

Children, Youth and Women's Health Service Research Report 2004

University Department of Paediatrics

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1

Human papillomavirus vaccine study

DM Roberton, MS Gold, HS Marshall, J Tidswell, M Clarke, J Walker, R Chen, D Weber, A De Garis, C Heath

This multicentre international clinical trial is being conducted to investigate a potential vaccine to prevent infection with human papillomavirus (HPV), a leading cause of cervical cancer in women. The study involves the administration of either HPV vaccine or HepA vaccine in a blinded fashion. This is a safety and immunogenicity study, however only the safety component is being conducted at the Women's and Children's Hospital with enrolment of 48 girls. Over 2000 girls between ten and 14 years of age have been enrolled worldwide. Follow up is continuing and completion expected late 2005.

2

Long term follow up of combination hepA-hepB vaccine study

DM Roberton, MS Gold, H Marshall, M Clarke, D Weber, A De Garis, J Tidswell

The primary combination HepA-HepB vaccine study was completed in 2002. Of the 122 participants involved in the primary study, 88 consented and returned in 2003 to participate in a follow up study. Participation in the follow up study involved a blood draw approximately 24 months after their first dose of vaccine in the primary study to investigate long term immunity in the study groups. Participants were invited back again in 2004 for their year three visit. Almost all of the year two participants, and a further seven participants from the original study who were unable to attend the year two follow up agreed to return for the year three blood test resulting in a total of 94 participants at this time point. Results of year two blood draws were received late 2004 and are currently being reviewed.

3

Human metapneumovirus study

DM Roberton, MS Gold, HS Marshall, JA Walker, J Tidswell, M Clarke, D Weber, A De Garis

Human metapneumovirus (hMPV) is a recently discovered respiratory virus that can cause severe



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respiratory infection in high risk infants. In 2004, we continued to approach parents of babies at risk of severe respiratory infection who were admitted to hospital with a lower respiratory infection. Families were invited to participate in this study which involved collecting a nasal sample for detection of hMPV and the capture of information related to the admission. To date we have collected a nasal wash sample from 22 eligible infants at the Women's and Children's Hospital. These samples are snap frozen and sent to a central laboratory for processing. Over 500 participants have been enrolled worldwide and although we are yet to receive individual results, recent information suggests that approximately 11% of samples tested in the US sites participating in this study have been shown to be positive for hMPV.

4

EPAAC – early prevention of asthma in the atopic child

MS Gold, M Kummerow, J Aldis, C Heath, M Clarke, H Marshall, DM Robertson, J Tidswell

During 2004, follow up continued for children enrolled into this multicentre international study looking at whether a particular compound can delay or prevent onset to asthma for a sub group of children with moderate to severe eczema. Worldwide, over 2000 were enrolled and approximately 100 have now completed their involvement with the trial. A prolongation study has recently been proposed. At the Women's and Children's Hospital, 16 children were enrolled of which three are still continuing and four were withdrawn. Participants involved in the trial receive study medication or placebo twice daily for 18 months. Results of this study are expected in 2005.

5

HibMenCY vaccine study

DM Robertson, MS Gold, HS Marshall, M Clarke, J Walker, R Chen, J Tidswell, D Weber, A De Garis, M Kummerow, C Heath

This multicentre study conducted in three centres across Australia was completed in 2004. The study involved 409 participants overall, with 69 participants enrolled through the Women's and Children's Hospital. The study investigated the safety and reactogenicity of a combined Haemophilus influenzae type b and meningococcal C and Y vaccine for use in infants at 2, 4 and 6 months of age. Preliminary results have been promising and further studies are planned to continue to evaluate a combined HibmenCY candidate vaccine.



