THE JENNER INSTITUTE
DEVELOPING INNOVATIVE VACCINES

JENNER INSTITUTE NEWS

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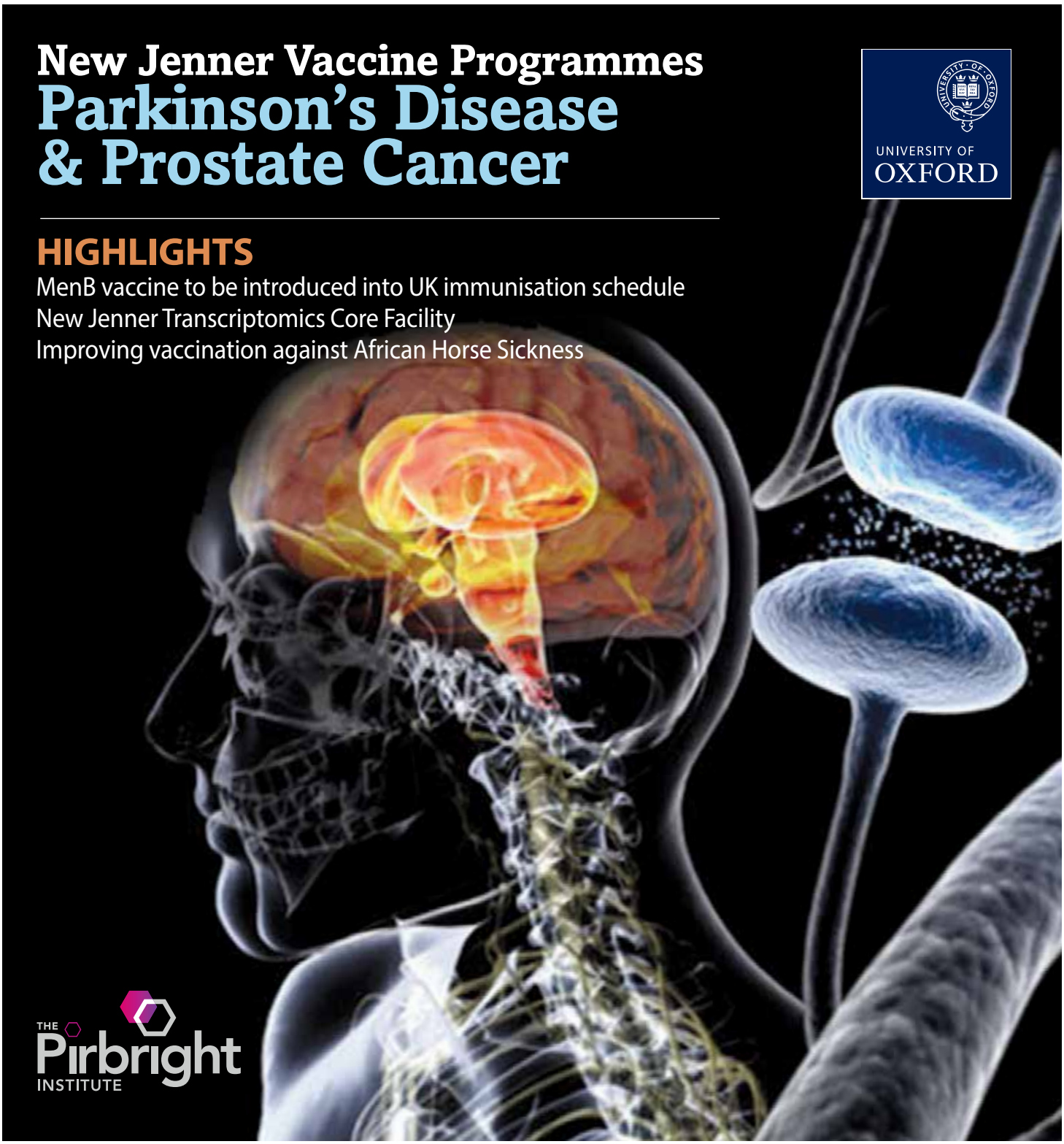
New Jenner Vaccine Programmes
Parkinson's Disease & Prostate Cancer

UNIVERSITY OF OXFORD

HIGHLIGHTS

MenB vaccine to be introduced into UK immunisation schedule
New Jenner Transcriptomics Core Facility
Improving vaccination against African Horse Sickness



THE Pirbright INSTITUTE

About the Jenner Institute

The Jenner Institute was founded in November 2005 to develop vaccines against major global diseases. Uniquely the Institute focuses on diseases of both humans and livestock and tests new vaccine approaches in parallel in different species. A major theme is translational research involving the rapid early-stage development and assessment of new vaccines in clinical trials.

The Institute comprises the vaccine research activities of 29 Jenner Investigators who head groups spanning human and veterinary vaccine research and development. Together the Institute Investigators constitute one of the largest non-profit sector research and development organisations in vaccinology.

Jenner Institute Investigators, through the support of many funders, are developing vaccine candidates against major global infectious diseases. New vaccines against malaria, tuberculosis and HIV are currently in field trials in the developing world. Research is also underway on livestock vaccines against foot and mouth disease, avian influenza, bovine tuberculosis and other major causes of economic loss. Recently, the Institute has also initiated research programmes in vaccines against non-communicable diseases, ie. Prostate Cancer and Parkinson's Disease.

The Institute is a partnership between the University of Oxford and The Pirbright Institute. It is supported by the Jenner Vaccine Foundation, a UK registered charity, and advised by a Scientific Advisory Board. The Jenner Vaccine Foundation provides strategic advice to the Institute, elects Jenner Investigators and has funded vaccine research space and facilities.

The leadership of the Institute is undertaken by the Director, Prof Adrian Hill (University of Oxford) and an Executive Committee of representatives from the partnering institutions.

Going Overseas

Report from the first 'Vaccinology in Africa' Masters' level Course held in Accra, Sept 2013

Course participants and lecturers outside the Noguchi Conference Centre.

By Dr Egeruan Babatunde Imoukhuede – Clinical Project Manager, Field Trials

The first "Vaccinology in Africa" course was successfully conducted at the Noguchi Memorial Institute for Medical Research (NMIMR) in Accra, Ghana from 2 – 6 September 2013. The five-day course was jointly organised by the Jenner Institute, Fondation Mérieux, and the Noguchi Memorial Institute for Medical Research. Funding for the course was provided by the Jenner Vaccine Foundation, GlaxoSmithKline (GSK) and Fondation Mérieux.

The course covered the main aspects of vaccinology, the vaccine development process, biomanufacturing, regulatory and ethical issues, and resonated with the 'One Health' agenda by highlighting human and veterinary links and synergies from scientific, technological and regulatory perspectives. The daily course themes included Principles of Vaccinology (Day 1), Vaccine Technologies and their Development (Day 2), Major Vaccine Targets (Day 3), Vaccine Development (Day 4), and Clinical Trials and Vaccine Development in Developing Countries (Day 5).

The course was aimed at students (MSc, PhD), researchers and professionals resident in Africa. Thirty participants resident in West Africa, selected from a total of 152 applications, attended the course. Due to the high number of applications from all over Africa, the aim is to rotate the course in different regions of the continent on a yearly basis.

The faculty included high-profile lecturers drawn from the Oxford Vaccinology Programme, the Fondation Mérieux's Advanced Course of Vaccinology (ADVAC), and West African vaccine experts. Within the 5-day period of the course, a total of 37 presentations were made by 17 speakers.

