Cambridge Infectious Diseases Meeting

&

Wellcome Trust-Cambridge CGHR Launch

Wednesday 13th November

Robinson College, Cambridge

Event Programme

Cambridge Infectious Diseases 3rd Annual Meeting of Minds		
9.30	Welcome	**Prof. Sharon Peacock**, Director, Cambridge Infectious Diseases
9.45	Major genetic risk factor for visceral leishmaniasis lies at the heart of eliciting CD4 T cell immunity	**Dr Michaela Fakiola**, Cambridge Institute for Medical research
10.20	Viral inhibition of DNA-PK dependent DNA sensing	**Dr Brian Ferguson**, Department of Pathology
10.55	Genetics and evolution of clonally transmissible cancers in dogs and Tasmanian devils	**Dr Liz Murchison**, Department of Veterinary Medicine
11.30	*Tea & Coffee*	
12.00	Pandemic Influenza, HIV, SARS, MERS... are we prepared for future infectious threats?	**Prof. Ab Osterhaus**, ERASMUS MC
13.00	*Lunch*	
Wellcome Trust-Cambridge Centre for Global Health Research Launch		
14:00	Introduction to the WT-CCGHR	**Prof. David Dunne**, Director of the WT-CCGHR
14.10	Wellcome Trust's vision for CCHRs	**Dr Jimmy Whitworth**, Head of International Activities, Wellcome Trust
14.30	Health Research and Capacity Building in Uganda	**Prof. Nelson Sewankambo**, Principal- Makerere University College of Health Sciences; WT-CCGHR Co-PI; Director of the THRiVE Consortium in East Africa
15.00	Cambridge-Makerere Research Project in Maternal Health. Why is pregnancy such a risky time for African women?	**Prof. Ashley Moffett**, Department of Pathology & **Dr Annettee Nakimuli** (Department of Obstetrics & Gynaecology, Makerere University)
15:30	*Tea & Coffee*	
15:50	Research and Capacity Development: The contributions of MRC/UVRI Uganda Research Unit on AIDS	**Prof. Pontiano Kaleebu**, Director, MRC/UVRI Research Unit on AIDS
16.20	The African Partnership for Chronic Disease Research: a framework for epidemiology, genomics and public health research in Africa	**Dr Manjinder Sandhu**, Department of Public Health and Primary Care; Wellcome Trust Sanger Institute
16.50	Developing digital infrastructure for global health	**Dr. Alan Blackwell**, Computer Laborator; Co-Director of Crucible Network
17.10	Not what you'd expect: Responding to complex health transitions in Southern Africa	**Prof. Steve Tollman**, Director, MRC/Wits Rural Public Health and Health Transitions Research Unit (Agincourt), Univ. of Witwatersrand, South Africa
17.40	Closing remarks	**Prof. James Wood**, Dept. of Vet Med; WT-CCGHR Co-PI

Cambridge Infectious Diseases

9.30 Welcome
Prof. Sharon Peacock, Director, Cambridge Infectious Diseases

Chair: Professor Jim Kaufman
Departments of Pathology and Veterinary Medicine

9.45 Major genetic risk factor for visceral leishmaniasis lies at the heart of eliciting CD4 T cell immunity
Dr Michaela Fakiola, Cambridge Institute for Medical research

Visceral leishmaniasis (VL) or Kala-azar is a debilitating parasitic disease caused by protozoa of the *Leishmania donovani* complex. The importance of host genetic factors in human susceptibility to VL is indicated by familial clustering and high sibling risk ratios, however human genetic studies undertaken to date have largely been underpowered. In collaboration with the Wellcome Trust Case Control Consortium 2 we recently reported the first genome-wide association study (GWAS) of VL across major foci of disease caused by *L. donovani* in India and *L. infantum* chagasi in Brazil. The *HLA-DRB1-HLA-DQA1* locus was highlighted as the single major genetic determinant of VL, crossing the epidemiological divides of geography and parasite species. The risk/protective alleles at the top associated variants were further correlated with specific *HLA-DRB1* allele groups emphasising the importance of antigen presentation during infection. By addressing questions regarding the differential expression of HLA-DRB1 molecules and the repertoire of pathogen peptides presented by the specific risk *versus* protective HLA-DRB1 alleles, important leads can be provided in understanding and modifying the T-cell mediated responses. This knowledge can contribute towards the development of improved strategies for vaccine and therapeutic interventions taking into consideration the major genetic component of disease, which lies at the heart of eliciting T cell immunity.

