# University of Oxford

# MEDICAL SCIENCES DIVISION

# JOHN RADCLIFFE HOSPITAL

# Nuffield Department of Obstetrics & Gynaecology

# &

# Department of Paediatrics

# Graduate Handbook 2012



# INTRODUCTION

Welcome to the 2011-12 academic year in our graduate studies programme. This year sees an exciting new development. Those of you in the NDOG will notice that, whereas in previous years we have joined forces with the Nuffield Department of Clinical and Laboratory Sciences, this year we have teamed up with the Department of Paediatrics. It was felt that our two departments are more natural partners, covering as we do research into human development from fertilisation to childhood. The aim of establishing a joint graduate studies programme is to foster relationships between students in our two departments, giving access to a wider range of skills and techniques which may lead to future collaborations. The joint Graduate Symposium provides an important opportunity for students to present their work for the first time to a wider audience; an important skill for your future career.

The purpose of this handbook is to set out in an easily accessible form the main milestones that graduate students face during their time in Oxford. If you are in your first year of the programme then your supervision arrangements should now be in place. You will obviously be familiar with the main supervisor by now. A second supervisor to facilitate your research project is highly recommended by the division. Your college also provides an Advisor, who is intended to act in a mentoring or pastoral capacity. Each department has a Director of Graduate Studies (DGS) who is in place to oversee the graduate programme – see the following page for a full run-down of your DGS and Graduate Committee. Make sure that you have regular meetings with your laboratory supervisor to discuss your progress, future plans and any concerns you may have. The supervisor should also guide you through the formal processes (e.g. transfer of status) required in the programme and these are outlined in the handbook. If both of you are unsure, then contact the DGS. The latter will also facilitate and ensure that you participate in the divisional training programme and details are summarised in this handbook. We look forward to interacting with each of you during the tenure of your graduate programme.

Ian Sargent
Director of Graduate Studies
NDOG

Philip Goulder
Director of Graduate Studies
Department of Paediatrics

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# WHAT TO EXPECT – YEAR BY YEAR

## Year 1

The first year of any graduate programme is a vital one to ensure progression towards the final degree. New students need to "cut their teeth" with a myriad of new techniques and cope with an environment that is distinctly different to their undergraduate one. A key step is the support of their **supervisor** and their laboratory members. The student should be acutely aware of their project, including its aims and some idea of the course of events. There are also a number of ancillary skills that need to be acquired. One of the most important is to raise their **writing and communication skills**. After all, science is about communicating new ideas and hypotheses! The following list provides the recommended meetings, seminars, courses and events for all graduate students in their first year of study:

1. Meet with supervisor, co-supervisor and preferably your advisor to discuss the project.

2. Induction Lecture with the Director of Graduate Studies – start of the first year.

3. Attend the Graduate Symposium.

4. Medical Sciences Skills Training Programme
   *(i) Presentation Skills*
   *(ii) Writing Skills for PRS students - Reports*
   *(ii) Managing Research*
   *(iv) Teaching Skills 1*

   Information on courses and how to apply: www.medsci.ox.ac.uk/skillstraining

   E-mail queries: courses@medsci.ox.ac.uk

5. Safety Induction Lecture within your Local Department.

6. Attend safety required courses for specific skills (e.g. radiation or animal handling).

7. Attend research seminars within the division.

## Second Year

Two words come to mind for the second year of a graduate course – consolidation and assessment. The first is to build on the expertise and data accumulated during the first year. Lessons will no doubt be learnt from the experience and you are now accumulating more laboratory skill with each passing week. Your project should be **well defined** and refined by now and the main focus will be to tackle those important scientific questions.

To make sure that things are moving on the Medical Division requires some form of assessment. This is the formal **Probationer Research Student (PRS) to DPhil Transfer** and has been described on page 10 as well as in your divisional handbook. The DPhil transfer process has changed this year. Previously students were allowed up to 6 terms to transfer but, starting with the 2011 intake, this process must now be completed within 4 terms. This is a positive move which will help to identify any problems early in the process, allowing plenty of time for them to be rectified. If there are any questions, then please don't hesitate to contact a member of the Graduate Studies Committee for clarification! We are here to help out. Remember, that this procedure is not so much a critical assessment of your data; it is an assessment of your plans, progress and likelihood of completion.

There are also a number of event, courses and seminars that you should attend. The list below provides you with an idea of the minimum requirements.

1. Provide a 10-15 minute seminar at the NDOG-Paediatric Symposium

2. Prepare report for the PRS to DPhil or MSc transfer process

   Need Graduate Progression forms? Download from
   www.ox.ac.uk/students/course_guidance_supervision/graduates/forms/

3. Successfully complete the PRS to DPhil or MSc transfer procedure according to University requirements

*4.* Medical Sciences Skills Training Programme:
   *(i) GRAD School Personal Effectiveness Course*
   *(ii) Managing & Applying Research*
   *(iii) Career Planning in Sciences*
   *(iv) Teaching Skills 2*
   *(v) Writing Skills – Papers and Thesis*

   Information on courses and how to apply: www.medsci.ox.ac.uk/skillstraining
   E-mail queries: courses@medsci.ox.ac.uk

5. Attend research seminars within the division

## Third Year

The final year of a three year DPhil programme is obviously another important one and if the planning and effort have been up to scratch, then it should be a matter of keeping things rolling along. No talk of panic should be heard! It may seem fraught and the prospect of writing a thesis looms large for anybody. Hopefully you've had some experience with writing your transfer report, maybe a manuscript or even a review. The courses on planning your project will bear fruit in this final year, as will those on writing skills. If you are worried or lurching towards panic stations, then talk to your supervisor, your co-supervisor, college tutor or the graduate studies director. We have plenty of advice and experience with graduate studies – so make use of it. The list below provides you with the minimum suggested programme of studies for the final year. It also points to some VERY IMPORTANT aspects of the formal examination of your DPhil.

1. Meet with supervisor, co-supervisor and your advisor to organise the final year (i.e. examination process)

2. Complete the **confirmation of status** towards the middle of the year. Don't forget this as you won't be able to submit till this is complete!

   Need Graduate Progression forms? Download from
   www.ox.ac.uk/students/course_guidance_supervision/graduates/forms/

3. Attend research seminars within the division

4. Prepare a poster or research seminar for the NDOG-Paediatrics Graduate Symposium

5. Medical Sciences Skills Training Programme:

   *(i) Introductory Funding Workshop*
   *(ii) Get That Job*
   *(iii)Word: Building long documents www.oucs.ox.ac.uk/itlp/courses*
   *(iv) Viva preparation*
   *(v)Teaching Skills 2&3*

6. **Appoint examiners** – recommendations to the Medical School for ratification

7. Formal **submission of the thesis** via the Exam Schools and NOT directly to examiners

All the necessary forms can be found at:

http://www.ox.ac.uk/students/course_guidance_supervision/graduates/forms/

# MEDICAL SCIENCES DIVISION

## Skills Training Programme

Information on courses and how to apply: www.medsci.ox.ac.uk/skillstraining

**E-mail Queries:** courses@medsci.ox.ac.uk

The Medical Sciences Division seeks to equip all Graduate Research Students and Research Staff with a comprehensive set of transferable and research skills. The aim is to maximise each researcher's potential, enabling participants to see beyond the day-to-day demands of their own research. Students build the foundation for a successful career through communication, networking and team-building as well as through excelling in their own research area. As a guide, the Research Councils recommend that graduate students spend 10 days a year on additional skills training.

The Division's programme consists of over 80 half, one and 3.5 day courses as well as lunchtime seminars run on the Division's three sites (John Radcliffe, Churchill and South Parks Rd). The programme supplements departmental training and provides additional networking opportunities across the Division, promoting collaboration and cross-disciplinarity. DPhil students in the Medical Sciences Division may attend free of charge.

Students and their supervisors are strongly encouraged during their first term and throughout the course of their studies to spend time revisiting their individual training requirements, planning a training timetable and developing their CV. In addition both supervisors and students are encouraged to use the facility within the Graduate Supervision System (GSS) to record training requirements which are then fed back to the Training Officer to follow up and offer advice regarding the availability of courses and events which would fulfil their training requirements.

The Divisional programme consistently receives positive feedback with over 80% of students who have attended a course recommending attending a course as a good use of their time.