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DTPa-033 – fifth dose DTPa local reaction study

MS Gold, P Quinn, H Marshall, D M Robertson, M Clarke, J Tidswell, A De Garis, D Weber, S Lee

All participants completed their involvement in this study in 2004. Overall, approximately 50 eligible children were enrolled into this study through four sites in Australia. Our site enrolled 24 children who had had a large local reaction to their 4th dose of the DTPa vaccine and were randomised to receive either the routine DTPa vaccine for their scheduled 5th dose or a lower dose dTpa vaccine in a blinded manner. We are currently in the process of measuring antibody levels and avidity in blood samples collected from the children before and 25-30 days after their 5th dose of the vaccine. Clinical data regarding subsequent local reactions are also currently under investigation. The study groups have not yet been unblinded however we are expecting this to occur early 2005.

7

USES – ultrasound study of extensive swelling reactions

H Marshall, MS Gold, DM Robertson, P Quinn

This study examined use of ultrasound as a measure of extensive swelling reactions following either DTPa (Infanrix®) or dTpa (Boostrix®) vaccine. Twelve children, aged four to six years of age were enrolled in the study following a severe local reaction to DTPa vaccine affecting the upper arm. An ultrasound examination of the affected limb was conducted and swelling of muscle and subcutaneous tissue was measured and compared to measurements in the non affected limb (control). Swelling of the subcutaneous tissue was more pronounced than muscle tissue. There was no joint involvement demonstrated.

8

Varicella survey

H Marshall, P Ryan, DM Robertson

The aim of this study was to assess the uptake of varicella vaccine in South Australian children under circumstances where varicella immunisation is recommended but is not funded by Government. The study examined the main reasons that determined a parent's decision whether or not to have their child immunised with varicella vaccine. A Computer Assisted Telephone Interview was conducted, with data collected on over 1000 children. Information was obtained on past history of chicken pox infection and receipt of varicella vaccine to protect children against infection. Parents were asked to provide reasons why they chose or chose not to have their children immunised against varicella infection. Less than half the children in the study population had received varicella vaccine. Reasons why parents had not had their children immunised included lack of awareness about the vaccine and cost.

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SA vaccine safety data linkage project (SAVeS)

M Gold, S Dugdale, M Watson, M Higgins

The safety of vaccines is critical to sustaining the Australian national immunisation programme. An important component of vaccine safety monitoring is the post-licensure surveillance of adverse events following immunisation (AEFI). This is usually performed by the passive surveillance of AEFI's but the main problem is under-reporting and the inability of passive surveillance to establish a causal relationship between a particular adverse event and a given vaccine. Each year approximately 800,000 vaccines are administered in SA whilst there are between 400 and 500 AEFI's reported. The aim of SAVeS project is to evaluate the acceptability and feasibility of data linkage for the surveillance of vaccine safety. The project will survey immunisation providers and the public and establish linkage between the Australian Childhood Immunisation Register and childhood admissions to the Women's and Children's Hospital and Flinders Medical Centre.

10

The identification of markers for the differential response of children with eczema following treatment with probiotics

M Gold, P Quinn, R Butler, S Lee

Eczema is the most common childhood skin condition and currently affects one in 10 Australian children. Eczema is becoming more common for reasons which are not yet well understood. When severe eczema occurs this can be very disabling and does exact a high health cost for individuals and the community. Approximately 80% of children who have eczema will develop asthma and hayfever in later life and 30% of young children with eczema may have food allergies. Any safe, effective and inexpensive way to prevent and treat eczema will have enormous health benefits.

Probiotics are natural bacteria which are safe and often taken as a dietary supplement. Interestingly, recent studies have shown that when probiotics are given to mothers and newborn babies this may prevent some of these infants from developing eczema. In addition, when probiotics are given to infants with established eczema some infants have an improvement of their eczema. The reason(s) for this differential response to probiotics is not well understood.

The aim of this study is to see if older children with eczema respond to probiotics and to identify possible intestinal and inflammatory markers which may predict this differential response. Recruitment is continuing in this study at this time.