10.20 Viral inhibition of DNA-PK dependent DNA sensing
Dr Brian Ferguson, Department of Pathology

The host response to DNA virus infection includes the direct detection of viral DNA by the innate immune system which then initiates an inflammatory response. The pattern recognition receptors responsible for DNA sensing are under intensive research and, although several putative sensors have been proposed, in most cases their biological relevance is currently unknown. Here we show that DNA-dependent protein kinase (DNA-PK) can act as a DNA sensor in fibroblasts and in vivo and is important for sensing DNA viruses such as vaccinia (VACV). In addition we present the discovery that a VACV protein, C16, can inhibit DNA sensing by directly binding DNA-PK and disrupting its ability to interact with foreign DNA. Removal of the gene which encodes C16 from VACV attenuates the virus in vivo and results in a more potent innate immune response to the infection. This discovery not only validates the biological relevance of DNA-PK as a DNA sensor for DNA viruses but furthers our understanding of how viruses such as VACV evolve to combat the host immune response.

10.55 **Genetics and evolution of clonally transmissible cancers in dogs and Tasmanian devils**
Dr Liz Murchison, Department of Veterinary Medicine

Tasmanian devil facial tumour disease (DFTD) and canine transmissible venereal tumour (CTVT) are the only two known naturally occurring clonally transmissible cancers. These are cancers that are spread between individuals by the transfer of living cancer cells. DFTD, spread by biting, has caused a collapse in the Tasmanian devil population and is threatening this species, the largest marsupial carnivore, with extinction. CTVT is a sexually transmitted disease that affects dogs. It is the oldest known somatic cell lineage and first arose several thousand years ago. We have sequenced the complete genomes of DFTD and CTVT in order to elucidate features of the individuals that originally spawned these two somatic lineages and trace the evolutionary histories of the clones as they spread through their respective host populations. I will compare and contrast features of the DFTD and CTVT genomes and discuss the extent to which host genetic variation may influence transmissible cancer susceptibility.

Tea and Coffee

KEYNOTE LECTURE

12.00 **Pandemic Influenza, HIV, SARS, MERS... are we prepared for future infectious threats?**
Prof. Ab Osterhaus, ERASMUS MC

Professor Ab Osterhaus is the Head of the Institute of Virology of the Erasmus Medical Center Rotterdam. His research focuses on linking viruses to diseases of animals and man and on the fundamental basis of natural and vaccine induced immunity against viruses. His main interests are on respiratory- and/ or zoonotic virus infections where he is well known for his leading role in the discovery of novel (respiratory) viruses, both in animal and man, including the highly-pathogenic avian influenza viruses H5N1 (1997) and H7N7 (2003), and the SARS coronavirus. He has a broad experience in leading research projects in the fields of vaccine development and immunopathogenesis of virus infections of man and animals. He is a Director of the WHO Collaborating Centre for Arboviruses and Haemorrhagic Fever Reference and Research, member of the SARS aetiology network and member of the Temporary Committee on Foot and Mouth Disease of the European Parliament. Osterhaus operates at the crossroads of virology, immunology, human- and animal health. Over the last 25 years, Prof. Osterhaus has identified more than a dozen "new" viral pathogens. He is author of more than 580 peer reviewed scientific papers.