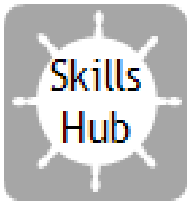
**The courses, seminars and events cover:**

- Basic and Advanced Research Techniques
- Bioinformatics
- Project Management
- Career Development
- Writing and Presentations Skills
- Statistics and Data Analysis
- Funding and Grant Writing
- Ethics
- Teaching Skills
- English Language Skills
- Personal Development, Team Working and Networking
- Intellectual Property
- Preparation for Academic Practice
- Research Skills

## Thinking about teaching? - Preparation for Academic Practice

Teaching skills courses cover training for tutorials, small and large group teaching, lecturing and lab-based teaching, with the latter generally delivered by Departments. Training is provided at three levels (usually starting in the second year of study): 'Preparation for Learning and Teaching at Oxford', 'Developing Learning and Teaching' and assembly of a Teaching Portfolio. Participants who complete courses are added to the Divisional teaching register and are able to explore teaching opportunities both within and outside the University.
Those wishing to complete a portfolio (usually third year students and research staff) are assigned a mentor to guide them in development of their teaching and as they compile their portfolio. Successful completion of a portfolio results in accreditation as an Associate Fellow of the UK's Higher Education Academy. This qualification is required by many Universities for employment as a University Lecturer.
**COURSES** - http://www.medsci.ox.ac.uk/skillstraining/coursecatalogue/academic
PART 1 - Tutorial and Small Group Teaching
PART 2 - Lecturing and Class Teaching
PART 3 (optional) – Developing Learning and Teaching
(including portfolios, mentoring and accreditation).

## Skills Hub




**Skills Hub** can be accessed through WebLearn and contains details of all the skills training courses and events available across the University. Weblearn can be accessed using your single sign-on details: https://weblearn.ox.ac.uk/portal/hierarchy/

## Online Courses

Online courses are available via WebLearn - https://weblearn.ox.ac.uk/portal

1. Avoidance of Plagiarism (completion of this course is extremely important)
2. Publishing in Arts
3. Publishing in Sciences
4. Project Management in the Research Context
5. Intellectual Property in the Research Context
6. Ethics 1 - Good Research Practice
7. Ethics 2 - Working with Human Subjects
8. Career Planning in the Sciences
9. Career Planning in the Arts, Humanities and Social Sciences
10. Managing Your Research Supervisor / Principal Investigator
11. Attending a Conference, Presenting & Networking
12. Enterprise 1 - Are you an entrepreneur?
13. Enterprise 2 - Opportunity recognition, creation & evaluation
14. Enterprise 3 - Resources (people, teams, finance)

**Research Skills Toolkit –** Provides an introduction for all new graduates to the many service providers within the University including Library Services, Language Centre, Careers Service and OUCS.

The Research Skills Toolkit is an induction event being developed in association with the University Computing Services and provides a more hands-on approach with students participating in short exercises as a means to familiarise themselves with the wide range services available. In addition elements of this event are tailored for the specific needs of graduate students within each Division. For the Medical Sciences Division ethics, statistics, bioinformatics, genomics and intellectual property will all be included. The event will also include an introduction to the Medical Sciences Skills Training Programme which includes both face-to-face and online courses.

**Researcher Development Framework (RDF) -** The RDF describes the knowledge, behaviours and attitudes of researchers and encourages them to aspire to excellence through achieving higher levels of development. It will be invaluable for planning, promoting and supporting the personal, professional and career development of researchers in higher education.
http://www.medsci.ox.ac.uk/skillstraining/coursecatalogue/RDF.doc/view

**Researcher Development Statement (RDS) -** The Researcher Development Statement (RDS) sets out the knowledge, behaviours and attributes of effective and highly skilled researchers appropriate for a wide range of careers.
http://www.medsci.ox.ac.uk/skillstraining/coursecatalogue/RDS.pdf/view

## GRAD Schools

GRADschools Personal Effectiveness Course is designed to help you reflect upon and develop the skills you have as a postgraduate researcher. The course encourages you to consider how you can apply your skills now and in the future and aim to help you make more informed choices about the next step of your career. For further information, email courses@medsci.ox.ac.uk

www.medsci.ox.ac.uk/skillstraining

CHECK IT OUT!

# MONITORING PROGRESS AND ASSESMENT PROCEDURES

The NDOG-Paediatric Graduate Studies Committee requires that the principal supervisor is able to provide continuous guidance to each student – or ensure that the student has access to suitably qualified scientific staff within the laboratory. The supervisor(s) role in ensuring adequate progress and the provision of a sufficient scientific training environment will be paramount. However, the NDOG-Paediatric departments also provide measures of assessment external to the direct supervisor(s). Consequently, each student will have a specific internal assessor appointed from academic staff within the department, but not directly associated with the project. In addition, a prerequisite of any studentship at the University of Oxford is that a college supervisor be appointed to oversee progress and quality of local environment. Together, the direct supervisor, internal assessor and college supervisor provide a team dedicated to monitoring and assessment of studentships within NDOG-Paediatrics. The actual assessment/monitoring process is continuous, however, the following stages are key periods for this procedure:

## 1. Commencement of Studies:

The supervisor(s), student and internal assessor meet to discuss the nature of research to be undertaken and to identify key milestones that need to be met during the studentship. In addition, a programme of workshops and seminars deemed relevant to the student should be developed at this stage.

***The supervisor or student must let the Director of Graduate Studies know who their internal assessor and college advisor are.***

## 2. Post-first Academic Year.

The most significant assessment procedure occurs at the end of first year in order to ensure that the foundations for the research project have been laid. This process is known as the ***PRS to D Phil Transfer*** and is a mandatory requirement at the University of Oxford. Students prepare a 3,000 word (maximum) written dissertation outlining their project. The student and two assessors (of whom one may be your internal assessor) meet to discuss all aspects of the research, formulate the key future goals and address and concerns the student may have. A written report is sent to the laboratory supervisor, college supervisor and graduate studies office detailing whether the probationary student may be admitted to full DPhil status.

## 3. Commencement of final Year:

The student, supervisor and internal assessor meet to discuss the current status of progress and determine how to ensure that the project will reach a successful conclusion by the end of the three year period. At this stage the student should be in a position to assess their career development options in conjunction with the supervisory team. The University of Oxford also has a mandatory requirement for the completion of a ***Confirmation of Status*** during this year. If this is not completed, the student cannot submit a thesis for examination!

## 4. Termly – Supervisor's and Student's Reports:

Finally, at the end of each term during tenure, you are required to submit a report (via the Graduate Supervision System (GSS) website (http://www.admin.ox.ac.uk/gss/) to give your own assessment of your progress. You will be sent reminders from the Division. The "reporting windows of opportunity" to complete your forms are fixed periods so make sure you submit on time. Your supervisor(s) is/are also required by the University of Oxford to submit a written progress report to the Director of Graduate Studies, Graduate Office and College Supervisor (students are also informed of the contents) to ensure that continued progress is being met. Students are expected to retain a copy of their termly progress reports for presentation to the Graduate Studies Committee each year – see point 5.

## 5. Yearly – NDOG and Paediatric Graduate Studies Committees:

At the end of each academic year you will be required to meet with NDOG or Paediatrics Graduate Studies Committee to discuss your programme for the preceding year. At this meeting you will be required to present documentation of participation at the following:

- Meetings with the supervisor and advisor
- Formal skills training (e.g. workshops)
- Seminars, lectures and conferences attended
- Presentations, including at Journal Club given
- Publications
- Skills checklist

The APPENDIX to this handbook provides you with the forms that need to be filled in throughout your graduate studies and you should present this to the committee at the yearly meeting. You will also need to provide the termly supervision reports from your supervisor and yourself to the Committee. This meeting is also an opportunity for you to discuss any concerns you may have regarding the Graduate Training or seek advice on the programme.

## UNIVERSITY OF OXFORD

### Complaints and academic appeals within NDOG & Paediatrics

1. The University, the Medical Division and NDOG-Paediatrics all hope that provision made for students at all stages of their programme of study will make the need for complaints (about that provision) or appeals (against the outcomes of any form of assessment) infrequent.

2. However, all those concerned believe that it is important for students to be clear about how to raise a concern or make a complaint, and how to appeal against the outcome of assessment. The following guidance attempts to provide such information.

3. Nothing in this guidance precludes an informal discussion with the person immediately responsible for the issue that you wish to complain about (and who may not be one of the individuals identified below). This is often the simplest way to achieve a satisfactory resolution.

4. Many sources of advice are available within colleges, within faculties/departments and from bodies like OUSU or the Counselling Service, which have extensive experience in advising students. You may wish to take advice from one of these sources before pursuing your complaint.