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Health service needs for children in rural South Australia

D Petchell, D Robertson, J Beilby

This project is a study of the provision, by general practitioners, of hospital based paediatric services in rural and remote South Australia. Data sources are the Australian Bureau of Statistics, Dept of Health (SA) databases, and hospital staff and general practitioner questionnaires. All data have been collected and analysis is near completion. The profile of acute care needs is similar, using DRG data, to that of metropolitan hospital services. However the workforce needs, particularly for nursing and allied health services in paediatrics, show important areas for improvement. A trial of education support programs has been undertaken and evaluation of the effectiveness of the interventions is nearly complete.

12

Maintenance and expansion of cord blood haemopoietic stem cells *RJ*

D'Andrea, J Hutton, S Barry; with C Story (Haematology); I Lewis (Institute of Medical and Veterinary Sciences)

This study is being performed with a view to investigating the capacity of Bone Morphogenic Protein (BMP) 4 to contribute to maintenance of haemopoietic stem cells (HSC). We have shown that BMP4 is produced by a fetal liver-derived stroma cell line (AFT024) and contributes significantly to expansion of co-cultured CB-derived HSC. Secreted BMP4 protein accumulates in AFT024 supernatant. Blockade of BMP4 activity in this co-culture model using noggin or neutralising BMP4 monoclonal antibody reduced HSC expansion based on phenotypic and functional criteria. Importantly, blockade of BMP4 activity with neutralising antibody led to net loss of HSC and halved the capacity of the cultured cord blood stem cells to support long-term repopulation in the NOD-SCID xenograft model. We are now investigating the possibility of using recombinant BMP4 in defined culture systems with the aim of establishing conditions supporting clinical ex vivo haematopoietic stem cell (HSC) maintenance and expansion.

13

Australian familial haematological cancer study

RJ D'Andrea, C Butcher, J Wrin; with G Suthers, M Altree (Familial Cancer Unit); H Scott (Walter & Eliza Hall Institute); T Hughes (Institute of Medical and Veterinary Sciences)

This is a proposal to develop a resource for biomedical research into the genetic basis of familial haematological malignancy. The proposal is modelled on the successful program for establishing a resource of data and biological samples for use in research into familial breast cancer (KConFab). We are identifying kindreds with familial haematological malignancy, recording pedigree data, collecting clinical



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and demographic data about family members, and storing biological samples (blood, tissue) from both affected and unaffected family members. We have identified 10 families that have three or more relatives with leukaemia. We will use established high throughput methods of mutation analysis as well as developing novel techniques that allow us to screen multiple "candidate genes" for their contribution to these familial haematological malignancies.

14

Gene profiling and detection of novel genes involved in normal myelopoiesis and myeloid leukaemia

R D'Andrea, A Brown, C Wilkinson, T Sadlon, S Barry, D Salerno, M Peters, C Kok, J Wrin; with T Gonda (Centre for Immunology and Cancer Research); G Goodall (Institute of Medical and Veterinary Sciences); P Solomon (Adelaide University)

We have utilised a powerful microarray time-course study to identify genes associated with proliferation/survival and promoting or blocking differentiation of myeloid progenitors. This has generated a substantial primary dataset representing the events associated with these processes. We have used a number of strategies to further define and prioritise differentially expressed genes. This has involved expression analysis and a number of computational approaches looking for commonalities in expression patterns from other myeloid models and leukaemia profiling studies. We are now beginning functional testing of 9 candidate regulatory genes which will be over-expressed and/or knocked down using retroviral constructs in a myeloid cell line model and in primary haemopoietic progenitors *in vitro*.

15

Molecular identification of regulatory T cells

S Barry, E Melville, S Bresatz, D Robertson, F Shannon, D Fitzpatrick

The recent identification of regulatory T cells (Tregs) as a key mediator of central and peripheral tolerance has led to an increase in our understanding of the cellular mechanism of this process. There is however, very little known about the molecular basis of this process, and the identity of key proteins that mediate regulatory function remains unclear. The identification of a transcription factor named FoxP3 in both mouse and human Tregs defines a committed T cell subset that has regulatory capacity. This project aims to identify the genes directly regulated by FoxP3 and to determine their role in the regulatory phenotype. We are using a number of direct and indirect molecular approaches such as Chromatin Immunoprecipitation and micro array analysis to profile gene regulated by FoxP3, and we will validate their role in regulatory function by direct assays and by over expression or gene ablation studies. The candidate genes identified in this approach may lead to therapeutic leads for intervention in the function of regulatory cells, and will also have application for diagnostic analysis of regulatory cell function.