Wellcome Trust-Cambridge Centre for Global Health Research (WT-CCGHR) Launch

14:00 **Introduction to the WT-CCGHR**
Prof. David Dunne, Director of the WT-CCGHR and the Cambridge-Africa Programme

14.10 **Wellcome Trust's vision for CHRs**
Dr Jimmy Whitworth, Head of International Activities, Wellcome Trust

Dr Jimmy Whitworth qualified in medicine from Liverpool University in 1979. He trained in general (internal) medicine at various hospitals on Merseyside before working for Save The Children Fund in Upper River Division of The Gambia in 1983-5. After a short spell at the Liverpool School of Tropical Medicine, Jimmy ran a research project on ivermectin for onchocerciasis in Sierra Leone for the Medical Research Council. In 1990 he was appointed Clinical Lecturer, later Senior Clinical Lecturer at the London School of Hygiene and Tropical Medicine. In 1995 he was seconded to direct the Medical Research Council Programme on AIDS in Uganda based at the Uganda Virus Research Institute in Entebbe. This large research programme is multidisciplinary, focusing on public health issues relevant to Uganda. These include aspects of infection with HIV-1, subsequent disease, how to deal with the medical and social consequences of the epidemic, and the development of strategies for AIDS control. Activities range from virology and immunology to social science, covering clinical studies, epidemiology and statistics. Many of the trials faced difficult ethical challenges. Jimmy was Chairman of the Uganda Virus Research Institute Committee for Science and Ethics for seven years from 1995 to 2002. Jimmy was returned to London in 2002, but continued to direct the MRC AIDS Programme in Uganda until 2003. In September 2004 he took up the post of Head of International Activities at the Wellcome Trust.

14.30 **Health Research and Capacity Building in Uganda**
Prof. Nelson Sewankambo, Principal- Makerere University College of Health Sciences; WT-CCGHR Co-PI; Director of the THRiVE Consortium in East Africa

Prof. Nelson K. Sewankambo is the Principal (Head) of Makerere University College of Health Sciences and previously Dean of Makerere University Medical School. He has devoted his last 15 years of professional life to the advancement of medical education, research, and capacity development. He is the Coordinator of the IDRC funded International Chairs Initiative that focuses on the evaluation of knowledge translations platforms. He is the Regional Coordinator of Supporting Use of Research Evidence for Policy (SURE Project), which aims to promote the use of evidence in health policy decisions. Prof. Sewankambo also initiated a successful research capacity building consortium involving seven African institutions (4 universities and 3 research institutes) and two universities in the UK –the THRiVE Consortium. He is providing leadership for an Africa-wide initiative for Strengthening Research Capacity in Africa (ISHReCA). In 2010, with NIH funding, he spearheaded the start of a national MEPI consortium of Uganda Universities to jointly address the country's health professional education needs. He has participated in a number of key global health initiatives and committees for example he is a member of the FAIMER Board. In 2012, the Institute of Medicine (IOM) elected Prof. Sewankambo as one of its members: this is considered one of the highest honours in the fields of health and medicine, and recognises an outstanding professional achievement.

15.00 **Cambridge-Makerere Research Project in Maternal Health. Why is pregnancy such a risky time for African women?**

Prof. Ashley Moffett, Department of Pathology & Dr Annettee Nakimuli (Department of Obstetrics & Gynaecology, Makerere University)

The implantation of the placenta in the uterus may be considered as an allograft, and this raises the question as to why there is maternal tolerance to this non-self tissue. In addition, placental trophoblast cells are highly invasive a situation that can be dangerous unless controlled. Insufficient trophoblast invasion, in contrast, results in poor placentation and problems in pregnancy such as pre-eclampsia and fetal growth restriction. Prof. Moffett's group have found that the immunology of implantation exhibits many features of the innate immune system rather than the adaptive immune system seen in contemporary transplantation immunology. The immune cells that participate in implantation are Natural Killer (NK) cells and the hypothesis that they are testing is that recognition of Major Histocompatibility Complex (MHC) antigens on the surface of placental trophoblast cells regulates placentation and the depth of trophoblast invasion. Genetic combinations of NK receptor genes in the mother and particular HLA-C allotypes in the fetus are associated with pre-eclampsia. Studies are now underway to look at the KIR/HLA-C combinations in other diseases of pregnancy such as miscarriage and fetal growth restriction. They are also investigating the role of the trophoblast-specific HLA class I molecules, HLA-G and its interaction with ILT receptors expressed by uterine maternal dendritic cells. Although the function of the distinctive uterine NK cells is still unknown there are now indications that they may have important roles in both placentation and uterine mucisal function, notably effects on the spiral arteries. Prof Moffett has been the Cambridge mentor for Dr Annettee Nakimuli's research in Uganda for the past four years.