On Day 4 of the course, I gave a talk entitled "Safety considerations in the conduct of clinical trials of candidate vaccines". The presentation highlighted the importance of the harmonisation of safety data collection in vaccine trials as well as discussing the safety elements in a clinical trial protocol, based on a recent publication which I co-authored (Bonhoeffer J, et al. Template protocol for clinical trials investigating vaccines – Focus on safety elements. Vaccine. 2013 Nov 12;31(47):5602-20).

Judging from the feedback received at the end of the course, students and faculty were pleased to have attended and considered this a worthwhile venture to be be sustained. ■

Course participants with lecturers from The Pirbright Institute: From left to right, Gautier Ouedrago (Institut de Recherche en Sciences de la Santé, Burkina Faso), Ibrahim Dadari (Clinton Health Access Initiative, Nigeria), Bryan Charleston (The Pirbright Institute), Ousmane Traore (Institut de Recherche en Sciences de la Santé, Burkina Faso), Geraldine Taylor (The Pirbright Institute), Arnold Luuse (Navrongo Health Research Centre, Ghana).

Vaccinology in Africa

A five-day Master's level course

The next *Vaccinology in Africa Master's Level Course* will take place 13 – 17 October 2014, at the International Livestock Research Institute (ILRI), Nairobi, Kenya. The course is jointly organised by the Jenner Institute, University of Oxford, ILRI, and the Fondation Mérieux, with financial support from the Jenner Vaccine Foundation, Fondation Mérieux, GSK, and other funders.

Courtyard at the ILRI campus (Nairobi)

The first 'Vaccinology in Africa' course was held in Accra, Ghana, in September 2013. This year, 30 students from East Africa are expected to participate, with a faculty of around 15 international lecturers, drawn from the Oxford Vaccinology Course and the Fondation Mérieux's ADVAC course, as well as prominent African vaccine experts.

The course will be covering the main aspects of vaccinology, the vaccine development process, biomanufacturing and well as regulatory and ethical issues. The course is aimed at students, researchers and professionals resident in East Africa. Delegate numbers will be limited to 30 participants. ■

Preliminary programme

Day 1: Principles of Vaccinology

- Overview of human and veterinary vaccinology
- Public health and vaccines: a WHO perspective
- The vaccine development pathway – an industry perspective
- Vaccine Immunology
- Vaccine manufacturing
- Vaccines: needs and opportunities
- Policy development and new vaccine introduction

Day 2: Vaccine technologies & their development

- Vaccine immunogenicity & correlates of protection in clinical trials
- Adjuvants for vaccines
- New technologies: vectored vaccines
- Conjugate and other pneumococcal vaccines
- Reverse vaccinology for meningococcal vaccines
- Public and Media perception of vaccines
- Workshop on vaccine design

Day 3: Major Vaccine Targets

- Malaria Vaccines
- Influenza Vaccines
- Men-A conjugate: a vaccine for Africa
- Veterinary vaccine development: some major needs
- PPR and RSV vaccines
- Foot and mouth disease vaccines
- Immunomonitoring in endemic areas – tutorial session

Day 4: Vaccine Development and Clinical Trials

- Phase I trials in the vaccine's country of origin
- Vaccine testing in semi-immune populations
- Good Clinical Practice in African trials
- Epidemiology and aspects of the design of vaccine field trials
- Safety considerations in the conduct of clinical trials of candidate vaccines
- QC and QA processes in vaccine trials
- HIV Vaccine trials
- Tuberculosis vaccine trials

Day 5: Vaccine Development in Developing Countries

- Pre-clinical studies to Phase I clinical trials in developing countries
- Veterinary vaccine development in African settings
- Vaccines for enteric pathogens
- Large scale intervention trials
- Statistical Analysis of vaccine trials
- Regulatory and ethical issues in vaccine development & deployment in African settings
- Large scale funding opportunities: EDCTP, Gates, Wellcome & others

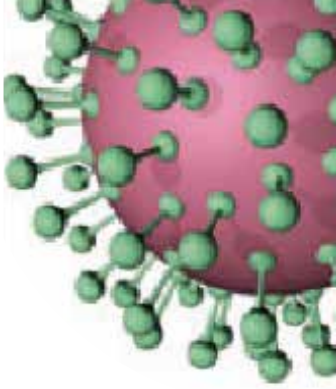
How to apply:

Participation is competitive and based on individual applications. 15 places are available for residents of Kenya which will cover course fees, accommodation and meals. A further 15 bursaries are available for those living farther afield within the region of East Africa, which also include travel expenses.

Application deadline is 1st June 2014

Application form available to download from:
www.jenner.ac.uk/vaccinology-in-africa

Scientists working in the advanced animal health laboratories of ILRI, in Nairobi, Kenya



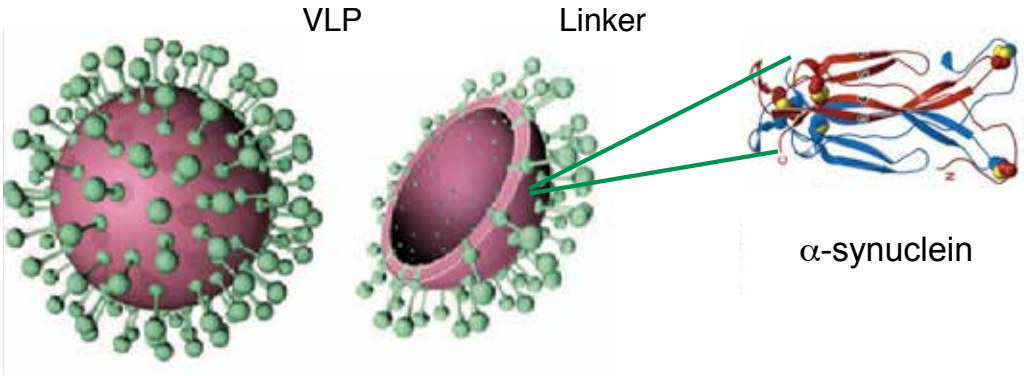
This year marks a significant broadening of activities at the Jenner Laboratories in Oxford. Alongside the major vaccine programmes against infectious diseases, the Institute will now also address vaccines against non-infectious diseases and cancers.

There have been two prime drivers of this initiative. Firstly, the recruitment of Martin Bachmann to the post of Professor of Vaccinology at the University of Oxford, who is a leader in the development of virus-like particle vaccines, especially against chronic non-infectious diseases. For 10 years, Prof Bachmann has developed vaccine candidates against cytokines, nicotine, hypertension and the neurofibrillary tangles of Alzheimer's disease while chief scientist of a biotech company in Zurich. He will now head the new Parkinson's Disease Vaccine Programme at the Jenner Institute, and in parallel, contribute to the design of new virus-like particles (VLP's) for some of the Institute's infectious disease programmes.

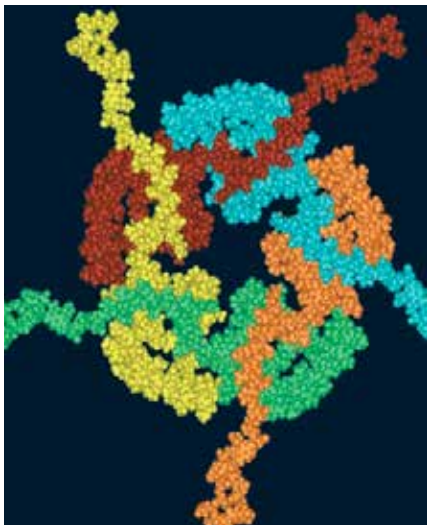
New Jenner Vaccine Programmes

Parkinson's Disease

Parkinson's disease is a progressive and devastating illness caused by a loss of dopamine-producing neurons in the brain. The loss of this neurotransmitter causes neurons to fire abnormally, resulting in patients becoming less able to direct and control their movements. There is currently no therapy with lasting efficacy, which constitutes a significant challenge to the long-term treatment of patients with this neurodegenerative condition.