5. General areas of concern about provision affecting students as a whole should, of course, continue to be raised through Joint Consultative Committees or via student representation on the faculty/department's committees.

**Complaints**

6. If your concern or complaint relates to provision made ***by NDOG-Paediatrics,*** then you should raise it with the Director of Graduate Studies (Professor Ian Sargent – NDOG, Professor Philip Goulder – Paediatrics) as appropriate. Within the department the officer concerned will attempt to resolve your concern/complaint informally.

7. If you are dissatisfied with the outcome, then you may take your concern further by making a formal complaint to the University Proctors. A complaint may cover aspects of teaching and learning (e.g. teaching facilities, supervision arrangements, etc.), and non-academic issues (e.g. support services, library services, university accommodation, university clubs and societies, etc.). A complaint to the Proctors should be made only if attempts at informal resolution have been unsuccessful. The procedures adopted by the Proctors for the consideration of complaints and appeals are described in the Proctors and Assessor's Memorandum [http://www.admin.ox.ac.uk/proctors/pam/] and the relevant Council regulations [http://www.admin.ox.ac.uk/statutes/regulations/]

8. If your concern or complaint relates to teaching or other provision ***made by your college***, then you should raise it either with your tutor or with one of the college officers, Senior Tutor, Tutor for Graduates (as appropriate). Your college will also be able to explain how to take your complaint further if you are dissatisfied with the outcome of its consideration.

**Academic appeals**

9. An appeal is defined as a formal questioning of a decision on an academic matter made by the responsible academic body.

10. For undergraduate or taught graduate courses, a concern which might lead to an appeal should be raised with your college authorities and the individual responsible for overseeing your work. **It must not be raised directly with examiners or assessors.** If it is not possible to clear up your concern in this way, you may put your concern in writing and submit it to the Proctors via the Senior Tutor of your college. As noted above, the procedures adopted by the Proctors in relation to complaints and appeals are on the web [http://www.admin.ox.ac.uk/statutes/regulations/].

11. For the examination of research degrees, or in relation to transfer or confirmation of status, your concern should be raised initially with the Director of Graduate Studies. Where a concern is not satisfactorily settled by that means, then you, your supervisor, or your college authority may put your appeal directly to the Proctors.

12. Please remember in connection with all the cases in paragraphs 5 - 7 that:

(a) The Proctors are not empowered to challenge the academic judgement of examiners or academic bodies.

(b) The Proctors can consider whether the procedures for reaching an academic decision were properly followed; i.e. whether there was a significant procedural administrative error; whether there is evidence of bias or inadequate assessment; whether the examiners failed to take into account special factors affecting a candidate's performance.

(c) On no account should you contact your examiners or assessors directly.

13. The Proctors will indicate what further action you can take if you are dissatisfied with the outcome of a complaint or appeal considered by them.

# THE RESEARCH ENVIRONMENT IN NDOG, PAEDIATRICS AND THE UNIVERSITY OF OXFORD

The stimulating research environment within the University of Oxford and the Medical Sciences Division provides an ideal mechanism to facilitate the exposure of graduate students to;

i. Medical science and related technologies at a national and international level
ii. The complex interface between the scientific community, the general public and the commercial environment

The student exposure to these broad areas is facilitated by departmental, divisional and university-based schemes involving seminar series, workshops and practical involvement as outlined below. Participation is encouraged and monitored at the various stages of assessment.

## 1. Scientific Environment.

- The University Graduate Studies office conducts themed training days (e.g. genetic technologies in biological sciences, communication in science, structural biology) incorporating leading scientists from UK Universities
- The NDOG-Paediatric Graduate Symposium provides a forum for oral presentations and interactions between graduate students and post-doctoral research fellows
- Students are encouraged to attend seminar series at the departments of Biochemistry, Physiology Clinical Medicine and the Weatherall Institute for Molecular Medicine that feature prominent national and international scientific speakers
- Attendance at conferences is positively encouraged and most of the academic staff are regularly invited presenters at UK/international meetings. Funding to attend is possible through granting bodies that fund departmental research, through membership of relevant scientific societies (e.g. Biochemical Society, British Cancer Society & British Society for Immunology) and also through the Oxford College to which the student is assigned
- Training seminars by the Oxford Safety Office ensure that students understand correct working practices and health and safety issue allied to scientific research

## 2. Public/Commercial Interface.

The University of Oxford recognises the need to exploit the research-commercial interface and to facilitate technological transfer; they have established the ISIS Innovation Department which provides training to all members of staff in:

- Understanding Intellectual Property Issues and applying for patents and licences
- Setting up a spin-out company
- Establishing consultancy agreements

## Research resources and facilities available within the Nuffield Department of Obstetrics & Gynaecology

The Nuffield Department of Obstetrics and Gynaecology is based on the John Radcliffe site, on level 3 of the Women's Centre. The Department encompasses multi-disciplinary research across a wide range of important issues in human reproduction. This ranges from genetic studies, the dissection of molecular and cellular mechanisms underlying normal and aberrant reproductive tissue function through clinical studies in women's health and pregnancy to epidemiological research. In particular, the Department has an international reputation in research into feto- maternal disorders, pre-eclampsia, infertility, endometriosis, menopause, mitochondrial DNA disorders, with collaborative research in gynaecological cancers. The clinical and laboratory programmes are based in the Women's Centre and there are collaborations with the School's Institutes, the University's Science departments and with researchers outside Oxford.

- The laboratories of the Nuffield Department are fully equipped for a wide range of molecular and cell biology work.

- Specialised equipment includes a ***computerised image analysis facility*** and ***Becton Dickinson LSR II 6 colour flow cytometer***, a full range of ***microscopes*** (stereo, fluorescence, inverted and phase contrast) and ***instrumentation for exosome and microvesicle detection***.

- Core facilities include a tissue culture suite, genetic modification laboratory, and isotope laboratory.

The Department has responsibility for teaching obstetrics and gynaecology to the clinical students of which there are a total of 100 in each of three years. At any one time there are likely to be approximately 15 clinical students in the department. The Department is also responsible for the provision of a substantial portion of the clinical services in obstetrics and gynaecology in the John Radcliffe Hospital. These close links with the clinical service ensures excellent provision of clinical material for research.

# RESEARCH GROUPS WITHIN NDOG

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**Head of Group** Dr Christian Becker
**Subject Area** Role of angiogenesis in endometriosis & ovarian cancer
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**Head of Group** Dr Kevin Coward
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**Head of Group** Professor Stephen Kennedy
**Subject Area** Genetics of endometriosis, chronic pelvic pain & infertility
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**Head of Group** Dr Karl Morten
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**Head of Group** Emeritus Professor Christopher Redman
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**Head of Group** Professor Ian Sargent
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**Head of Group** Professor Jose Villar
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**Head of Group** Dr Dagan Wells
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**Head of Group** Dr Suzannah Williams
**Subject Area** The role of the oocyte in regulating fertility
**E-mail** suzannah.williams@obs-gyn.ox.ac.uk

# Research resources and facilities available within the Department of Paediatrics

Professor Goulder's primary laboratory is based in the Peter Medawar Building for Pathogen Research in Oxford. His research is focused on the South African HIV epidemic, with the principal goal of understanding the role of T-cell immunity in successful long-term immune control of HIV infection in adults and children. The Goulder Group studies cohorts of children and adults attending clinics in South Africa, in Durban, KwaZulu-Natal, and also in Kimberley, Northern Cape, in addition to smaller cohorts of HIV-infected study subjects attending clinics in the Thames Valley region in UK. The goal of this work is to define the immune responses that are effective in control of HIV, and that an effective HIV vaccine would need to induce. The particular interest of the group is in determining the nature of the vaccine, and the optimal timing of vaccination. The category-3 laboratory facilities are equipped with adequate hoods (including respectively four and two laminar flow hoods), incubators, freezers and liquid nitrogen facilities. The group also has shared use of two FACSCalibur flow cytometers, one LSR-II multicolour flow cytometer (13 colour), FPLC and ABI automated sequencers.

The laboratory for "Developmental Immunology" is situated at the Weatherall Institute of Molecular Medicine (WIMM). Professor Georg Hollander's research focuses on the genetic and epigenetic programmes that regulate the development of the adaptive immune system, in particular that of the thymus and its T cell compartment. The large laboratory is very well equipped and together with the numerous state-of-the-art core facilities of the Institute provides a unique environment for cutting edge immunological research. The laboratory's environment allows for proximate interdisciplinary interactions and the exposure to a lively seminar series on a wide range of biomedical research topics given by internal and external speakers.

