# Oxford-MRC DTP Symposium

27 June 2019

MRC Medical Research Council

UNIVERSITY OF OXFORD

Oxford-MRC Doctoral Training Partnership

# Programme

**09:00** **Registration + Tea and Coffee**

**09:30** **Opening remarks**
Director of Oxford-MRC DTP

**09:40** **Student Talks – Session 1**

**Barnabas Williams** – Jenner Institute
*"Plasmodium falciparum RH5 interacting protein (PfRipr): a blood-stage malaria vaccine candidate"*
**Rosie Little** – DPAG, MRC Harwell
*"Examining vesicles & fgf signalling in the mouse node"*
**Giulia Pilla** – Dunn School of Pathology
*"Maintenance of virulence in Shigella: identification of potential targets to treat shigellosis"*

**10:40** **Coffee break**

**11:10** **Student Talks – Session 2**

**Mary Kempnich** – Department of Experimental Psychology
*"Social networks in transition – adapting to university."*
**Nidi Tapoulal** – Burdon Sanderson Cardiac Science Centre, DPAG
*"Neuropeptide-Y causes coronary microvascular constriction and is associated with reduced ejection*

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| | *fraction following ST-elevation myocardial infarction"*<br>**Imran Yusuf**<br>*"Phenotyping the Cdhr1$^{-/-}$ mouse model for the development of gene therapy for CDHR1-associated retinal degeneration"* |
| **12:10** | **Keynote lecture**<br>**Professor Peter Donnelly FRS FMedSci** – WCHG<br>*"Using genomics to impact health and healthcare"* |
| **13:00** | **Lunch Break and Poster Presentations** |
| **14:00** | **MRC DTP Oxford Alumni Presentations**<br><br>**Amy Varney – Vice President of Operations at OxStem**<br><br>**Bo Jing – CEO of Oxford Nanoimaging**<br><br>**Cecilia Chui – Project Officer at the Wellcome Trust** |
| **14:45** | **Introduction to Intellectual Property**<br>**Sarah Jones** – Oxford University Innovation |
| **15:00** | **Coffee break** |

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| **15:15** | **Panel discussion: Bioentrepreneurship for DPhil Students** |
| **16:15** | **Closing remarks and Awards Ceremony** |
| **16:30** | **Drinks Reception & Networking** |
| **17:15** | Symposium Finish |

# Student Talk Abstracts

## Session 1

### Plasmodium falciparum RH5 interacting protein (PfRipr): a blood-stage malaria vaccine candidate.

**Barnabas Williams.** L. King, D. Pulido-Gomez, S. Draper.

Jenner Institute

*Plasmodium falciparum* is the most deadly of the five Plasmodium species that cause malaria. An estimated 200 million infections and 400,000 deaths occur each year despite decades of control and eradication efforts. Vaccines remain the most cost effective tool in the fight against infectious disease; however, an efficacious malaria vaccine is still not available. The multiple lifecycle stages of *P. falciparum* offer numerous targets for vaccine development. A vaccine against blood-stage malaria could prevent severe clinical malaria and complement naturally acquired immunity. The most promising blood stage vaccine candidate to date is PfRH5, currently being evaluated in clinical trials. PfRH5 exists in a complex with two other proteins: PfRipr and CyRPA, each of these proteins is a potential vaccine target. We have found that antibodies raised against PfRipr effectively block the invasion of erythrocytes by *P. falciparum*. Furthermore, we have found that the invasion blocking antibodies bind to a small 88 amino acid region of PfRipr which corresponding to EGF like domains 7-8. Immunisation of mice with PfRipr-EGF(7-8) conjugated to a viral like particle via the SpyTag-SpyCatcher system generates high quality *P. falciparum* invasion blocking antibodies. This work demonstrates that PfRipr-EGF(7-8) is an effective blood-stage malaria vaccine candidate.

## Examining vesicles & fgf signalling in the mouse node.

**Rosie Little.** R. Walker, J. Keynton, D. Norris

Department of Physiology, Anatomy & Genetics, Cilia, Development & Disease Group, MRC Harwell Institute

**Introduction**

Left-right patterning is set up early in development. Cilia in the pit of the mouse left-right organiser, the node, rotate to cause leftwards fluid flow, breaking symmetry. Immotile cilia at the node edge have been proposed as mechanosensory. An alternative hypothesis suggests Nodal Vesicular Parcels (NVPs) carry signalling molecules via fluid flow (Tanaka et al, 2005), for detection by immotile cilia. Fgf signalling has a role in left-right patterning, (Meyers & Martin, 1998) but it's precise function and mechanism is unclear.