Schematic presentation of the chemical conjugation of α-synuclein to VLPs (Image: Medicago Inc.)



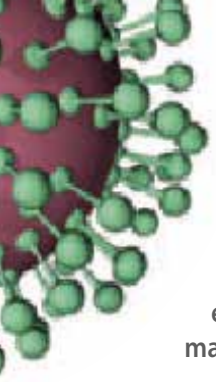
Assembly of α-synuclein into pentamers, currently held to be the initiating step of Parkinson`s disease
(Image: https://www.michaeljfox.org/)

Overexpression of α-synuclein has been identified as a major cause for the development of Parkinson`s disease (PD) in humans. It has been noted that as little as a 1.5 or 2-fold upregulation of α-synuclein can cause familial Parkinson's Disease. Lewy bodies, protein clumps consisting mainly of aggregated α-synuclein, are a histological hallmark of the disease. It is unclear whether these large α-synuclein aggregates are responsible for the pathology or whether small α-synuclein oligomers may also be toxic and cause disease. Therapies based on antibodies targeted against α-synuclein should therefore preferably employ antibodies of broad specificity capable of recognizing soluble, oligomeric, as well as aggregated α-synuclein.

The use of strong adjuvants is particularly counter-indicated in this context, since these "helper-substances" usually enhance antibody responses by increasing potentially dangerous T helper cells.

Next generation VLPs will avoid these issues as strong antibody responses can be induced in the absence of adjuvants. The Jenner Institute has recently launched a new research programme which aims to develop a vaccine against Parkinson`s disease by employing virus-like particles (VLPs) to induce strong antibody responses against the disease-causing α-synuclein. The programme is being led by Prof Martin Bachmann and Dr Aadil El-Turabi, who are both experts in bringing VLP-based vaccines to the clinic.

Preclinical efficacy will be evaluated in collaboration with Oxford Parkinson's Disease Centre (http://opdc.medsci.ox.ac.uk/). Provided the vaccine proves effective in mouse models, these results will constitute preclinical proof-of-concept and will, upon adequate demonstration of preclinical safety, lead to progression towards clinical trials. ■



The other stimulus was the clinical demonstration of viral vector prime-boost regimes inducing potent CD8+ T cell immunity against a variety of infectious pathogens, which provided the background for testing this technology in cancer immunotherapy. A collaboration with Oxford University's Head of Surgery and prostate cancer expert, Professor Freddie Hamdy, and a six million euro FP7 award catalysed this plan, and the first prostate cancer vaccine candidate is currently at GMP manufacture, as Programme Leader Irina Redchenko explains below.

in non-infectious diseases

Prostate Cancer

A new programme aiming at the development of a vaccine for prostate cancer builds on the application of a heterologous viral-vectored vaccination platform successful in an infectious disease setting. The programme is led by Dr Irina Redchenko, and supported by Drs Frederica Cappuccini and Stephen Stribbling.

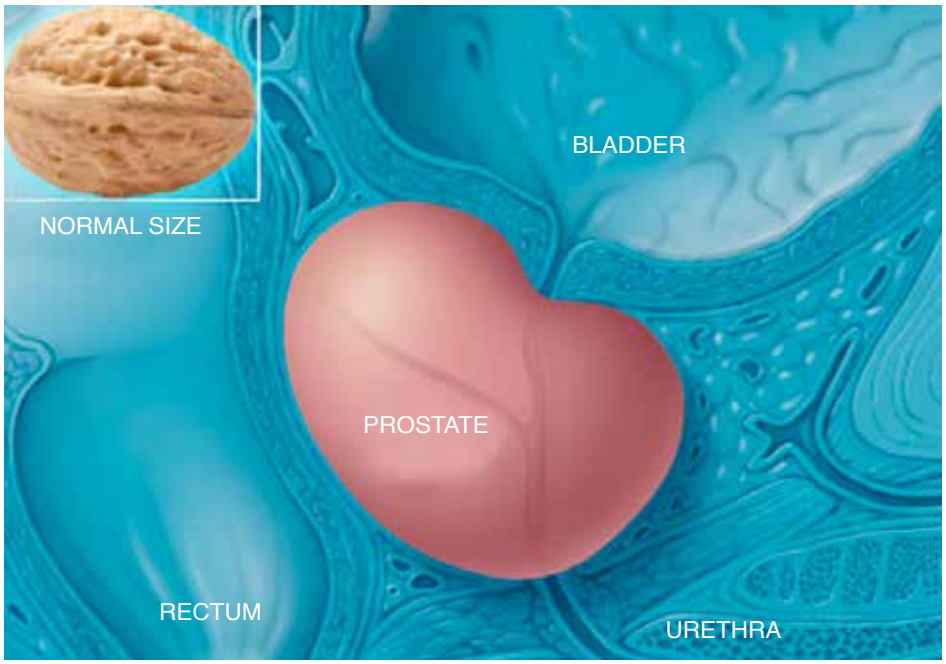
Of all cancers, prostate cancer is one of the best targets for immunotherapy:

The prostate gland is not an immune privileged site as was thought before.

Most patients are diagnosed early, therefore the immune system is not compromised by immunosuppressive drugs.

Slow growth of prostate tumours provides the best chance for a vaccine to take effect.

The organ is dispensable, so potential autoimmunity will not be problem.



Prostate cancer is the most prevalent non-cutaneous malignancy and the second most common cause of cancer-related deaths among men in developed countries. Median survival of patients with metastatic castration resistant prostate cancer is 2 years. Treatment options for advanced prostate cancer are limited, and immunotherapy is one of them.

The only licensed therapeutic antigen-specific prostate cancer vaccine, Sipuleucel-T, is an individualized treatment that costs over $90,000 per patient and provides a modest survival benefit of 4.5 months, so clearly a more efficacious and affordable vaccine is needed.

Our first objective is to break an immunological tolerance to prostate-associated self-antigens and induce tumour protective prostate specific immune response. We will evaluate already identified and novel prostate cancer antigens in transplantable and autochthonous prostate cancer mouse models to define the most immunogenic and protective vaccine for further clinical development.

In parallel, with support of the recently awarded EU grant, we will initiate clinical trials in intermediate risk prostate cancer patients by deploying a heterologous prime boost strategy targeting a "pan"-tumour antigen, 5T4, already studied in clinic in a homologous vaccination setting.