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Surface profiling of cord blood regulatory T cells

S Barry, E Melville, S Bresatz, J Couper, M Gould, D Millard, H Zola

Presently the exact identify of regulatory T cells remains unclear. We aim to use traditional monoclonal antibody technology to profile the CD4+ CD25+ve regulatory T cells and define and further characterise these rare cells. A panel of ~390 monoclonal antibodies exists as part of the Human Leukocyte Differentiation Antigens Workshop (HLDA), of which Prof Zola is chair., and approximately 120 of these antibodies bind to T cells. We will purify cord blood Treg cells and then employ a 3 colour staining protocol to identify the CD4+ CD25 dual positive cells. These will be interrogated for the binding characteristics of T cell surface antigens, and the expression of FoxP3 in these sub groups will be determined. By relating FoxP3 expression to sub groups of CD4+ CD25+ Tregs we will establish a better isolation protocol, and relate this to regulatory function in suppression assays. Once a more refined profile is defined we will use it to analyse patient T cell samples from both normal and autoimmune populations including type 1 diabetes and asthma/allergy/atopy. We aim to define functional or numerical defects in Treg populations in the patient population, and use this information for early diagnosis of disease.

17

Lentiviral vectors for gene delivery and gene ablation

S Barry, E Melville, R D'Andrea, T Sadlon, S Wood, C Strathdee, B Mosley, D Cosman

Manipulation of primary T cells has a key limitation in that these cells are refractory to standard transfection protocols. Also, since they are often of low mitotic index, they are only infected at low efficiency by murine retroviruses, as these viruses require cell division for integration. With the exception of murine stem cell virus, further complications arise due to the silencing of retroviral LTR promoters in bone marrow and lymphoid tissues. The recent development of HIV1 based lentivectors provides an attractive option for gene delivery into T cell and stem cell populations, as these viruses carry the necessary cis elements to facilitate nuclear transport and integration in the absence of cell division. We have developed a suite of lentiviral vectors for stable gene delivery into primary cells both for gene therapy and gene discovery applications, and more recently for gene ablation using RNA interference. We aim to target genes required for regulatory function in T cells and examine their role by either over expression or gene ablation. This technology will be applied to a wide variety of function based discovery projects.



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Automated function based gene identification using an arrayed viral library

S Barry, R D'Andrea, T Gonda, B Gabrielli, S Grimmond, B Wilson

The need for elucidating the functions of the vast number of genes identified by genome sequencing projects is now clear to all; we know little or nothing of the functions of more than half of the genes that such projects have revealed. We propose to establish a first-of-its-kind facility that will enable genome-scale identification of genes based on their function, using a new implementation of retroviral expression cloning. Such a facility will present scientists at the University of Queensland and our collaborating institutions with unique opportunities to identify genes involved in a broad range of important biological processes, including many with significant health implications. This in turn will lead to fundamental insights and identification of genes that may encode targets for therapeutic interventions. In order to capitalise on the advantages of retroviral expression cloning and simultaneously overcome several limitations of conventional approaches, we propose to:

- Construct an arrayed retroviral library of sequence verified, full-length cDNA clones, that will ultimately represent all human genes; and
- Combine this with high-throughput automation of retrovirus production and screening.

