£46,000	1999	2001
Dr. Cliona O'Farrelly	Novel antimicrobial peptides from hen egg yolk.	Strategic Research Grant, Enterprise Ireland	£46,000	1999	2001
Dr. Cliona O'Farrelly	Antimicrobial peptides	Department of Agriculture (Grant Extension)	£90,000	1999	2000

Dr. Cliona O'Farrelly/ Prof. Barry Bresnihan/ Dr. John Hegarty/ Dr. Joe Duffy	Lightcycler	HRB Equipment Grant	£40,000	1999	2000
Dr. Ken McDonald	Intensive vs routine management in congestive cardiac failure.	Irish Heart Foundation	£36,000	1998	2000
Dr. Cliona O'Farrelly/ Dr. John Hegarty	The molecular biology of hepatic T lymphocyte differentiation.	HRB	£36,000	1998	2001
Dr. Teresa Maguire	Relationships between Ets and proteases in breast cancer.	Irish Foundation for Breast Diseases	£40,000	1998	2001
Dr. John Hegarty/ Dr. Cliona O'Farrelly/ Dr. Derek Doherty/ Dr. Dermot Kelleher/ Prof. William Hall/ Dr. Kingston Mills	Virus variants and host immune responses in the resolution and progression of chronic liver disease following Hep C virus infection.	HRB Unit Grant	£741,972	1997	2002
Dr. Charles Gallagher	Exercise limitations in Cystic Fibrosis.	HRB	£16,000	1999	2002
Dr. Clare O'Connor	The role of Rho A in the control of pulmonary vascular resistance in normal and chronically hypoxic lungs.	HRB	£80,000		
Prof. M.X. FitzGerald/ Dr. Catherine Godson	Equipment Grant Chemiluminescent Nitric Oxide Analyser	HRB	£50,000		
Prof. J. Bannigan/ Dr. S. Giles/Dr. R. Ettarh	Equipment Grant Frozen Section Facility	HRB	£36,000		
Dr. J. Laffey	Investigation of the protective effects of hypercapnic acidosis in sepsis-induced acute lung injury.	Irish Lung Foundation	£20,000		
Dr. Cliona O'Farrelly/ Dr. John Hegarty/ Prof. William Hall	Conway Research Fellowship	Conway Institute	£60,000	2000	2002
Dr. Cliona O'Farrelly/ Dr. Tina Deignan	Hepatitis C viral load quantification in lymphocyte sub-populations and correlation with CD81 expression: implications for treatment and prognosis.	HRB	£23,100		
Dr. Cliona O'Farrelly Dr. Evelyn Murphy/ Dr. Teresa Maguire/ Dr. Norma O'Donovan/ Dr. Leonie Young	Labsystems Fluoroskan Ascent FL Combined Flometric/Luminometric microplate reader	HRB Equipment	£31,092.46	2000	
Dr. Cliona O'Farrelly/ Prof. Barry Bresnihan/ Dr. Oliver FitzGerald/ Dr. Evelyn Murphy/ Prof. TJ McKenna/ Dr. Leonie Young	Nikon Eclipse E600 Microscope plus Floresence filter blocks with lucia digital live imaging system	HRB Equipment	£39,119.30	2000	
Prof. TJ McKenna	ACTH regulation of adrenocortical steroidogenesis.	HRB Project Grant.		2000	

# Personnel- Research Laboratories

**Director:**

Cliona O'Farrelly

**Laboratory Co-ordinator:**

Laura Madrigal-Estebas  
Carolyn Law

**Senior Research Scientist**

Andrew Lloyd

**Post-Doctoral Fellows**

Maria Benito  
Damien Brady  
Patrick Costello  
Margaret O'Brien  
Norma O'Donovan  
Joan O'Keeffe

**Newman Scholars**

Malcolm Garland  
Evelyn Murphy  
Leonie Young

**Research Assistants**

Deirdre Foley  
Susan Gaines  
Martina Gogarty

**Ph.D Students (Science)**

Sinead Barry  
Susan Behan  
Yvonne Buggy  
Shane Curran  
Jonathan Dean  
Denise Drudy  
Lucy Golden-Mason  
Sinead Kelly  
Tony Kenna  
Alice McEvoy  
Neil O'Brien  
Rosemary O'Hara  
Caroline O'Shea

**Ph.D Students (Medicine)**

David Kane

**Under Graduate Students**

Brigid Browne  
Belinda Byrne  
Sile Doyle  
Adrian Fitzsimons  
Patrick Hayden  
Irene Hayes  
Lucille Kavanagh  
Naomi Lowe  
Stephen McCarroll  
Orla McEvoy  
Carol Murphy  
Helen Stunnell

**MD Students**

Alan Bohan  
Michael Curry  
Anna Kelly  
Eithne Murphy

**M.Ch.**

Raghu Varadarajan

**Clinical Research Fellows**

John Cahill  
Suzanne Corcoran  
Jonathan Dodd  
Malcolm Garland  
Mairead Horan  
Louise Kelly  
Conor O'Brien  
Abdul Sulieman

**MSc. Students**

Rachel Cullen  
Maria Mulligan

**Research Nurses**

Emma Kiernan  
Blainead O'Connor  
Aoife O'Keeffe  
Mary Ryder  
Lorna Timmons  
Bronagh Travers

**Part-Time/Visiting**

**Research Staff**  
Heather Crosby  
Robert Geraghty  
Emma Kilbride  
Kevin McMahon  
Jill Mackerel  
Gemma More  
Sinead O'Connor  
Dominic Parkinson