Combining our pre-clinical findings and the lessons from 5T4 clinical trials we will aim at making a novel prostate cancer vaccine available for clinical development. ■

New Jenner Transcriptomics Core Facility

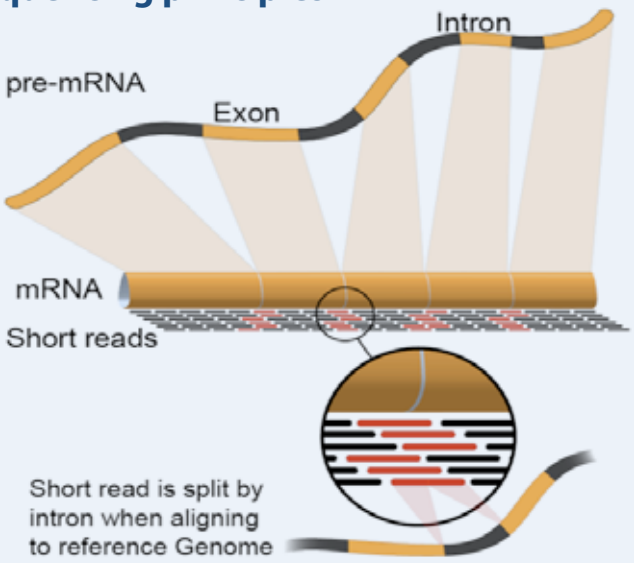
The Jenner Institute's Transcriptomics Core Facility was established in late 2013 with the support of a Wellcome Trust Strategic Award.

The award was granted to Prof Adrian Hill (Principal Investigator, Oxford), Prof John Fazakerley (Pirbright) and Prof Glyn Hewinson (AHVLA). The facility is managed by Prof Sarah Gilbert, under the scientific leadership of Dr Adaikalavan Ramasamy (Senior Leadership Fellow in Bioinformatics) and his team, Dr Julius Muller (Bioinformatician), Dr Amanda Stranks (Post-Doctoral Scientist) and Dr Eneida Parizotto.

The principal aims of the Core Facility are to assist Jenner Investigators in identifying transcriptomic correlates of immunogenicity and efficacy for a broad range of human and veterinary vaccines, and to evaluate new immunomodulatory molecules suggested by transcriptomic findings in vectored vaccines.

The Jenner Transcriptomics team, from left to right: Dr Julius Muller, Dr Eneida Parizotto, Dr Amanda Stranks, and Dr Adai Ramasamy.

RNA-sequencing principles

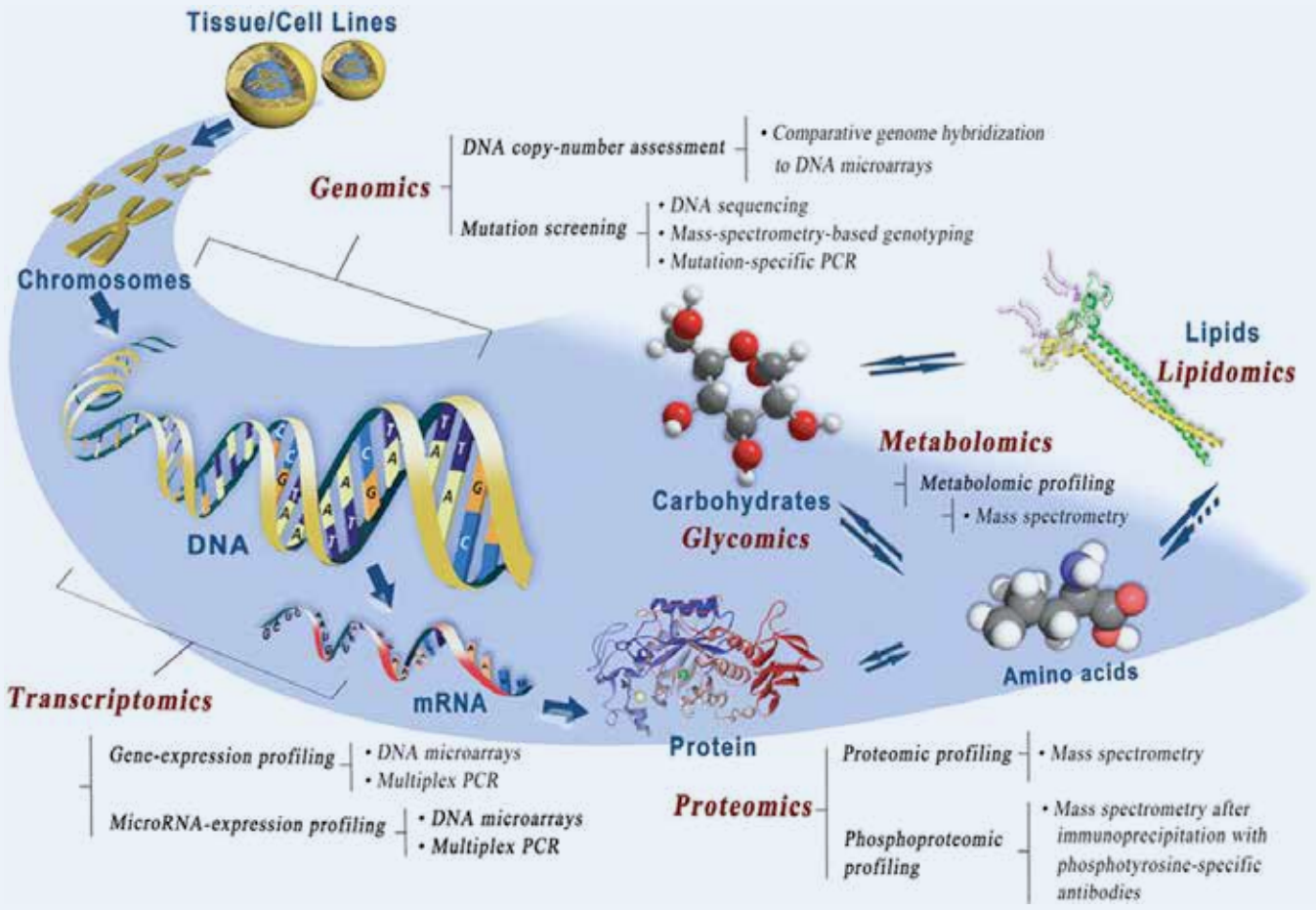


What is transcriptomics?

Simply put, it is the study of gene expression levels in a comprehensive manner. Genes are expressed from DNA and different sets of genes are expressed depending on nutrient availability, environmental factors, external signals as well as the presence of infectious agents (bacteria, fungi, protozoa, viruses, worms). For example, we expect to see many immune-related genes to be expressed (or expressed at higher levels) in people and animals that have infections like malaria or tuberculosis. Furthermore, we would expect different sets of immune-related genes to be expressed at different times.

Gene to transcript: Genes are encoded by DNA which provides a template for transcription of RNA. Analysis of transcripted RNA sequences forms the basis of modern transcriptomics approaches (image courtesy of Wikimedia Commons).

Schematic representation of the 'omics disciplines



Recent technological developments mean that we are now able to study the entire transcriptome, i.e. tens of thousands of genes, simultaneously. Two popular measuring tools are gene expression microarrays and RNA-sequencing.

Studying the transcriptomics of vaccines allows us not only to understand and check for correct immune responses but also to identify new key markers that are associated with immunogenicity (the ability to induce immune responses). Using these novel markers would allow us to quickly evaluate many more candidate vaccines for further testing.

Transcriptomics can also be used to understand why some vaccinees are not protected when challenged with the infectious agents, while others are. Understanding these differences can potentially lead to new ideas for vaccine development.

The transcriptomics core facility provides:

Funding for consumables
Wet lab services
Bioinformatics analyses

The Core Facility can fund a maximum of 50% of the study lab consumables costs for Jenner Investigators and the funding committee meets every four months. The wet lab services include RNA quality assessment and extraction to prepare for microarray hybridization or RNA-sequencing.