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Expansion and transdifferentiation of human cord blood stem cells

S Barry, R D'Andrea, J Hutton, I Lewis

The molecular basis of the regulatory T cell phenotype is poorly understood, but this cell population has the capacity to suppress the proliferation of antigen specific T helper cells targeted to auto antigens, and is central to the tolerance process in rodents and man. This phenotype is co-ordinately regulated by the transcription factor FoxP3. For this reason cell based therapy for autoimmune disorders is a viable concept. A readily expandable population of cells is a prerequisite for this goal, and stem cells provide an ideal starting point, as they have the capacity to differentiate into all haemopoietic lineages. Cord blood stem cells also have this capacity, and are unencumbered by moral and ethical issues on their derivation, since they are harvested after birth from the placenta. Recently the role of the Notch ligands in lymphoid differentiation has been confirmed for both embryonic stem cells and haemopoietic stem cells. Delta like 1 signalling has been shown to drive the T cell differentiation of both populations, and the phenotype of these cells is indistinguishable from natural thymic emigrant T cells *in vivo*. We aim to over express this gene in cord blood derived stem cells, and expand them in the presence of feeder stromal cells expressing Delta like 1, and establish transdifferentiation into regulatory T cells. These cells can be expanded *in vitro* and either used as antigen naïve tregs, or co-cultured with dendritic cells and disease specific autoantigen, to generate functional Treg.

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Staff participating in research

Prof MS Sawyer

MBBS, PhD, Child Psych, FRCPC, FRANZCP; Head of Unit

Prof DM Robertson

MD, FRACP, FRCPA; McGregor Reid Professor of Paediatrics

Prof HL Tan

MBBS, MD, FRACS, FRCS; Prof Head of Paediatric Surgery

A/Prof R D'Andrea (Affiliate)

BSc(Hons), PhD; Chief Medical Scientist (Joint appointment CHRI/QEH)

Dr JD Kennedy

MD, FRCP, FRACP; Senior Lecturer and Deputy Head

A/Prof JJ Couper

MBBS, MD, FRACP; Senior Lecturer, Deputy Head of Diabetes & Endocrinology

Dr RTL Couper

MB, ChB, FRACP; Senior Lecturer

Dr M Gold

MD, FRACP, FACP; Senior Lecturer

Dr M O'Keefe

PhD, FRACP, DCCH; Senior Lecturer

Dr C Boros

MBBS, FRACP, PhD; Senior Lecturer

Dr H Marshall

MBBS, DCH; Senior Medical Officer - Vaccine Research Unit

Dr R Chen

MB BS, FRACGP, DCH, DRANZCOG; Research Medical Officer

Dr M Kummerow

MBBS, DCCH, FRACP; Medical Consultant

Dr J Walker

MBBS; Research Medical Officer

Dr P Quinn

MBBS, FRACP; Paediatric Immunologist, Postgraduate Student

Dr D Petchell

MBBS, FRACGP; Postgraduate Student

Dr D Bates

BSc (Hons), PhD; Principal Research Officer

Dr S Barry

BSc (Hons), PhD; Senior Research Fellow

Dr A Koditwakku

MBBS; Postgraduate Student



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G Harvey

Dip Med Lab Sci; Laboratory Manager

M Clarke

B Appl Sci (Med Lab Sci), G Dip Sci.Tech Comm; Clinical Trials Coordinator

J Aldis

Cert Med Lab Sci

A Pollard

Technical Assistant

S Nobbs

Dip Med Lab Sci

J Tidswell

BSc; Study Coordinator

D Weber

RN, RM, D ApplSci Nursing; Study Coordinator

L DeGaris

RN, Grad Cert Emerg Nursing; Study Coordinator

C Heath

RN; Study Coordinator

E Melville

BSc (Hons); Research Assistant

S Bresatz

BSc (Hons); Research Assistant

S Lee

BMPD, BSc (Hon) Physiology; Grant Funded Scientist

Dr A Brown

BSc (Hons), PhD; Leukaemia Foundation Research Fellow

C Butcher

M Med Sci; Research Assistant

J Hutton

BSc (Hons); Postgraduate Student

C Kok

BSc (BiomedSci); Undergraduate Student

M Perugini

BMed & Pharm Biotech (Hons); Postgraduate Student

Dr T Sadlon

BSc (Hons), PhD; Senior Research Officer

D Salerno

BSc (Hons); Research Assistant

Dr C Wilkinson

BSc (Hons), PhD; Senior Research Officer



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J Wrin

BSc; Research Assistant

International and interstate travel and presentations

R D'Andrea

Centre for Immunology and Cancer Research, Brisbane, Sep 2004

Haematology Society Australia and New Zealand, Melbourne, Oct 2004

H Marshall

9th National Immunisation Conference/1st PHAA Asia Pacific Vaccine Preventable Diseases