**Methods**

Replicating Tanaka's protocol for live imaging of NVPs by incubation of embryos with the lipophilic dye DiI.
Investigation into expression and localisation of FGFRs in embryonic nodes and ciliated MEF cells through in situ hybridisation and immunofluorescence analysis.

**Results & Discussion**

SEM analysis of nodes show cell death and anomalous structure following incubation with DiI or mock control DMSO as per Tanaka's protocol. This casts doubt on the conclusions drawn by the use of DiI as a reagent for live imaging in this manner and the validity of NVPs as a mechanism of breaking L-R symmetry. FGFR1&2 are candidates for a role in L-R patterning due to IF data showing localisation to MEF and nodal cilia respectively.

## Maintenance of virulence in Shigella: identification of potential targets to treat shigellosis.

**Giulia Pilla.** G. McVicker, J. Martyn, C. Tang

Dunn School of Pathology

*Shigella* is the major cause of human bacillary dysentery worldwide. It evolved from the commensal *Escherichia coli* following acquisition of a large plasmid, pINV, which carries genes that enable *Shigella* to infect the host. If *Shigella* loses these genes, it becomes avirulent. Therefore, maintenance of the plasmid is essential for the retention of virulence. However, pINV imposes a significant fitness cost on *Shigella*. Here, I have defined the mechanisms by which *Shigella* retains virulence by investigating the pINV-encoded maintenance systems that the bacterium employs to prevent loss of pINV. I have focused on the pINVs of *Shigella flexneri* and *Shigella sonnei*, which are responsible for 90% episodes of shigellosis. My studies show that *S. flexneri* more efficiently maintains pINV than *S. sonnei* and this is mainly due to distinct differences in the maintenance systems encoded by the *S. flexneri* plasmid. Furthermore, the *S. flexneri* plasmid can reversibly integrate into the chromosome, providing a strategy to maintain virulence while circumventing fitness cost associated with the plasmid. Finally, characterisation of the maintenance systems of pINV has revealed novel targets that I have edited by a CRISPR-Cas system, inducing loss of virulence in *Shigella* and, thus, validating a potential strategy to treat shigellosis.

## Session 2

**Social networks in transition – adapting to university.**

**Mary Kempnich**. M. Hewstone.

Department of Experimental Psychology

Leading more mobile lives can involve challenges, such as integrating into a new social environment. Since the size and cohesiveness of our friendship circles predict how well we cope with stress, this instability can make us vulnerable. However, little is known about how our relationships adapt to periods of transition. By following 90 undergraduate students' transitions from school through their time at university, I investigated how relocating affects individuals' relationships and mental health. Respondents filled out a social network questionnaire at three months intervals throughout their first year, and once more in their third year. Crucially, the first wave of data collection took part before the students moved to Oxford, allowing a base-line assessment of their ego-networks and well-being levels.

Moving initially caused significant increases in homesickness and decreases in well-being. However, once respondents' networks stabilised, levels of anxiety, loneliness, and adjustment difficulties fell. Thus, fluctuations in mental health appeared to be mirrored by the respondents' network developments.

Given that contemporary Western societies face increases in mobility, these findings have implications beyond the higher education context. They suggest that transitivity not only affects an individual's network composition and maintenance, but also that such network changes might influence mental health.

# Neuropeptide-Y causes coronary microvascular constriction and is associated with reduced ejection fraction following ST-elevation myocardial infarction.

**Nidi Tapoulal.** N. Herring.

Burdon Sanderson Cardiac Science Centre, Department of Physiology, Anatomy and Genetics

**Aims:** The co-transmitter neuropeptide-Y (NPY) is released during high sympathetic drive, including ST-elevation myocardial infarction (STEMI), being vasoconstrictor. We hypothesized NPY levels correlate with reperfusion and recovery following primary percutaneous coronary intervention, and how NPY constricts the coronary microvasculature.