Bioinformatics, statistical and other dry lab analytical services are available at no cost to Jenner Investigators. These include data management, quality control of data and analyses of the transcriptomics data from a wide variety of platforms, as well as re-using publicly available datasets for replication, or meta-analyses with their own datasets.

Contact Dr Adai Ramasamy (adaikalavan.ramasamy@ndm.ox.ac.uk) if you are interested in exploring the use of transcriptomics in your research. ■

Jenner Investigator Profiles

Dr Adrian Smith

My career has focussed on the basic mechanisms of immune protection against infectious diseases and the comparative immunology of vertebrates. Having completed a PhD in the field of Parasite Immunology at the University of Nottingham under the guidance of M. Elaine Rose and Derek Wakelin I took up a postdoctoral position with Adrian Hayday at Yale. During my time at Yale we focussed on mechanisms of immunity in the gut and the function of murine TCRγδ+ T cells. Employing a parasite infection model of the intestine (*Eimeria vermiformis*) we reported some of the early in vivo functions for γδ T cells including regulation, pathogen killing (without memory) and an ability to drive self-reactive B cell responses.

Upon my return to the UK in 1998 I established the Enteric Immunology Group at the Institute for Animal Health (now The Pirbright Institute) where we extended our work on gut immune mechanisms using various infection systems (principally *Eimeria* spp. and *Salmonella enterica*) in murine and avian hosts. We also began to explore the similarities and differences in immune mechanisms that operate in birds and mammals. One major research focus was the identification and functional characterisation of the chicken Toll-like Receptors including two found in birds but not mammals (TLR15 and TLR21). The Enteric Immunology Group also began to develop novel antigen discovery platforms to define which antigens stimulate protective responses rather than those that simply stimulate a response. This is a particular problem with antigenically complex pathogens.

In 2008 I joined the Department of Zoology at the University of Oxford where my group focuses on the comparative immunology of vertebrates and vaccine design. My group retains a strong interest in pattern recognition receptors (PRRs), in particular how we might exploit PRR to develop species-tailored adjuvants. We continue to work on the problem of protective antigen discovery with our genetic approaches in Apicomplexan parasites and the Protecta Antigen Finding (PAF) platform. The PAF project is currently focussed on antigen discovery for vaccines against *Chlamydia* infections. We also work on the development and application of tools to study T cell receptor repertoire analysis in different species. We use repertoire analysis tools to address fundamental aspects of immune function and vaccine development in birds and mammals. The group works with a variety of infection systems including bacterial and parasitic pathogens. We also collaborate with other Jenner Investigators applying some of our methods to viral infections such as Influenza and Marek's Disease.

Key Publications:

1. Boyd, A.C., Peroval, M.Y., Hammond, J.A., Prickett, M.D., Young, J.R. and Smith A.L. (2012) Toll-like Receptor 15 is unique to avian and reptilian lineages and recognises a novel yeast-derived agonist. J Immunol: 189:4930-4938
2. Peroval, M.Y., Boyd, A.C., Young, J.R. and Smith A.L. (2012) A critical role for MAPK signalling pathways in the transcriptional regulation of Toll like receptors. Plos One: 2013;8(2):e51243
3. Mideo, N., Reece, S.E., Smith, A.L. and Metcalf, C.J.E. (2012) The Cinderella Syndrome: Why do malaria-infected cells burst at midnight? Trends in Parasitology 29(1):10-12
4. Inagaki-Ohara, K., Sakamoto, V., Dohi, T. and Smith, A.L. (2011). Gamma-delta T cells play a protective role during infection with *Nippostrongylus brasiliensis* by promoting goblet cell function in the small intestine. Immunology, 134, 448-458
5. Blake, D.P., Billington K., Copestake S., Oakes R.D., Quail M.A., Wan, K-L,, Shirley M.W. and Smith A.L. (2011) Genetic mapping identifies novel highly protective antigens for an Apicomplexan parasite. Plos Pathogens, 7 (2) e1001279
6. Mwangi, W. N., L. P. Smith, Baigent, S.J., Beal, R. K., Nair, V. and Smith, A. L. (2011). Clonal Structure of Rapid-Onset MDV-Driven CD4+ Lymphomas and Responding CD8+ T Cells. PLoS Pathog 7(5): e1001337.
7. Huang G-J, Smith AL, Gray DH, Cosgrove C, Singer BH, et al. 2010 A Genetic and Functional Relationship between T Cells and Cellular Proliferation in the Adult Hippocampus. PLoS Biol 8(12): e1000561.
8. Gibbons DL, Haque SF, Copestake SL, Wells JW, Noble A, Smith AL, Hayday AC. (2009). Suppression of airway inflammation by a natural acute infection of the intestinal epithelium. Mucosal Immunol. 2: 144-55

Linda Dixon

I undertook an undergraduate degree in Biochemistry at University of Sussex and PhD in Molecular Biology at University of Edinburgh. I carried out postdoctoral research at Edinburgh University and the Friedrich Miescher Institute in Basel Switzerland before joining The Pirbright Institute (formerly IAH) to lead a group working on African swine fever virus (ASFV).

This large DNA virus causes a haemorrhagic fever with a high socio-economic impact in affected countries. The lack of a vaccine limits options for disease control. My group has focussed on research underpinning the development of effective vaccines. Our approach has been to determine genome sequences of isolates to help define the molecular determinants of virulence. We have also studied the mechanisms by which ASFV evades host defences and have characterised ASFV proteins that inhibit host pathways involved in transcriptional activation of host immune response genes. These include proteins that inhibit NF-kB, calcineurin, interferon induction and stress-activated responses. This knowledge has been applied to the rational development of candidate live attenuated ASFV vaccines by targeted gene deletions. In collaboration with Haru Takamatsu and Geraldine Taylor at Pirbright we have compared host responses in vitro and in vivo and induction of protective immune responses in pigs immunised with these gene manipulated and natural attenuated ASFV strains. We have also collaborated with these groups and The Jenner Institute to screen ASFV antigens for those important in induction of protective immunity, in particular those which induce strong CD8+ T cell responses. This information will be applied to development of candidate virus-vectored vaccines. In addition I provide advice on ASFV nationally to DEFRA and internationally as an OIE expert and am Chair of the *Asfarviridae* Study Group of the International Committee on Taxonomy of Viruses.

Key Publications:

1. Abrams C. C. ,Goatley L. , Fishbourne E. Chapman D. Cooke L. Oura C. A. Netherton C. L. Takamatsu H-H Dixon L. K. 2013. Deletion of virulence associated genes from attenuated African swine fever virus isolate OUR T88/3 decreases its ability to protect pigs against challenge with virulent virus Virology 443, 99-105
2. Chapman D. A. G., Darby A. C., Da Silva M., Upton C., Radford A. D., Dixon L. K. 2011. Genomic analysis of highly virulent Georgia 2007/1 isolate of African swine fever virus. Emerging Infectious Diseases 17, 599-605
3. King K., Chapman D., Argilaguet J. M., Fishbourne E., Hutet E., Cariolet R., Hutchings G., Oura C. A. L., Netherton C. L., Moffat K., Taylor G., Le Potier M. F., Dixon L. K., Takamatsu H. H. 2011. Protection of European domestic pigs from virulent African isolates of African swine fever virus by experimental immunisation. Vaccine 29, 4593-4600
4. Chapman, DAG., Tcherepanov, V., Upton C. and Dixon LK. 2008. Comparison of the genome sequences of non-pathogenic and pathogenic African swine fever virus isolates J Gen. Virology 89, 397-408
5. Miskin, JE., Abrams, CC., Goatley, LC., Dixon, LK. 1998. A viral mechanism for inhibition of the cellular phosphatase calcineurin. Science 281, 562 -565