The Oxford Vaccine Group (OVG), led by Professor Andrew J Pollard, has a major focus on the prevention of life-threatening infections in children through the design, development and evaluation of vaccines. OVG are based at the Centre for Clinical Vaccinology and Tropical Medicine at the Churchill Hospital. In addition, a research team is based at Patan Hospital in Kathmandu, Nepal, running surveillance of invasive bacterial infections in children admitted to the hospital and studies of life-saving vaccines for the local population. The group has specifically focused on the development of B cell memory after immunization with glycoconjugate vaccines and has found correlations between the generation of memory during priming and the persistence of the immune response. A major programme is focused on the development of a novel serogroup B meningococcal vaccine from preclinical studies through to clinical trials. The group also undertakes sero-epidemiological studies and is examining acquisition of natural immunity to various organisms in the UK and Nepal. Resources at the Vaccine Centre include an outpatient facility, an extensive office area for trials administration and a fully equipped laboratory with capabilities for working with category 2 and category 3 microorganisms. The research staff has a broad expertise in bacteriology, molecular biology and immunology.

Dr Sullivan's clinical research group has been studying the nutritional assessment and management of children with neurological impairment who have severe feeding difficulties. These studies have ranged from epidemiological and quality of life studies to intervention assessments of gastrostomy feeding and body composition studies of

various nutritional enteral feeds. Current research involves a randomised controlled trial of a neurotropic supplement designed to capitalise on the brain's plasticity and ameliorate some of the long-term neuro-developmental consequences of perinatal brain damage.

# DEPARTMENT OF PAEDIATRICS

## *RESEARCH GROUPS CONTACTS*

| | |
|---|---|
| **Head of Group** | Dr Peter Sullivan |
| **Name of Group** | Gastroenterology and Nutrition Group |
| **PA** | Helen O'Neil |
| **Email** | Helen.o'neil@paediatrics.ox.ac.uk |
| **Telephone** | 01865 234248 |

| | |
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## CURRENT PAEDIATRIC GRADUATE STUDENTS

| Last Name | First Name | Supervisor | Start Date | Email Name | Title |
|---|---|---|---|---|---|
| Tsai | Sherry | | 2008 | chen.tsai@queens.ox.ac.uk | |
| Grant | Clare | Pollard | 2009 | clare.grant@paediatrics.ox.ac.uk | Investigating primary and secondary B cell responses in cattle after immunisation with existing and novel vaccines. |
| Waddington | Claire | Pollard & Angus | 2009 | claire.waddington@paediatrics.ox.ac.uk | Understanding Typhoid Disease: A Human Challenge Model in Healthy Adult Volunteers. |
| Juarez Molina | Claudia | Goulder | 2010 | claudia.juarezmolina@paediatrics.ox.ac.uk | Impact of HLA-B*35 subtype differences on HIV outcome in Mexico |
| O'Connor | Daniel | Pollard | 2010 | daniel.oconnor@paediatrics.ox.ac.uk | To identify genetic determinants influencing immunological responses and persistence to serogroup C meningococcal conjugate vaccine. |
| Ramasamy | Maheshi | Pollard & Kelly | 2010 | maheshi.ramasay@paediatrics.ox.ac.uk | Immunogenicity of polysaccharide and conjugate quadrivalent meningococcal ACYW-135 vaccines in healthy adult volunteers – a randomised clinical trial. |
| Truck | Johannes | Pollard & Kelly | 2010 | johannes.truck@paediatrics.ox.ac.uk | Investigation of the B-cell response to pneumococcal vaccines given to children and adults |
| Weissmueller | Nikolas | Schiffter & Pollard | 2010 | nikolas.weissmueller@paediatrics.ox.ac.uk | Microparticle Approaches to Needle-Free Delivery of Hib Vaccines |
| Adland | Emily | Goulder | 2011 | emily.adland@paediatrics.ox.ac.uk | |
| Brener | Jacqui | Goulder | 2011 | jacqui.brener@wolfson.ox.ac.uk | |
| Darton | Thomas | Angus & Pollard | 2011 | thomas.darton@jesus.ox.ac.uk | |
| Kopuri | Anil | Sullivan | 2011 | anil.kopuri@wolfson.ox.ac.uk | |
| Gedicke | Malenka | | 2011 | malenka.gedicke@cardiov.ox.ac.uk | Aortic flow patterns in bicuspid aortic valve disease visualised with 4D flow imaging |
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|---|---|---|---|---|---|
| Abdul Al Farawati | Samer | Wells | 2008 | samer.alfarawati@obs-gyn.ox.ac.uk | Preimplantation Genetic Diagnosis |
| Chi | Jim | Brady, McVeigh & Schnabel | 2008 | wen.chi@magd.ox.ac.uk | MRI Image Analysis For Abdominal And Pelvic Endometriosis |
| Kang | Youn-jung | Aplin & Coward | 2008 | youn-jung.kang@obs-gyn.ox.ac.uk | Peri- and post-implantation human development and human embryonic stem cells |
| Konstantinidis | Michalis | Wells | 2008 | michalis.konstantinidis@obs-gyn.ox.ac.uk | Preimplantation Genetic Diagnosis - new methods for the diagnosis of genetic disorders in human preimplantation |
| MacLeod | Lorna | Poulton & Wells | 2008 | lorna.macleod@obs-gyn.ox.ac.uk | Study of the feasibility of using pre-implantation genetic diagnosis (PGD) in mitochondrial DNA disorders. |
| Ramadan | Walaa | Coward | 2008 | walaa.ramadan@obs-gyn.ox.ac.uk | Do multiple isoforms of phospholipase C zeta play differential roles during egg activation and early embryogenesis? |
| Vazquez Arango | Pilar | Murphy | 2008 | pilar.vazquez@obs-gyn.ox.ac.uk | Human embryonic stem cells |
| Brooks | Alexandra | Sargent | 2009 | alexandra.brooks@obs-gyn.ox.ac.uk | Analysis of urinary exosomes in normal and pre-eclamptic pregnancies |
| Collins | Sally | Noble & Impey | 2009 | sally.collins@obs-gyn.ox.ac.uk | An investigation of potential new markers for impaired placentation in early pregnancy |
| Dragovic | Rebecca | Sargent | 2009 | rebecca.dragovic@obs-gyn.ox.ac.uk | Measurement and characterisation of microparticles and exosomes in pre-eclampsia |
| Ioannou | Christos | Papageorghiou & Javaid | 2009 | christos.ioannou@obs-gyn.ox.ac.uk | Three dimensional ultrasound and fetal skeletal development |
| Knight | Hannah | Kennedy & Villar | 2009 | hannah.knight@obs-gyn.ox.ac.uk | Severe Maternal Morbidity: Barriers to the Implementation of Evidence-based Interventions in the Developing World |
| May | Katie | Becker & Kennedy | 2009 | katie.may@obs-gyn.ox.ac.uk | Study of potential non-invasive biomarkers for endometriosis |
| Al Yahyaei | Zahraa | Sargent | 2010 | zahraa.alyehyaei@obs-gyn.ox.ac.uk | The role of IL-33 and ST2 in early pregnancy |
| Kemp | Bryn | Kennedy | 2010 | bryn.kemp@obs-gyn.ox.ac.uk | A Systematic Review of Maternal & Perinatal Health in Kilifi, Kenya - Can Ultrasound Predict Adverse Fetal Outcome? |
| Knight | Caroline | Papageorghiou | 2010 | caroline.knight@obs-gyn.ox.ac.uk | Personalised Perinatal Monitoring (using 3D fetal ultrasound scanning) |
| Potter | Michelle | Morten | 2010 | michelle.potter@obs-gyn.ox.ac.uk | Nanotherapeutics: targeting cell metabolism as a therapy in paediatric cancer |
| Fathima | Sana | Noble & Papageorghiou | 2010 | sana.fathima@hertford.ox.ac.uk | Development of a probabilistic atlas for the fetal brain |

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|---|---|---|---|---|---|
| Finkton Jr. | Darryl | Villar | 2011 | darryl.finkton@magd.ox.ac.uk | Effect of environmental factors on fetal/infant growth and perinatal outcomes |
| Lodge | Tiffany | Morten & Poulton | 2011 | tiffany.lodge@obs-gyn.ox.ac.uk | To develop treatments for mitochondrial disease by investigating the mechanisms associated with acute liver failure and autophagy activating anti epileptic sodium valproate. |
| Kaune Galaz | Heidy | Williams | 2011 | heidy.kaunegalaz@dpag.ox.ac.uk | Elucidating the mechanism of premature ovarian failure |
| Yelumalai | Suseela | Coward | 2011 | suseela.yelumalai@jesus.ox.ac.uk | Potential effects of iatrogenic damage during conventional ART upon sperm protein expression, function and degradation |
| Poli | Maurizio | Child & Wells | 2012 | maurizio.poli@obs-gyn.ox.ac.uk | Novel molecular markers for human gametes and embryos competence |