**Methods & Results:** Peripheral venous NPY levels were significantly ($p<0.05$) higher in patients with STEMI (n=45) compared to acute coronary syndromes/stable angina (ACS/SA, n=48) or normal coronary arteries (NC, n=16). Overall coronary sinus (CS) and peripheral venous NPY levels were positively correlated (r=0.79). STEMI patients with highest CS-NPY levels had lower coronary flow reserve, and higher index of microvascular resistance. After 48 hours higher levels of myocardial edema and microvascular obstruction on cardiac MRI, and lower ejection fractions and ventricular dilatation 6 months later. NPY (100-250nM) caused significant vasoconstriction of rat coronary microvasculature, increasing vascular smooth muscle calcium waves and coronary vascular resistance in Langendorff-hearts. These effects were blocked by Y1-receptor antagonism (BIBO3304, 1M). NPY (250nM) also significantly increased infarct size following left coronary artery ischemia-reperfusion ($p<0.001$). Immunohistochemistry of human coronary microvasculature demonstrated presence of vascular smooth muscle Y1-receptors.

**Conclusions:** High CS-NPY levels correlate with microvascular dysfunction, greater myocardial injury, and reduced ejection fraction 6 months post-STEMI. NPY constricts the coronary microcirculation via the Y1-receptor, worsening infarct size. Y1-receptor antagonists may be a useful PPCI adjunct therapy.

# Phenotyping the *Cdhr1*$^{-/-}$ mouse model for the development of gene therapy for *CDHR1*-associated retinal degeneration.

**Imran H. Yusuf**[1,2], Robert E. MacLaren[1,2], Peter Charbel Issa[1,2]

1. Nuffield Laboratory of Ophthalmology, University of Oxford, Oxford, UK. 2. Oxford Eye Hospital, Oxford, UK.

**Rationale:** Biallelic variants in *CDHR1* result in retinal degeneration and untreatable blindness in humans. The *CDHR1* transgene is sufficiently small for AAV encoding, suggesting AAV gene replacement as a feasible therapeutic strategy. A *Cdhr1*$^{-/-}$ mouse exists for *in vivo* evaluation of gene therapy in pre-clinical studies. However, detailed phenotyping of the *Cdhr1*$^{-/-}$ mouse has not been undertaken.

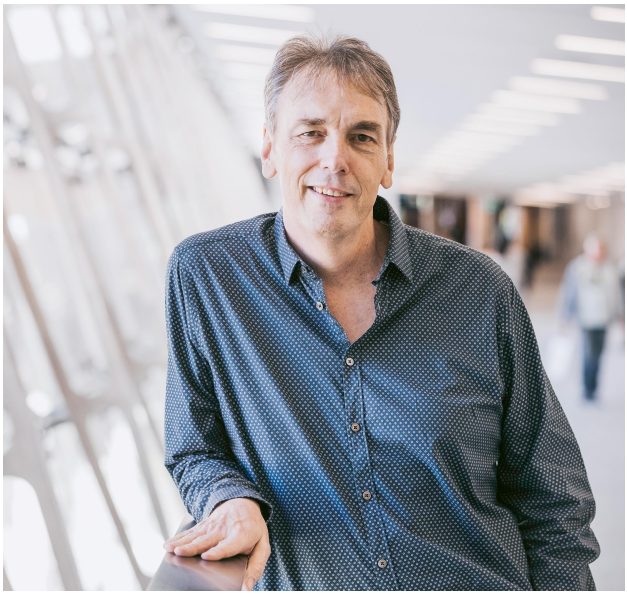
**Aim:** To phenotype the *Cdhr1*$^{-/-}$ mouse with a view to downstream development of AAV gene replacement for *CDHR1*-associated retinal degeneration.

**Methods:** The *Cdhr1*$^{-/-}$ mouse was phenotyped using retinal imaging with optical coherence tomography (OCT) *(n=8)* over 12 months and dark- and light-adapted electroretinography (ERG) *(n=36)* over 15 months.

**Results:** The *Cdhr1*$^{-/-}$ mouse demonstrates retinal thinning on OCT imaging at 3,6,9 and 12 months compared to *Cdhr1*$^{+/+}$ mice ($p<0.0001$ at all time points; two-way ANOVA). Dark-adapted A-wave amplitudes on ERG are reduced at 2,3,6, and 15 months in *Cdhr1*$^{-/-}$ mice versus wildtype ($p<0.0001$ at all time points; two-way ANOVA), and light-adapted B-wave amplitudes are also reduced ($p=0.0004$; two-way ANOVA).