Dr Annettee Nakimuli studied Medicine at Makerere University and a Kulika Trust Scholarship enabled her to obtain a Master of Medicine in Obstetrics and Gynaecology as the leading student of her year. She is a lecturer in the Department of Obstetrics and Gynaecology at Makerere, with research experience from cervical cancer and pre-eclampsia studies, and a clinical trial on induction of labour. Her primary research interest is pre-eclampsia, a major cause of maternal death in Uganda. Her PhD research is (as a Wellcome Trust-funded MUII Fellow, mentored by Prof. Ashley Moffett) focuses on interactions between Natural Killer (NK) cell Killer Immunoglobulin-like Receptors (KIR) and trophoblast HLA-C in relation to first trimester trophoblast invasion. As pre-eclampsia may be less common in HIV-infected women and increases with anti-retroviral treatment (ART), her research on a large case-control study of pre-eclampsia at Mulago Hospital, Kampala, is focusing on KIR and HLA-C genes, and HIV and ART. Dr Nakimuli's molecular genetic studies in Cambridge have received supplementary funding from the Cambridge Trophoblast Research Centre.

15:30 ***Tea & Coffee***

15:50 **Research and Capacity Development: The contributions of MRC/UVRI Uganda Research Unit on AIDS**

Prof. Pontiano Kaleebu, Director, MRC/UVRI Research Unit on AIDS; WT-CCGHR Advisor

Prof. Pontiano Kaleebu is the Director MRC/UVRI Uganda Research Unit on AIDS, and the Head of MRC-UVRI Basic Sciences Programme. He is also Deputy Director of Research at the Uganda Virus Research Institute and Head of Immunology Department of UVRI. He was the Executive Director of the UVRI-IAVI HIV Vaccine Program until December 2010. He is Honorary Professor, London School of Hygiene and Tropical Medicine, Faculty of Infectious and Tropical Diseases and a Honorary Professor Makerere University, School of Biomedical Sciences. He studied Medicine at Makerere University, graduating in 1986, and later studied for a Diploma in Immunology and a PhD at the Royal Postgraduate Medical School, Hammersmith Hospital and St Mary's Hospital part of University of London (Now Imperial College London). He joined the Uganda Virus Research Institute (UVRI) in 1988 and MRC-UVRI in 1995. His major areas of interest include understanding the protective immune responses against HIV, to contribute to the design of an HIV vaccine. Other interests are HIV vaccine trials, HIV molecular epidemiology and resistance to anti-retroviral drugs.
He has served on many national and International committees including WHO HIV vaccine advisory committee and the Global HIV Vaccine Enterprise Scientific committee. He chairs the National HIV drug resistance working group. He was the chair of the African AIDS Vaccine Programme Steering committee under WHO/UNAID for many years. He was admitted to the Fellowship of the Faculty of Medicine of Imperial College in 2011.