## Nuffield Department of Obstetrics & Gynaecology and The Department of Paediatrics

# GRADUATE SYMPOSIUM

## Open to ALL members of NDOG & Paediatrics

**Please come and support the students!**

## Tuesday 24th January 2012

**10.00 – 15.30**

**Ann Anderson Lecture Theatre**
**Level 3, Women's Centre,**
**John Radcliffe Hospital**

# NDOG & PAEDIATRICS GRADUATE SYMPOSIUM

## Tuesday 24th January 2012

| Time | Presenter | Dept | Title |
|---|---|---|---|
| 10:00 | **REGISTRATION & COFFEE** | | |
| 10:30 | **Ian Sargent** | **DGS (NDOG)** | **WELCOME** |
| 10:40 | Samer Al Farawati | NDOG | Are patients undergoing PGD for chromosome rearrangements at increased risk of aneuploidy affecting chromosomes unrelated to their rearrangement (interchromosomal effect)? |
| 11:00 | Daniel O'Connor | Paeds | To identify genetic determinants influencing immunological responses and persistence to serogroup C meningococcal conjugate vaccine. |
| 11:20 | Walaa Ramadan | NDOG | The oocyte activation factor, phospholipase c zeta (PLCζ): mechanisms of action and potential for human infertility treatment. |
| 11:40 | Maheshi Ramasamy | Paeds | Immunogenicity of polysaccharide and conjugate quadrivalent meninococcal ACYW-135 vaccines in healthy adult volunteers – a randomised clinical trial. |
| 12:00 | Pilar Vazquez | NDOG | The role of variant (v)U1 snRNAs in hES cell maintenance and differentiation |
| 12:20 | Zahraa Al Yahyaei | NDOG | Investigation of the expression of IL-33 and ST2 in human first trimester placenta and trophoblast cell lines. |
| 12:40 to 13:40 | **LUNCH BREAK & POSTER VIEWING: Rebecca Dragovic (NDOG), Christos Ioannou (NDOG), Claudia Juarez Molina, (Paeds), Katie May (NDOG),** | | |
| 13:40 | Lorna MacLeod | NDOG | A novel mouse model for imaging and quantifying mitophagy |
| 14:00 | Johannes Truck | Paeds | Investigation of the B-cell response to pneumococcal vaccines given to children and adults |
| 14:20 | Caroline Knight | NDOG | Assessment of fetal and neonatal nutritional status: preliminary results and future work |
| 14:40 | Nikolas Weismueller | Paeds | Microparticle Approaches to Needle-Free Delivery of Hib Vaccines |
| 15.00 | Michelle Potter | NDOG | Targeting the mitochondria as a therapy in cancer |
| 15:20 | **PRIZE GIVING, REFRESHMENTS & CLOSE Prizes sponsored by STARLAB UK and Jencons (a VWR Company)** | | |

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## GRADUATE SYMPOSIUM ABSTRACTS


### Samer Al Farawati, NDOG



**Abstract: Are patients undergoing PGD for chromosome rearrangements at increased risk of aneuploidy affecting chromosomes unrelated to their rearrangement (interchromosomal effect)?**

**The incidence of chromosomal abnormalities in human oocytes and embryos:**

The aim of my project is to study the incidence of chromosome abnormality in human oocytes and embryos, especially at the blastocyst stage, using molecular cytogenetic techniques such as fluorescent in situ hybridization, comparative genomic hybridization (cgh) and array comparative genomic hybridization (aCGH).

The relationship between chromosome anomalies and maternal age, repeated in vitro fertilization (IVF) treatment failure and recurrent miscarriage have been investigated in this project.

The most common method in IVF clinic to assess embryo quality depends on morphological criteria in different stages. Therefore, I have also studied the relationship between embryo morphology at the blastocyst stage and chromosome abnormality to find a link between both that could help embryologists to choose normal embryos in case if there was a link.

Carriers of chromosome rearrangements are at increased risk of implantation failure, miscarriages or even the birth of a child with congenital abnormalities or mental retardation due to losses or gains of chromosomal fragments involved in the rearrangement. Comprehensive chromosome analysis has been used to select embryos which are chromosomal normal or ones that carry the parental rearrangement, and the incidence of aneuploidies affecting chromosomes not involved in the rearrangement has been investigated.

I have been involved in the development of a new aCGH platform, which has the ability to simultaneously detect chromosome aberrations and can study the telomere length and mitochondrial copy number in the tested samples. The new array has been assessed using samples with known abnormalities. I am now trying to validate this platform using clinical samples, with the hope that it might find clinical application in the future.

## Daniel O'Connor, Paediatrics

**Abstract: To identify genetic determinants influencing immunological responses and persistence to serogroup C meningococcal conjugate vaccine.**

**Background:** Vaccination is the most effective means of preventing the morbidity and mortality associated with infectious diseases. The vaccination program against serogroup C meningococcal disease, introduced in the UK in 1999, has been very successful. However, some children do not respond adequately to the serogroup C meningococcal conjugate vaccine to confer persistent immunological protection. Genetic factors have been shown to greatly influence immune responses to vaccination, particularly in the young.

**Objective:** To identify genetic determinants influencing immunological responses and persistence to serogroup C meningococcal conjugate vaccine.

**Design and results:** We studied the influence of 721 single nucleotide polymorphisms (SNPs), across 131 candidate genes in 905 teenagers and the persistence of serogroup C meningococcal specific IgG concentrations and serum bactericidal antibody titres, following serogroup C meningococcal conjugate vaccination (MenC), and replicated associations in a second cohort of 351 children and infants. Single SNPs within Toll-like receptor 3 (rs7657186: p = 0.004) and CD44 (rs12419062: p = 0.01) were associated with persistence of MenC specific IgG concentrations. We then sequenced the exonic regions of the TLR3 gene to assess the influence of exonic SNPs and the primary responses to MenC vaccination, in a cohort of 318 infants. We found an association between a two allele haplotype (rs3775291-rs3775290) and lower MenC specific IgG responses, following primary MenC vaccination in infancy (P=0.009). We were then able to show a trend peripheral blood mononuclear cells (PBMCs) from individuals with this particular haplotype to be less responsive to Poly I:C (a artificial agonist for TLR3) stimulation in cell culture.

**Conclusion:** This may imply a novel role for TLR3 in humoral responses to serogroup C meningococcal conjugate vaccines.

## Walaa Ramadan, NDOG

**Abstract: The oocyte activation factor, phospholipase c zeta (PLCζ): mechanisms of action and potential for human infertility treatment**

Upon gamete fusion, mammalian oocytes are released from meiotic arrest coincident with a series of events known as oocyte activation which ultimately lead to zygote development and embryogenesis. It is widely believed that the sperm-specific protein phospholipase C zeta (PLCζ) is released into the oocyte upon fusion and initiates $Ca^{2+}$ oscillations which regulate oocyte activation.

Studies have shown that reduced amounts, abnormal localisation patterns, and aberrant forms of PLCζ underlie certain types of male-factor infertility, prompting interest in the mechanisms regulating PLCζ expression in developing sperm. Intracytoplasmic sperm injection is often used to treat male-factor infertility, but is known to fail in 1 – 5 % of cases. In mouse oocyte studies, the co-injection of ICSI-failed human sperm with PLCζ mRNA successfully rescues oocyte activation ability, prompting significant interest in PLCζ as a clinical therapeutic.

Using quantitative immunofluorescence techniques, this project investigated PLCζ localisation patterns and expression levels in epididymal mouse sperm at different levels of maturity, and in mice of different ages, in order to improve our understanding of temporal and spatial PLCζ expression and assess the effect of aging upon egg activation ability. Recognising the need for improved antibody specificity, a bacterial expression system is being utilised to purify recombinant PLCζ protein in order to generate the first monoclonal anti-PLCζ antibody. In addition, mammalian expression systems are being used to generate an active purified recombinant PLCζ protein for therapeutic application.

Initial findings suggest a significant change in PLCζ localisation pattern with progressive sperm maturity, and the potential for reduced egg activation ability with increased male age. Collectively, these studies should extend our fundamental knowledge of how PLCζ is expressed in developing sperm, assist in the translation of PLCζ as a clinical therapeutic, and evaluate PLCζ as a potential biomarker for egg activation ability.