**Conclusion:** The *Cdhr1*$^{-/-}$ mice demonstrates structural and functional evidence of progressive retinal degeneration affecting both rod and cone photoreceptors, mimicking the human phenotype. The *Cdhr1*$^{-/-}$ mouse model is ideal for evaluation of AAV.CDHR1 gene replacement.

# Keynote Lecture



## Using genomics to impact health and healthcare

**Professor Peter Donnelly FRS FMedSci**

Professor of Statistical Science at the Wellcome Centre for Human Genetics, University of Oxford

Peter Donnelly is CEO of Genomics plc and Professor of Statistical Science in the Wellcome Centre for Human Genetics at the University of Oxford where he was Director from 2007-2017.

Peter grew up in Australia and after graduating from the University of Queensland he studied for a doctorate in mathematics as a Rhodes Scholar at Oxford. He has subsequently undertaken a successful academic career, and after Professorships at the Universities of London and Chicago, he returned to Oxford in 1996. Peter played a major role in the development of coalescent models in population genetics and statistical methods for the analysis of genetic and genomic data.

Many of these methods, have become standards in the field and are widely used, including STRUCTURE, PHASE, and IMPUTE.

Peter was centrally involved in many of the major national and international projects in genetics, including, the International HapMap Project and the Wellcome Trust Case Control Consortium a large international collaboration studying the genetic basis of more than 20 common human diseases and conditions in over 60,000 people which he chaired. Subsequently he led an Oxford collaboration with Illumina which pioneered whole-genome sequencing in clinical medicine. In addition to his work in understanding the genetic basis of human diseases, Peter has used genetic data to learn about the demographic history of human populations, and to understand meiosis.

In 2014, along with several colleagues, Peter founded Genomics plc. He became the company's CEO in 2017. Genomics is based in Oxford and Cambridge and now employs around 50 people. Its focus has been to assemble the largest database of its kind, which combines data from research studies on individuals which link their genetic data with molecular, cellular, and biomarker measurements, and disease outcomes. Genomics plc has developed sophisticated statistical and machine learning algorithms to extract novel insights from this platform, creating a step change in our ability to understand human biology. The company uses these insights in precision health, by using genetics to enable the identification of subgroups of individuals at increased risk of particular diseases, and in drug development, by using *in silico* analyses of genetic information to identify new drug targets and to understand the likely efficacy and safety of potential novel medicines.

Peter is a Fellow of the Royal Society and of the Academy of Medical Sciences, and an Honorary Fellow of the Institute of Actuaries, and has won multiple academic awards. His TED talk has been downloaded over a million times. This year he has been recognized for his many achievements in Queen's Birthday Honours List.

# MRC DTP Oxford Alumni

**Bo Jing – CEO of Oxford Nanoimaging**

Bo Jing (CEO) studied Mathematics at ETH Zurich before focusing on his passion of creating tools that enable new kinds of scientific discoveries. He developed ONI's flagship product, the Nanoimager, during his PhD at Oxford and co-founded ONI. ONI has created the world's first portable microscope able to take movies of individual molecules inside living cells. Founded in 2016, it has attracted VC funding in 3 rounds, and the team has grown to 100 people in 2018.

**Amy Varney - Vice President of Operations at OxStem**

Amy Varney obtained her doctorate in Medicinal Chemistry at the University of Oxford. Amy's research was focused on assay design and drug discovery/development within the epigenetic field of methyl marker modifications. Through the Systems Approaches to Biomedical Sciences Industrial Centre for Doctoral Training (SABS-CDT) Amy was part of entrepreneurial and commercial programs, including in association with Oxford's Saïd Business School, which led to her joining the OxStem team. Amy joined the company in 2015 and assisted with the spin-out of OxStem and all four of the first subsidiaries; acting as liaison point across the collaborating University of Oxford departments.