16.20 **The African Partnership for Chronic Disease Research: a framework for epidemiology, genomics and public health research in Africa**

Dr Manjinder Sandhu, Department of Public Health and Primary Care; Wellcome Trust Sanger Institute

Dr Manjinder Sandhu studied physiology at King's College, London University. He then completed masters' and doctoral training in epidemiology and public health and molecular epidemiology at the London School of Hygiene and Tropical Medicine and the Department of Public Health and Primary Care (PHPC), University of Cambridge, respectively. Following his PhD studies, Manj was awarded an MRC Fellowship in cardiovascular genetic epidemiology and in 2004 was appointed University Lecturer in Epidemiology at PHPC, University of Cambridge. He is actively involved in research training. His is a former Course Director for the MPhil in Epidemiology Degree, taking academic and strategic responsibility for research training in epidemiology and statistics. As part of his current academic post, he lectures on the MPhils in Epidemiology and in Public Health. He is also a member of the Degree Committee of the Faculty of Clinical Medicine, which oversees the Faculty's masters' and doctoral programmes. As part of a joint appointment with the University of Cambridge, Manj joined the Wellcome Trust Sanger Institute Faculty as a Group Leader in 2009.

Manj's research focuses on the integration of principles and procedures underlying population genetics and epidemiology. Together with current and emerging genome-wide technologies, this approach provides unparalleled opportunities to identify the biological mechanisms underlying the development of complex diseases and traits. His work has largely centred on the genetic basis of cardiometabolic traits and diseases, particularly lipid metabolism and coronary artery disease, and the use of genetic tools for causal inference. Manj isdeveloping epidemiological resources to explore genomic diversity and its impact on infectious and cardiometabolic risk factors and diseases in sub-Saharan African populations, as part of a public health and epidemiological research programme.

16.50 **Developing digital infrastructure for global health**

Dr. Alan Blackwell, Computer Laboratory; Co-Director of Crucible Network

Dr. Alan Blackwell has qualifications in professional engineering, computing and experimental psychology. He has 15 years experience of designing industrial systems, electronic and software products. He has taught design courses and supervised postgraduate design research students in Computing, Architecture, Psychology, Languages, Music, Fine Art and Engineering. He works regularly with social scientists and policy researchers, as well as on the design of next generation digital technologies.

Crucible is a research network within and around the University of Cambridge. Its purpose is to encourage interdisciplinary collaboration of technologists with researchers in the Arts, Humanities and Social Sciences (AH&SS). The main focus of this collaboration is on design as a meeting point for widely differing research disciplines. Crucible activities include the establishment of new research programmes, training of researchers, input to policy bodies, and identification of suitable funding sources for research in interdisciplinary design. Crucible provides both a scientific and organisational framework for this research. Prof Blackwell will be working closely with the WT-CCGHR.

17.10 **Not what you'd expect: Responding to complex health transitions in Southern Africa**

Prof. Steve Tollman, Director, MRC/Wits Rural Public Health and Health Transitions Research Unit (Agincourt), Univ. of Witwatersrand, South Africa; WT-CCGHR Advisor

Prof. Steve Tollman directs the MRC/Wits Rural Public Health and Health Transitions Research Unit (Agincourt), heads the Health and Population Division in the School of Public Health, University of the Witwatersrand, and is guest professor in the Centre for Global Health Research, Umeå University, Sweden. He recently took on the role of Principle Scientist with the INDEPTH Network. In 1979, he graduated from the University of the Witwatersrand, Johannesburg, SA with a Bachelor of Science degree majoring in Anatomy and Physiology. He continued his studies at Wits, obtaining his Bachelor of Medicine and Bachelor of Surgery degrees in 1984. Further studies took him to Oxford, UK and Harvard, USA, culminating in a PhD in Public Health and Epidemiology from Umeå University, Sweden.

Steve was founding Board Chair of the International Network for the Demographic Evaluation of Populations and Their Health in Developing Countries (INDEPTH) and is principal investigator for Network efforts in Adult Health and Aging. He is currently the Chair of the Public Health and Tropical Medicine Interview Committee (PHATIC) at the Wellcome Trust, and serves as a member of fellowship interview panels convened by the MRC, UK, as well as the National Academies of Science, USA, addressing the continuing epidemiological transition in sub-Saharan Africa. His current research interests focus on adult health and aging, non-communicable diseases & chronic care.

17.40 **Closing remarks**

Prof. James Wood, Dept. of Vet Med; WT-CCGHR Co-PI; CID Committee member, and a leader of the Cambridge-Africa Programme

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