## Maheshi Ramasamy, Paediatrics

**Abstract: Immunogenicity of polysaccharide and conjugate quadrivalent meningococcal ACYW-135 vaccines in healthy adult volunteers – a randomised clinical trial.**

**Background:** In the absence of a serogroup B meningococcal vaccine, quadrivalent vaccines against serogroups A,C,W-135 & Y offer the broadest possible protection against disease. Both conjugate and polysaccharide quadrivalent meningococcal vaccines are licensed for use in the UK. However, polysaccharide vaccines have been associated with poor immune responses and hyporesponsiveness.

**Objective:** To investigate polysaccharide-induced hyporesponsiveness by measuring the B cell responses to a quadrivalent meningococcal conjugate vaccine and a quadrivalent plain polysaccharide vaccine.

**Methods:** We conducted an open-label parallel group randomised clinical trial in 150 healthy adult volunteers aged 18-70 between June 2009 and October 2010 in Oxfordshire, UK. Participants were randomised to receive either 2 doses of a conjugate quadrivalent ACWY vaccine 28 days apart (Group 1, n=75), or one dose of a polysaccharide quadrivalent ACWY vaccine followed by one dose of a conjugate quadrivalent ACWY vaccine 28 days later (Group 2, n=75). Between-group comparisons were made to investigate polysaccharide induced hyporesponsiveness, as assessed by serum bactericidal assays (SBA) performed at baseline, and at 7 and 28 days after each vaccination.

**Results:** The SBA GMTs at 28 days post conjugate vaccination were higher in Group 1 participants who had not received a prior dose of polysaccharide vaccine (40.7, 107.9, 112.6 and 31.4 for serogroups A,C, W-135 and Y respectively) than in Group 2 participants who had received prior polysaccharide (15.9, 39.3, 34.0 and 13.4 respectively). The response to a conjugate booster was greater at 7 days in the conjugate primed Group 1 (35.0, 96.3, 74.6 and 27.6), than in the polysaccharide primed Group 2 (25.1, 59.0, 58.3 and 19.0), but this had lost significance by day 28 post boost. Adverse events were similar in each group.

**Conclusions**: Prior vaccination with polysaccharide appears to impair the subsequent response to conjugate vaccination. This is consistent with previously described polysaccharide induced hypo-responsiveness, but might also indicate differences in the magnitude or phenotype of B cells responding to the two different vaccines. In addition, despite prior data indicating that it may act as a T-dependent antigen, the serogroup A polysaccharide component of the vaccines appears to behave in the same way as serogroup C, W-135 & Y polysaccharides.

Clinicaltrials.gov identifier: NCT00901940

**Pilar Vazquez Arango, NDOG**

## Abstract: The role of variant (v)U1 snRNAs in hES cell maintenance and differentiation

The diversity of the proteome is in part due to the process of alternative splicing, whereby some or all of the exonic sequences within a gene are retained and the intronic sequences are removed; thus constituting an important level of gene regulation in a given tissue or developmental stage.

In the field of regenerative medicine, human embryonic stem (hES) cells offer the potential to treat degenerative diseases and replace damaged or non-functional tissue. However, it is not fully clear how hES cells can be directed into specific cell lineages. Therefore, understanding gene regulation at the level of the spliceosome in hES cells will give insights into the expression of key proteins at specific stages and thus be crucial to the development of new treatments.

Data from our lab indicates that there are genes, previously classified as pseudogenes, that encode for variants of the U1 small nuclear (sn)RNA, a key component of the spliceosome. These variant (v)U1 snRNA genes are transcriptionally active and differentially expressed in hES cells and HeLa cells. In addition, changes in the levels of the vU1 snRNAs lead to transcription and splicing defects of endogenous mRNAs *in vivo* (O'Reilly D. et al., *unpublished*).

We have analysed the expression of vU1 snRNA genes in four different hES cell lines and showed by qRT-PCR analysis, using gene-specific primers, that all vU1 snRNA genes are expressed at equivalent levels in all cell lines. Furthermore, a subset of the vU1 snRNA genes is down-regulated upon differentiation into embryoid bodies. We hypothesize that vU1 snRNAs may play a significant role in transcription and alternative splicing events in hES cells and their differential expression may be key to hES cell differentiation during development.

## Zahraa Al Yahyaei, NDOG

**Abstract: Investigation of the expression of IL-33 and ST2 in human first trimester placenta and trophoblast cell lines**

During normal pregnancy, tolerance to the pre-implanting embryo by the maternal immune system depends on interactions of an array of cytokines secreted by both the mother and the embryo at the site of implantation. Human ST2 is a member of the interleukin (IL)-1 receptor like family of proteins with two isoforms, a cell surface receptor (ST2L) and a soluble decoy (sST2) produced by alternative splicing. Its ligand, IL-33 is a newly identified cytokine of the IL-1 family. IL-33/ST2 system has been associated with the induction of Th2 response evident in diseases such as asthma and vascular diseases.

Previous work in the lab detected the presence of IL-33 and ST2 in human third trimester placenta. In this study, we focus on the detection of IL-33 and ST2 in first trimester placenta and different human trophoblast cell lines in aims of understanding the role of the IL-33/ST2 system in maintaining earlier stages of pregnancy. The expression of ST2 and IL-33 was examined by using flow cytometry, Western blotting and immunofluorescence microscopy.

Both IL-33 and ST2 are detected in first trimester placental samples. sST2 is contained within the cells with nuclear localization. Absence of a functional ST2L receptor on the surface of trophoblast cells might explain the lack of responsiveness to IL-33. The significance of the nuclear localization is not yet known and further investigation is being carried to study its effect on modulation of trophoblast cell function.

**Lorna MacLeod, NDOG**

**Abstract: A novel mouse model for imaging and quantifying mitophagy.**

Mitochondria are dynamic organelles which engage in cycles of fission and fusion. Their principle role is the production of energy currency in the form of adenosine triphosphate molecules (ATP) by oxidative phosphorylation (OXPHOS). However, mitochondrial DNA (mtDNA) lies in close proximity to OXHPOS and due to inherent deficiencies in electron transport during OXPHOS, reactive oxidative species (ROS) is released, causing mtDNA damage with mutation levels increasing over time. Mitochondrial quality is maintained by the selective elimination of these organelles via a process of mitochondria targeted autophaghy (mitophagy), a process reliant on mitochondrial fission/fusion. We have generated a transgenic mouse strain which expresses the red fluorescent protein DsRed-monomer solely in mitochondria.

To observe mitochondrial morphology in tissues, animals were culled and organs flash frozen. Mitochondria in DsRed-monomer mice are labelled red in a number of tissues and appear to show tissue dependant morphology variation and localisation. To date, we have sections from cardiac tissue, kidney, gastrointestinal tract and embryos and placenta at E11.5 and E18.5. We have also generated mouse embryonic fibroblasts (MEFs) which show the brightest expression.

We use ImageStream (Amnis) to investigate the co-localisation of mitochondria and the autophagic marker LC3. Splenocytes were separated by mechanical disruption, untreated or treated with chloroquine for ~16 hours. Analysis shows a significant increase of red/green co-localisation in chloroquine treated samples.

The DsRed-monomer transgenic mouse could be extremely useful for studying mitophagy.

## Johannes Truck, Paediatrics

### Abstract: B cell response to pneumococcal vaccination

*Streptococcus pneumoniae* is a significant cause of mortality and morbidity in both children and older adults and routinely administered pneumococcal conjugate vaccines (PCVs) have had a major impact on disease rates. Vaccine-induced protection against pneumococcal infection is mediated by the generation of persistent serotype-specific functional antibodies and antigen-specific memory B-cells. Although many studies have investigated serotype-specific antibody responses following vaccination in different age groups, there is more limited information about the B-cell (subsets) underlying such an immune response.

This DPhil aims to investigate in detail the B-cell response to pneumococcal vaccines given to children and adults using a variety of different methods. A cultured ELISpot technique was used in a first study to compare serotype-specific memory B-cell frequency following immunisation of 3.5 year old children with a 13-valent pneumococcal conjugate vaccine (PCV-13) having been previously primed with either a 13-valent or 7-valent pneumococcal conjugate vaccine. In addition in the same study a novel FACS based method was used to identify antigen-binding B-cells by flow cytometry. Five ml of blood was sufficient to allow the identification of a variety of antigen specific B-cell subsets in the peripheral blood. The same method will be used in a detailed kinetics study of the antigen-specific B-cell subsets in response to either PCV-13 or the 23-valent pneumococcal plain polysaccharide vaccine in adults.