- *Reactogenicity and immunogenicity of a 2 dose hepatitis A/B vaccine in children*
- *Evaluation of live attenuated bivalent RSV-Parainfluenza III virus vaccine in children*
- *Ultrasound study of extensive limb swelling reactions in children following DTPa vaccination*

D Robertson, H Marshall, L Dinan, C Boros, M Gold

Festschrift in honour of Margaret Burgess, Royal Alexandra Hospital for Children, Sydney, Feb 2004

- *Immune responses to vaccines in premature infants*

D Robertson

Royal College of Physicians of Thailand Annual Scientific Meeting, Bangkok, April 2004

- *Connective tissue disorders in the adolescent*

Ruby Jubilee Meeting, University of Hong Kong, Sept 2004

- *Specialist training in paediatrics*
- *Arthritis in childhood*

D Robertson, H Marshall

Festschrift in honour of Margaret Burgess, Royal Alexandra Hospital for Children, Sydney, Feb 2004

- *Vaccines for the millennium baby (Oration)*
- *Immunisation in the premature infant*

S Barry

Establishment of research collaboration, Amgen, Seattle WA USA, Mar 2004

Keystone Symposium, Banff Canada, Mar 2004

- *Regulatory/Suppressor T cells*

CICR, Brisbane, invited speaker, Aug 2004

- *Research Seminar Series*

CICR, Brisbane, research collaboration meeting, Nov 2004

- *Viral Library Array*

ASI/HLDA meeting, Adelaide, invited chair and speaker, Nov 2004

- *T Cell Symposium*

WAMIR, Perth, invited speaker, Dec 2004

- *Research Seminar Series*



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International and interstate visitors

Prof Peter Klinken

Seminar: Novel Erythropoietin Signalling Pathways and Genes Involved in Hemopoietic Lineage Switching

Prof Thomas Gonda

Head Cancer Biology Program, Centre for Immunology and Cancer Research, Brisbane, invited speaker and collaboration meeting

Commercial developments

Nov 2004

Established Extramural Research agreement with Dr D Fitzpatrick, Amgen Inc, Seattle USA

Dec 2004

Negotiating with an interstate industry partner to support the stem cell transdifferentiation project

Other research-related activity

R D'Andrea

- Chair Program Committee, Australian Society for Immunology and Human Leukocyte Differentiation Antigens 8th International workshop. Adelaide Dec 2004
 - Member, Research Advisory Committee, WCH
-

Grants

RJ D'Andrea

Activated mutants as probes of GM-CSF receptor function

National Institutes of Health (USA)

US\$100,000

RJ D'Andrea, I Lewis

The role of bone morphogenic proteins in the ex vivo expansion of cord blood derived haemopoietic stem cells

Cancer Council SA

\$61,000

RJ D'Andrea, T Gonda, J Gecz, P Bardy, I Lewis, B To

Identification of growth factor receptor mutations in Polycythemia Vera

Leukemia and Lymphoma Society (USA)

US\$130,000

S Barry

Research Establishment Grant

Faculty of Health Sciences (CIA)

\$20,000 pa 2004-5



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Publications

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Improved folate status in children and adolescents during voluntary fortification of food with folate. *J Paediatr Child Health* (2004) 40: 44-47

Post-graduate degrees

H Marshall

Master of Public Health (MPH)

Paediatrics

Public Health

University of Adelaide

A P Kodituwakku

PhD

Paediatrics / CHRI

Paediatrics

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Children, Youth and Women's Health Service Research Report 2004

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