**Cecilia Chui - Project Officer at the Wellcome Trust**

Cecilia is a project officer at Vaccines team at the Wellcome's Trust in London, where she supports the team's strategies and activities on controlled human infection models since 2017. Prior to joining Wellcome, she has worked as a consultant on pharmaceutical market access, focussing on pricing and reimbursement issues in US, EU, China and Japan markets. Her academic background is in infectious diseases and immunology, and she has worked as a postdoc researching on HIV-1 vaccines in Oxford. Cecilia was born and bred in Hong Kong until she moved to London in 2004. She holds a PhD in Clinical Medicine from University of Oxford, and a BSc in Biochemistry from Imperial College London.

# Intoduction to Intellectual Property

**Sarah Jones**

Oxford University Innovation,
Licensing & Property Manager

# Bioentrepreneurship for DPhil Students

**Richard Auburn**

Oxford University Innovation
Senior Licensing and Ventures Manager

**Libby Wood**

SBS Entrepreneurship Centre
Lead Programme Manager

**Leah Thompson**

Enterprising Oxford
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# Posters

1. **Investigating the function of *Oxr1* in the adult mouse brain.** Eboni Bucknor, Silvia Corrochano, Peter Oliver.

2. **Can alchemical free energy methods predict the effect of DNA gyrase mutations on fluoroquinolone susceptibility?** Alice Brankin, Philip Fowler, Sarah Walker.

3. **Causal relevance of obesity on the leading causes of death in women and men: A Mendelian randomization study.** Jenny Censin. Sanne Peters, Jonas Bovijn, Teresa Ferreira, Sara Pulit, Reedik Mägi, Anubha Mahajan, Michael Holmes, Cecilia Lindgren.

4. **The association between short- and long-term memory across normal ageing.** Giedre Cepukaityte, Nahid Zokaei, Anna C. Nobre.

5. **Polymorphisms in the *TAPBP* gene correlate with long-term non-progression of perinatally-acquired HIV-1 infection in children and adolescents from a cohort in Harare, Zimbabwe.** Bethany Charlton, Nuntanuj Vutthikraivit, Louis-Marie Yindom, Rashida Ferrand, Sarah Rowland-Jones.

6. **Investigating the role of microRNAs during bacterial infection in man: *Salmonella* enterica serovar Typhi exposure and infection alters microRNA expression in peripheral blood mononuclearcytes in a human challenge study.** Ruth Drury, C Blohmke, C Jin, D O'Connor, I Mohorianu, AJ Pollard.

7. **Development of one-shot vaccine by microfluidic encapsulation.** Romain Guyon, Rik Van Der Veen, Tayo Sanders II, Adrian Hill, Eleanor Stride, Anita Milicic.

8. **Targeting loss of ataxia telangiectasia mutated (ATM) expression in solid tumours.** Letitia Harris. Anika Weber, John Moore and Anderson Ryan.

9. **Investigating the mechanisms of nuclear envelope re-assembly during mitosis in mammalian cells.** Lilli Hahn, Logesvaran Krshnan, Pedro Carvalho.

10. **Antigen presentation by intestinal epithelial cells during intestinal inflammation.** Cornelia Heuberger, Sebastian Pott, Fiona Powrie, Kevin Maloy, Johanna Pot.

11. **Identifying the repair mechanism for trapped PARP.** Shudong Li, Kristijan Ramadan.

12. **Hippocampal volume by age, sex, and APOE genotype: Nomograms derived from over 19,700 people in UK Biobanks.** Lisa Nobis, Sanjay G. Manohar, Stephen M. Smith, Fidel Alfaro-Almagro, Mark Jenkinson, Clare E. Mackay, Masud Husain.

13. **Phosphatase exclusion-based triggering and stoichiometry of the B-cell receptor.** Caitlin O'Brien-Ball, Martin Wilcock, Anna H. Lippert, James McColl, Aleks Ponjavic, Ana Mafalda Santos, Richard J. Cornall, David Klenerman Simon J. Davis.

14. **The T-cell activation marker for TB (TAM-TB): a new diagnostic tool for paediatric TB.** Laura Olbrich, Ahmed M, Held K, Behrends U, von Both U, Avsar K, Hoelscher M, Song R, Saathoff E, Geldmacher C, Heinrich N.

15. **Screening for the exogenous up-regulation of the neuroprotective gene OXR1.** Anna Parsons, Silvia Corrochano, Matthew Williamson, Mattéa Finelli, Peter Oliver.

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