Another important area of investigation is the evolution of the repertoire of B-cell receptor immunoglobulin genes during the course of an immune response to a vaccine. An investigation of the immunoglobulin gene sequences of antigen-specific B-cells identified by the novel FACS based antigen labelling method is an attractive approach and will be used in the already mentioned kinetics study. This genetic analysis provides a unique opportunity for understanding germinal centre activity from peripheral blood responses.

## Caroline Knight, NDOG

### Abstract: Assessment of fetal and neonatal nutritional status: preliminary results and future work

**Objectives:** The overall objective is to develop methods to characterise fetal body composition in-utero. For this purpose we aim to measure limb fat and relate this to neonatal outcome.

**Methods:** This is a prospective longitudinal study involving antenatal ultrasound, and neonatal anthropometry and body composition assessment. The present participants are optimally healthy women in the Intergrowth-21st study. Every 4-6 weeks from 16 weeks' gestation, standard 2D fetal measurements are taken, plus arm, thigh and subscapula, and 3D volumes. These images are analysed offline using tools developed through collaboration with the Institute of Biomedical Engineering. Within 24 hours of birth body composition is assessed using air displacement plethysmography ("PEAPOD"), and neonatal weight; length; head, arm and leg circumferences are measured.

**Results:** We have scanned 240 women 1-6 times each, totalling 640 scans. 63 of their babies have had "PEAPOD" measurements. We have started analysing the images by manual segmenting 2D arm fat. The Biomedical Engineers are developing 2D semi-automated techniques and 3D volume segmentation tool. We present preliminary results including reproducibility and a description of normal fetal fat development across gestation.

**Conclusions:** There is a small body of work on fetal limb volumes but this is the first to assess limb fat in longitudinal 2D cross-sections, 3D volumes, and correlate it with neonatal measurements to aid understanding and management of fetal and neonatal nutrition and growth.

**Future work:** We are expanding our methods and techniques to assess fetal thigh fat and 3D arm and thigh fat volumes; assess growth-restricted babies; and measure cord blood biomarkers for correlation with fetal fat. We will use fetal MRI to validate our ultrasound images and build an image bank for future research. This work should enable more sensitive assessments of growth and functional assessment of nutrition in-utero and improve personalised perinatal care (eg feeding regimes).

## Nikolas Weismueller, Paediatrics

### Abstract: Microparticle Approaches to Needle-Free Delivery of Hib Vaccines

*Haemophilus influenzae* type b (Hib) disease incurs severe morbidity and mortality in over 3 million cases annually. Highly efficacious Hib vaccines exist, but their cost makes global coverage an expensive undertaking. Vaccinations have a tremendous medical benefit, but as vaccine safety improves, hypodermic needles increasingly become a vector of disease. Particularly in resource poor countries, the dissemination of blood-borne pathogens associated with the use of needles has become a formidable burden to global health.

To contribute to a novel and cost-effective clinical vaccine delivery alternative, dry-powder formulations of the Hib polysaccharide conjugate vaccine carrier protein CRM197 were investigated for application in needle-free ballistic epidermal delivery.

Spray freeze dried formulations were investigated alongside a novel antigen-coated vaccine delivery particle made from β-tricalcium phosphate bioceramic. Protein analysis data suggest that protein-coated β-tricalcium phosphate particles conserve CRM197 tertiary structure and show less protein aggregation after resuspension compared to spray freeze dried polyol excipient particles.

**Michelle Potter, NDOG**

**Abstract: Targeting the mitochondria as a therapy in cancer**

Considerable progress has been made in both chemotherapy and radiotherapy in recent years but cancer is still a leading life-threatening illness. There is need for new and novel therapeutic approaches centred on our current knowledge of cancer biology.

Cancer cells have many phenotypical features. Two of these features are of particular interest to us: 1) their glycolytic profile (the Warburg effect) and 2) their sensitivity towards oxidative stress. We hope to take advantage of these features by restoring OXPHOS through the use of a drug called dichloroacetate (DCA) and combining this with a vitamin K3 and vitamin C cocktail which will expose the cells to an oxidant insult. We hypothesise that this combination therapy will exhibit a synergistic action without major toxicity in vivo.

Standard 2D monolayer cultures do not adequately address the complexity of in vivo tumour pathophysiology. 3D tumour spheroids better represent the tumour microenvironment especially when it comes to oxygenation and drug access. Currently I am working on developing a 3D model in which to test my hypothesis.

## Youn-Jung Kang, NDOG

### Abstract: Synergy between integrin αvβ3, osteopontin and growth factor pathways in embryo-epithelial adhesion at implantation

**Introduction:** Understanding of embryo implantation is critical to our basic knowledge of human reproduction. We hypothesized that integrin αvβ3 and its ligand OPN mediate the early interaction between embryos and endometrial epithelium during implantation, and that this interaction is modulated by growth factors locally secreted from the embryo.

**Materials & Methods:** Implantation assays were carried out by transferring either mouse embryos or embryo-sized beads (80-150µm) carrying pre-absorbed (2h) protein ligands: IGF-1, HB-EGF, OPN or BSA onto confluent epithelial (Ishikawa) cell monolayers. Cells were transfected with siRNA (100nM) targeting integrin αvβ3 or OPN prior to transfer of embryo or bead. The stability of attached mouse embryos or the number of attached beads was scored. Comparisons were made with the effect of IGF-1 or HB-EGF (50ng/ml) in solution at 0-48h.

**Results:** Following 24h of co-culture, embryos were loosely attached, and more stably after 48h. Embryo attachment stimulated local up-regulation of epithelial integrin αvβ3 and OPN as monitored by immunofluorescence. IGF-I/HB-EGF-coated beads similarly enhanced epithelial integrin αvβ3. Knock-down of αvβ3 reduced the rate of attachment, both of embryos and of beads carrying IGF-1, HB-EGF or OPN. OPN, which was confined to intracellular locations under control conditions, was cleaved to produce a 45kDa adhesion-active species, and migrated to the apical epithelial surface after 8h treatment with soluble IGF-1, but neither effect was observed in the presence of HB-EGF.

**Discussion:** Two embryo-derived growth factors, IGF-I and HB-EGF, can mediate initial attachment to the epithelium. The activity of IGF-I is dependent on both OPN and αvβ3. Surprisingly, HB-EGF also appears to operate through integrin αvβ3, but not through OPN. Thus, integrin αvβ3 may mediate implantation via two independent signalling pathways

## Christos Ioannou, NDOG

### Abstract: Fetal skeletal biometry using 3D ultrasound and the impact of maternal vitamin D concentration

**Background:** Previous research suggests that vitamin D deficiency during pregnancy may be associated with suboptimal fetal skeletal development, but direct evidence is lacking. Our objectives were 1) to develop a reliable method in order to measure the fetal femur volume (FVol) on 3D ultrasound and 2) to correlate FVol with maternal vitamin D concentration.

**Methods:** Three projects were undertaken. First, a simple method for FVol calculation was described which consists of three linear measurements and a volume equation; this method was validated by comparing the FVol measurement with the true volume of the femur measured by postmortem computed tomography (CT) following pregnancy termination. Measurement repeatability was assessed. Secondly, a cohort of pregnant women were selected on the basis of strict inclusion criteria in order to ensure uncomplicated pregnancies free of pathological growth; participants underwent serial ultrasound scans for FVol and multilevel analysis was used for the creation of a "prescriptive" FVol chart in pregnancy. Thirdly, a different cohort of pregnant women had anthropometric and nutritional information collected with questionnaires; serum vitamin D levels and FVol ultrasound at 34 weeks gestation; and neonatal bone mineral content (BMC) measurement following delivery with dual emission x-ray (DEXA) in order to investigate prenatal determinants of neonatal bone mass.

**Results:** The proposed method demonstrated satisfactory repeatability and excellent agreement with CT. A normal FVol chart was created and the regression equations for the median and percentile values were presented. Vitamin D demonstrated a significant correlation with FVol.

**Conclusions:** Fetal FVol is a reliable ultrasonographic marker of skeletal growth. Maternal vitamin D deficiency is associated with reduced fetal FVol. This finding has public health implications as reduced bone mass may increase the lifetime risk of osteoporosis, through fetal programming.