Dr Geraldine Taylor

I obtained a degree in Medical Microbiology from the University of Liverpool and a PhD from the University of London for studies on immunity to mycoplasma infections, which were undertaken at the Division of Communicable Diseases, MRC, Clinical Research Centre, Harrow. I then joined the Institute for Research on Animal Diseases (now The Pirbright Institute) to work on respiratory mycoplasma infections of calves. Following a short sabbatical at the University of Birmingham in Alabama, I returned to Compton to work on bovine respiratory syncytial virus (BRSV), which continues to be a major interest. BRSV is an important cause of respiratory disease in young calves and is closely related to human (H)RSV, a major cause of bronchiolitis and pneumonia in infants. Our studies on RSV have contributed to the development of the widely used mouse model of RSV infection, identification of the role of antibody and T cells in RSV infection, the role of BRSV proteins in pathogenesis, and to the development of the first candidate humanised monoclonal antibody for RSV prophylaxis. Current studies exploit the calf model of BRSV infection for the development of an adenovirus-vectored HRSV vaccine, which is being undertaken in collaboration with industry. I am currently head of the Vaccinology group at The Pirbright Institute and a Jenner Investigator.

In addition, the Vaccinology group is working towards the development of safe and effective vaccines against African swine fever (ASF), Peste des petits ruminants and bluetongue (BT). ASFV causes a severe and acute haemorrhagic disease in domestic pigs. The virus has recently spread through the Russian Federation toward the borders of Eastern Europe, and poses a significant threat to the European swine industry. We are aiming to identify the protective antigens of ASFV in order to develop a virus-vectored ASF vaccine. PPRV, which is closely related to measles virus, causes severe disease in sheep and goats. Current live attenuated vaccines do not enable differentiation of infected from vaccinated animals (DIVA), which would facilitate PPR control. We have therefore developed a single-shot, Ad-vectored PPR vaccine that completely protects goats against challenge with virulent PPRV and can be used with a DIVA test. BTV causes thrombo-hemorrhagic fevers in ruminants and is transmitted by biting midges. We are analyzing the interaction of the virus with components of the innate and adaptive immune response in order to increase understanding of the pathogenesis of this disease and to develop novel vaccines that will cross protect against multiple variants of BTV.

Key Publications:

1. Tempest PR, Bremner P, Lambert M, Taylor G, Furze JM, Carr FJ & Harris WJ (1991). Reshaping a human monoclonal antibody to inhibit human respiratory syncytial virus infection *in vivo*. *Biotechnology*. 9: 266-271
2. Taylor G, Thomas LH, Wyld SG, Furze J, Sopp P & Howard CJ (1995). Role of T-lymphocyte subsets in recovery from respiratory syncytial virus infection in calves. *J. Virol*. 69: 6658-6664.
3. Thomas LH, Cook RS, Wyld SG, Furze JM. & Taylor G. (1998) Passive protection of gnotobiotic calves using monoclonal antibodies directed at different epitopes on the fusion protein of bovine respiratory syncytial virus. *J. Inf. Dis*. 177: 874-880.
4. King K, Chapman D, Argilaguet JM, Fishbourne E, Hutet E, Cariolet R, Hutchings G, Oura CA, Netherton CL, Moffat K, Taylor G, Le Potier MF, Dixon LK, Takamatsu HH. (2011) Protection of European domestic pigs from virulent African isolates of African swine fever virus by experimental immunisation. *Vaccine*. 29:4593-600.
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Prof Martin Bachmann

Martin Bachmann has a PhD and a Masters degree with Honors from the Eigenössichen Technischen Hochschule Zürich (ETH). Martin carried out his PhD research in the lab of Prof. Rolf Zinkernagel and continued with post-doctoral work at the Princess Margaret Hospital, Toronto in the lab of Prof. Pam Ohashi. He then became a member of the Basel Institute for Immunology.

From 2002-2012, Prof Bachmann was Chief Scientific Officer at Cytos Biotechnology Ag, where he built up a research group of up to 50 people. In 2012, he returned to academia and is currently appointed as Professor of Immunology at the University of Oxford. In 2012, he founded a biotechnology company, Saiba GmbH in the fields of therapeutic vaccines and immune-modulation.

He serves on the Scientific Advisory board of several Companies and Institutions. Martin has published more than 200 peer-reviewed scientific papers, his publication h-index is 80 and he is inventor on more than 40 filed or granted patents. Martin has brought 7 compounds from the mouse model into man.

Prof Bachmann established that epitope repetitiveness is a geometric pathogen-associated molecular pattern (PAMP). He demonstrated that highly repetitive structures enhance B cell responses by efficiently cross-linking B cell receptors as well as effectively recruiting the innate humoral immune system. This offers an explanation for the high immunogenicity of viruses and many bacteria.

He has harnessed the concept of epitope repetitiveness as a molecular PAMP to develop a new vaccine platform. The basis of the vaccines are epitopes chemically conjugated to virus-like particles. Preclinical proof-of-concept (PoC) has been reached with numerous prophylactic and therapeutic vaccines. Using this technology, pioneering clinical PoC has been obtained for vaccines for the treatment of hypertension and smoking. He established that toll-like receptor 9 ligands packaged into VLPs are more potent than free toll-like receptor 9 ligands and at the same time exhibit better tolerability. Based on these insights he initiated numerous clinical trials, resulting in encouraging data for a vaccine against melanoma and clinical PoC for the treatment of allergy and asthma.

Key Publications:

1. Kopf, M., B. Abel, A. Gallimore, M. Carroll, and M.F. Bachmann. 2002. Complement component C3 promotes T-cell priming and lung migration to control acute influenza virus infection. Nat Med 8:373-378.
2. Tissot A.C., Maurer P., Nussberger J., Sabat R., Pfister T., Ignatenko S., Volk H., Stocker H., Müller P., Jennings G.T., Wagner F. and M. F. Bachmann 2008. Vaccination against Angiotensin II reduces Day-Time and Early-Morning Ambulatory Blood Pressure: Results of a Randomized Placebo-Controlled Phase IIa Study with CYT006-AngQb. Lancet 371:821-827
3. Beerli, R.R., M. Bauer, R.B. Buser, M. Gwerder, S. Muntwiler, P. Maurer, P Saudan, and M.F. Bachmann. 2008. Isolation of human monoclonal antibodies by mammalian cell display. Proceedings of the National Academy of Sciences of the United States of America 105:14336-14341.
4. Bessa J, Zabel F, Link A, Jegerlehner A, Hinton HJ, Schmitz N, Bauer M, Kündig TM, Saudan P, Bachmann MF. (2012). Low-affinity B cells transport viral particles from the lung to the spleen to initiate antibody responses. Proc Natl Acad Sci U S A 109:20566-20571

African horse sickness

A photograph of Culicoides imicola, the most common biting insect that transmits AHSV.