## Katie May, NDOG

### Abstract: Endothelial Progenitor Cells in Endometriosis

**Introduction:** Endometriosis is a common gynaecological condition associated with pelvic pain and subfertility. It is characterised by the presence of endometrial-like tissue outside the uterus. These endometriotic lesions often appear as highly vascularised deposits in the peritoneal cavity, indicating an important role for blood vessel development in disease progression. Circulating endothelial progenitor cells (EPCs) are a recently discovered cell type involved in vasculogenesis – new vessel formation without the need for existing vasculature. We sought to establish whether circulating EPC levels may be altered in the blood of women with endometriosis and, in particular, if these cells could be used as a biomarker of the disease.

**Methods:** Women awaiting laparoscopy for symptoms suggestive of endometriosis were recruited to the study. All women had regular menstrual cycles, and had not taken hormonal medication for at least three months prior to participation. Blood was collected on the morning of surgery, and peripheral blood mononuclear cells were isolated using density gradient centrifugation. Five colour flow cytometry was used to identify circulating EPCs as viable $CD31^{+}CD133^{+}CD34^{+}CD45^{-/dim}$ cells.

**Results:** 51 women were recruited to the study. Baseline characteristics were found to be similar between women with and without endometriosis. Levels of circulating EPCs were not significantly different in women with endometriosis. No differences in EPC levels were found between women with minimal-mild and moderate-severe disease.

**Conclusion:** Circulating EPC levels appear to be unchanged in women with endometriosis.

## Claudia Juarez Molina, Paediatrics

### Abstract: Impact of HLA-B*35 subtype differences on HIV outcome in Mexico

**Background:** Previous studies have consistently associated HLA-B*35 with rapid disease progression in the context of B clade HIV infection. HLA-B*35 subtypes of the PX group (such as HLA-B*3502/03/B*53) have particularly been associated with worse outcome. The mechanisms underlying these observations are not clear. This study focuses on the Mexican HIV epidemic where HLA-B*35 is expressed in approximately one-third of Mexicans.

**Methods:** The study cohort comprised 786 Mexican subjects with chronic HIV B clade infection. All subjects were HLA typed by sequence-based typing (Abbot). Viral load (VL) and CD4+T cell counts were determined by real-time PCR (Abbot) and multiparametric flow cytometry (BD), respectively. Gag and pol genes were amplified from plasma virus as previously described to determine clade of infection.

**Results:** Consistent with previous studies of B clade infected Caucasoid, HLA-B*57 and HLA- B*27 were the most protective alleles. In contrast with earlier work, no significant impact on VL setpoint or absolute CD4+T cell count was observed between the HLA-B*35 PY versus PX groups (p=0.6721 and p=0.4536 respectively). Diverse ranking of HLA-B*35 alleles according to median viral setpoints was observed. HLA-B*3508 was 2nd of 46 HLA-B alleles, while B*3502 was 45th. HLA-B*3501, a PY allele not considered a risk allele, was significantly associated with higher VL and lower CD4+T cell counts (p=0.0206 and p=0.0039 respectively).

**Conclusions:** These data suggests that, contrary to previous studies, certain HLA-B*35 alleles can be protective against HIV disease progression. We observe substantial differences in markers of HIV disease outcome associated with small differences between HLA-B*35 alleles. Defining the mechanisms underlying these differences will facilitate a better understanding of the mechanisms of immune control or lack of control of HIV and therefore are of direct relevance to HIV T-cell vaccine design.

## Clare Grant, Paediatrics

**Abstract: Using 454-deep sequencing to elucidate the bovine B cell response to Foot-and-Mouth disease virus.**

*Clare Grant, Karen Billington, Eric A Lefevre, John Hammond and Bryan Charleston*

*Institute for Animal Health, High Street, Compton, Nr Newbury, Berkshire, RG20 7NN. UK*

Foot-and-mouth disease virus (FMDV) vaccines induce a short duration of protective immunity and require regular repeat immunisation to maintain a high protective neutralising antibody titre. Little is known about the kinetics or the IgG V-region sequence usage of the antigen-specific plasma and memory B-cell responses post vaccination in cattle. Once the B-cell kinetics and IgG V-region sequence usage of the B-cell response in cattle have been elucidated to a model antigen we will apply this knowledge to a FMDV vaccination system.

The ELIspot assay has been previously used to demonstrate the kinetics of the bovine plasma and memory B-cell response to TNP–CGG in peripheral blood. In this study we have used PBMCs obtained from two calves that were immunised and boosted with TNP-CGG to determine the Vh gene sequence usage pre-booster and also at the peak of plasma cell response. Total RNA was extracted and stored from the PBMC samples taken daily and a duplicate IgG 5'RACE libraries were amplified from the samples of interest. 454-sequencing was then employed on the amplified pre-boost and peak antigen-specific IgG samples.

The kinetics of the TNP-CGG and FMDV specific plasma cell response showed a peak in antigen-specific IgG secreting cells at day 5 post-booster immunisation. The 454-sequencing data derived from one of the animals showed very little dominance of any one transcript pre-boost sample (i.e. polyclonal response). At the peak of antigen-specific plasma cell response there was a complete change in the sequences present with a dominance of several transcripts.

Future work will study B-cells in post immunisation efferent lymph, where there is a higher proportion of antigen specific cells and are detectable for a prolonged period allowing analysis of somatic hypermutation.

# APPENDIX

# Record of achievement

## Graduate Training Programme

The purpose of keeping this record is to document the progress of your research and training and your participation in the graduate training programme (GTP). This document should be brought to all your formal meetings with your supervisor/advisor.

**Record forms are provided here for the following activities:**

1. Meetings with the supervisor and advisor
2. Formal skills training (e.g. workshops)
4. Seminars and lectures attended
5. Conferences attended
6. Presentations given
7. Journal Club presentations
8. Publications
9. Skills checklist

*Please duplicate the forms as needed*

**INITIAL SUPERVISOR/ADVISOR MEETING**

## **Record form:** Initial Supervisor/Advisor Meeting (first month)

Name:……Supervisor:……..

Date of meeting:

| **RESEARCH PROJECT (to be completed by the Student following discussion with Supervisor prior to the meeting and should be made available to the Supervisor and Advisor prior to the meeting.)** |
|---|
| **Synopsis and overall aims:** |
| **Key initial objectives:** |

**Signature of Supervisor.....…. Date……..**

**Signature of Advisor.....…..... Date……..**

## Record Form: Supervisor/Advisor Meeting

*It is expected that there would be three meetings per year. Please duplicate form as needed.*

Name: ..... Supervisor: .....

Date of meeting: ……

| **PROGRESS REPORT** – ***To be completed by supervisor/advisor after the meeting. Should include comments on progress in training as well as progress in research.*** |
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| |

**Signature of Supervisor ..... Date ……..**

**Signature of Advisor ..…..... Date ……..**

Declaration by Student

I have discussed my progress with the Advisor and my Supervisor and have read and agree with the comments made above.

**Signature of Student..... Date ……**

## **Record Forms:** TRAINING WORKSHOPS AND SEMINARS ATTENDED

| Date(s) | Title/Topic/Skill |
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# PRESENTATIONS

**Record Forms:** All presentations (including abstracts) that you give should be recorded here

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**Record Forms:** All presentations by you to a Journal Club should be recorded here

| Date | Paper(s) discussed | Comment |
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# SEMINARS/LECTURES

**Record Form:** Seminars/lectures attended (students are expected to attend 25 seminars per year – this form should be photocopied)

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# CONFERENCES/MEETINGS

**Record Form:** Conferences/scientific meetings attended. Students are expected to attend at least one national or international meeting each year, and to present at meetings in the second and third years.

| Date(s) | Title and venue | Comment (including contribution) |
|---|---|---|
| | | |

# RECORD OF PUBLICATIONS

**TEACHING/SUPERVISING**

**Name:** ..... **Supervisor:** .....

| Date(s) | Activity (tutorials, demonstrating, supervising) |
|---|---|
| | |

| **COMPUTATIONAL SKILLS (indicating training received and level of competency)**<br><br>Excellent IT training course at all level are provided by the OUCS for free (www.oucs.ox.ac.uk/courses/) throughout the year. |
|---|
| (a) word processing (e.g. WORD) |
| (b) bibliography software (e.g. ENDNOTE) |
| (c) data processing, curve fitting, statistical and presentation software (e.g. EXCEL) |
| (d) presentation software (e.g. POWERPOINT) |
| (e) internet communication (e.g. Email, Internet explorer) |
| (f) bioinformatics software (e.g.GCG, Vector NTI)) |
| (g) Other (e.g. other applications include project-specific applications, computer programming, experience of different operating systems) |