Image: Steven Archibald, Pirbright Institute

Prospects of developing a new improved vaccination strategy

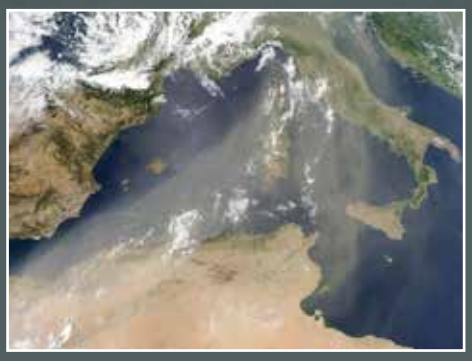
African horse sickness (AHS) is a lethal vector-borne disease of horses. It is endemic to Sub-Saharan Africa, but devastating outbreaks have occurred in non-endemic regions, including Europe. Vaccination plays a central role in the control of AHS but live attenuated vaccines, currently used in Africa, are deemed unsuitable for non-endemic countries.

Research conducted at The Pirbright Institute has shown that MVA-VP2, a recombinant modified Vaccinia Ankara virus (MVA-VP2) expressing the outer capsid protein of African horse sickness virus (AHSV), elicits protective immunity in a mouse model, and more importantly, in the target species the horse. Furthermore, recent data has demonstrated that a virus neutralising antibody response can be induced against multiple serotypes of AHSV by a polyvalent vaccination strategy based on MVA-VP2.

African horse sickness

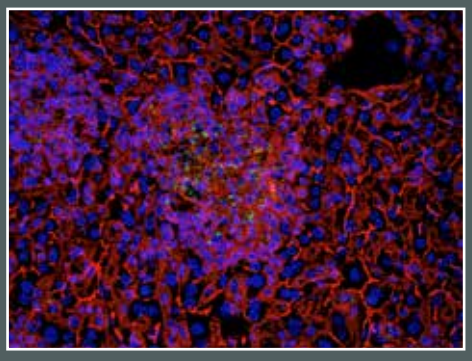
African horse sickness (AHS) is a highly lethal (up 95 % of case fatalities), viral, vector-borne disease of Equidae. It is transmitted by biting midges of the genus *Culicoides*, which also transmit bluetongue, a viral disease of sheep and cattle that has caused devastating outbreaks in Europe (including the UK) during the last two decades. AHS is normally restricted to Africa but in the past has spread to Spain (in 1966), and to Spain and Portugal (1987-1993) killing large numbers of horses. The northward spread of insect vectors able to transmit these diseases, associated with climate change, has significantly increased the risk of AHSV reaching Europe and the UK.

AHS is an OIE (Office International des Epizooties; World Organisation for Animal Health) listed disease based on its high negative impact on animal welfare, international trade and the economy of those countries affected by the disease.



Satellite photograph showing dust from the Sahara desert streaming out over the Mediterranean to Italy. These currents of air have been associated with the introduction of BTV infected Culicoides midges into Europe in the recent past and believed to be port of entry of AHSV into Spain in 1969.

Image source: Jeff Schmaltz, MODIS Rapid Response Team, NASA, GSFC



Development of an AHSV mouse model. Detection by immuno-fluorescence of AHSV antigen in the liver of an AHSV infected mouse (a). A liver tissue sample from a non-infected mouse was used as a negative control (b). Cell nuclei are stained in blue with DAPI, F-actin filaments of the cytoskeleton are stained in red with Rhodamine Phalloidin, and AHSV infected cells are stained in green with a FITC-conjugated anti-rabbit IgG bound to a an anti AHSV-VP7 rabbit polyclonal antibody.

Image source: Javier Castillo-Olivares and Ryan Waters, Pirbright Institute.

AHSV Vaccines

Vaccination plays an essential role in controlling AHS in Africa, but current AHS vaccines, based on live attenuated viruses, are considered unsafe and unsuitable for use in Europe. Killed virus vaccines are not currently available and render sero-surveillance assays ineffective. Therefore, a variety of modern vaccination strategies that are safer, more efficacious and compatible with differentiation of vaccinated from infected animals (DIVA), have been pursued over the years. However, none of these strategies have to-date successfully reached the market.

MVA based vaccines for AHSV

Dr Castillo-Olivares and colleagues at The Pirbright Institute, generated a vaccine candidate for AHS based on a recombinant Modified Vaccinia Ankara virus (MVA) that expresses the outer capsid protein (VP2) of AHSV, the main target of virus neutralising antibodies. This vaccine, designated MVA-VP2, expresses VP2 in host cells upon inoculation and elicits a fully protective virus-neutralising antibody (VNAb) response against infection in interferon alpha receptor gene knock-out (IFNAR -/-) mice and more importantly, in the target species, the horse. These pilot studies demonstrated 'proof of principle' for the use of MVA-VP2 for development of a highly protective, safe, DIVA vaccine against AHS.

Addressing the antigenic plurality of AHSV

Although antigenic relationships exist between some of the AHSV serotypes, immunity against AHS is type-specific. Therefore, any vaccination strategy against AHS must provide protection against the whole spectrum of AHSV serotypes. Serotype specificity resides primarily in the VP2, and the AHS Research Group at Pirbright is working on a vaccination strategy based on combining single MVA viruses, each expressing a different VP2 from a specific serotype. Interestingly, a pilot study in ponies has demonstrated that combined vaccination with recombinant MVA-VP2's from serotypes 4, 9 and 5 stimulated a VNAb response against AHSV strains of serotypes 4, 5, 6, 8 and 9, suggesting that a complete set of recombinant MVA's may not be required to achieve a fully efficacious vaccine.

Immunity induced by MVA-VP2 vaccination is mediated mainly by antibodies

Having demonstrated the protective capacity of MVA-VP2 vaccination, additional studies have been conducted by Pirbright researchers in collaboration with the Centro de Investigacíon en Sanidad Animal (CISA), Valdeolmos, Spain, to determine whether protection induced by the MVA-VP2 vaccine was mediated by antibodies. Passive immunisation experiments in mice demonstrated that this was the case since recipients of antiserum from MVA-VP2 vaccinates were completely protected against AHSV disease. Because AHS often induces in the horse a peracute or acute syndrome resulting in fulminant death of the affected animal, the latter findings opens the possibility of using MVA-VP2 vaccination induced antiserum as an emergency treatment against AHS. This possible therapeutic intervention is currently being explored more thoroughly at Pirbright.

AHS is a devastating disease from the animal welfare point of view but in addition, it has a huge negative economic impact on the equine industry, since it compromises trade between endemic and non-endemic countries. Transport in and out of these endemic countries requires long, complicated and expensive quarantine procedures. These trade restrictions are imposed for two reasons: a) AHS is endemic only in Africa and trade in horses could introduce this lethal disease to other, non-endemic countries; and b) The vaccines in use in South Africa are based on live attenuated viruses that induce an antibody response that does not allow vaccinated horses to be discriminated from those infected with the virus, making it difficult to confirm that a vaccinated horse is free of AHSV. Even the movement and circulation of the live vaccines to non-endemic countries would currently remove their AHSV-free status, potentially leading to further trade restrictions.

The availability of a safe, efficacious and DIVA-compatible AHSV vaccine, such as the MVA-VP2 vaccines, could protect against AHSV while still allowing animals exposed to AHSV (and therefore representing a risk of infection) to be identified by means of an already developed antibody test based on AHSV-VP7, a distinct virus protein antigen not included in the MVA-VP2 vaccine.

Further work is necessary to take this prospective vaccine candidate for AHS into the field, but the features of MVA-VP2 would improve control of AHSV globally by preventing animal loses, stopping the spread of infection, and facilitating movement of animals within endemic countries and also facilitating international trade. ■

A fatal case of AHS showing typical features of the pulmonary form ('dunkop') of the disease.

Image source: Gillian Robertson, Coastal Horse Care Unit, Kwazulu Natal, South Africa, Jan 2013.

PEACHI programme update

a year of challenges and progress

The PEACHI research programme headed by Jenner Investigators Ellie Barnes and Lucy Dorrell aims to prevent infection of hepatitis C and HIV-1 by immunisation with prime-boost viral vector vaccines.

Whilst 'PEACHI' conjures up images of tender fruits, summer pastels and effortless progress, it's been a challenging year for the PEACHI Jenner Investigators. Maybe we should have abandoned our logo in subtle hues and gone forth with a more traditional acronym; BLASTED, HIT, ROBUST, MASSOMICS, ACE, ACID and ACTION are just a few so-named existing FP7 awards. But PEACHI is what we are, and one year on from the official kick-off, all of us a year older and much wiser, things look very much on track.

PEACHI is an acronym for Prevention of hepatitis C (HCV) and HIV-1 infections through induction of potent T cell responses using prime-boost viral vector vaccine regimens. It is an ambitious project, with three Phase I experimental medicine studies involving both HCV and HIV vaccines planned during the 4-year project.

The goal of the PEACHI project is the development of simple, affordable and effective vaccine strategies that can be given alone or in combination to prevent hepatitis C virus (HCV), human immunodeficiency virus type 1 (HIV-1) and co-infection based on novel and powerful viral vectors for in vivo delivery of antigens.

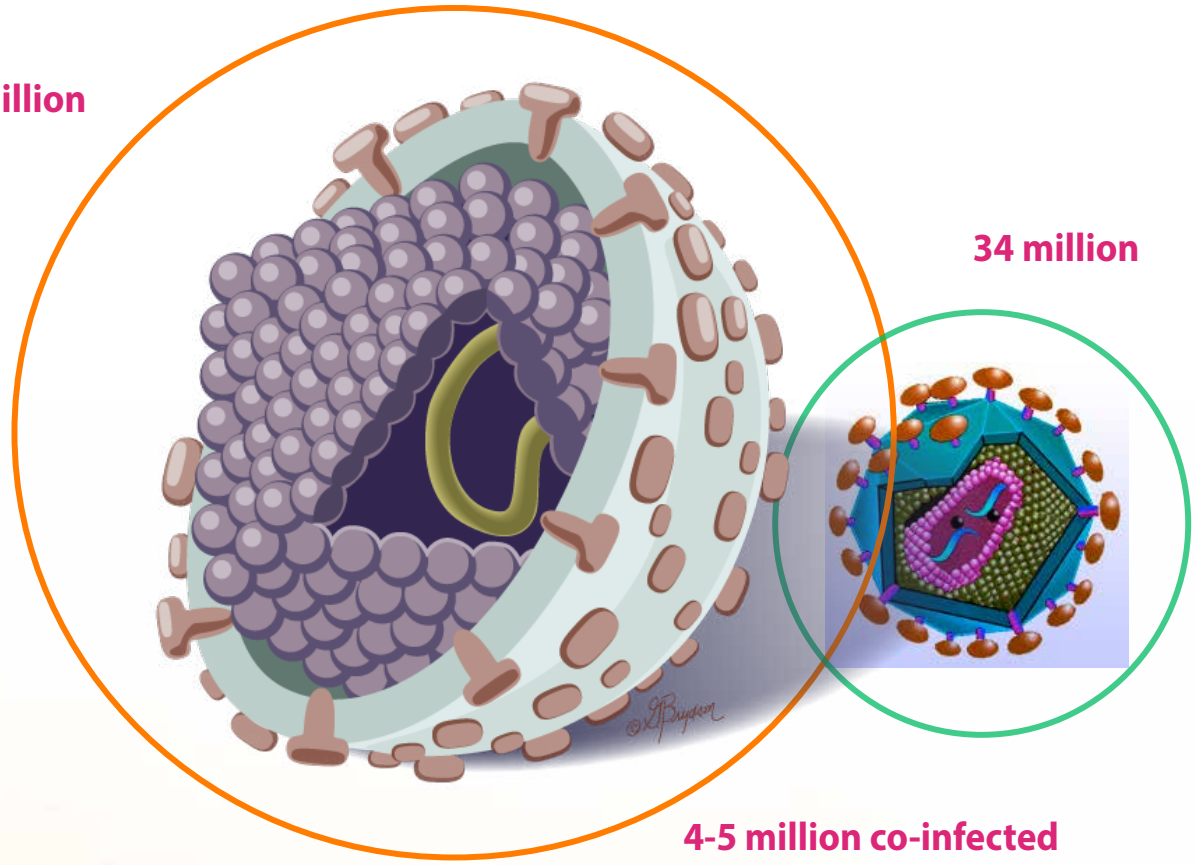
Our aims are to evaluate the safety and immunogenicity of prime-boost immunisations with candidate HCV vaccines based on Chimpanzee Adenovirus/MVA heterologous prime boost vaccination strategies in HIV-1 seropositive HCV-uninfected adults on HAART therapy, and to evaluate the safety and immunogenicity of simultaneous prime-boost immunisations of healthy volunteers with candidate HCV and HIV-1 vaccines (AdCh3NSmut / ChAdV63. HIVconsv and MVA-NSmut / MVA. HIVconsv).

We are currently aiming to improve the immunogenicity of the HCV vaccines through the production of second generation Chimp Ad and MVA (ChAd3 Ii-NSmut and MVA Ii-NSmut) vaccines employing the non-structural proteins of HCV linked to the human MHC class II invariant chain. These will be evaluated in both healthy volunteers and HIV-1 seropositive adults.

Alongside the well-established assays to assess vaccine-induced T cells, samples will be collected throughout the PEACHI studies and analysed by the newly established Jenner Institute Transcriptomics Core Facility. Antigen-specific T cells will be analysed at the single cell level and the quality of HCV- and HIV-1-vaccine induced T cell responses will be compared with naturally protective immune responses associated with clearance of HCV and long-term control of HIV-1, and we plan to develop whole blood assays as efficient immunological read-outs for clinical trials.

PEACHI was one of the last recipients of the European Commission's 'Framework Programme 7' (FP7) funding round, uniting partners from St. James's Hospital, Dublin, Kantonsspital St. Gallen, Switzerland, the Jenner Institute in Oxford, and Okairòs, Italy. The project hit the ground running in the spring of 2013.

Number of people living with HCV (left), HIV (right) or both infections, worldwide. HCV is a leading cause of non-AIDS deaths among people with HIV in Europe.



In the summer of 2013, Okairòs was bought out by GlaxoSmithKline (GSK) who was added as a partner to the consortium. The combination of Swiss, Irish, Italian and British academics, SME and major pharma should be transformative for the project - we all bring our unique skills and systems to the table. The first two clinical trial protocols are fully developed and patient recruitment is set to start later this summer.

The PEACHI consortium would like to take this opportunity to thank Dr Beth Turner, the PEACHI project manager, for her skilful approach over the last year, which has not only eased the journey so far but made it a rewarding one too.

The Oxford PEACHI team consists of Dr Beth Turner, Dr Lucy Dorrell, Dr Ellie Barnes and collaborators Prof Tom Hanke, Prof Paul Klenerman and Prof Adrian Hill. ■

www.peachi.eu/university-of-oxford/4575024070

peachi

Meningitis B vaccine set to be introduced into routine immunisation schedule in the UK

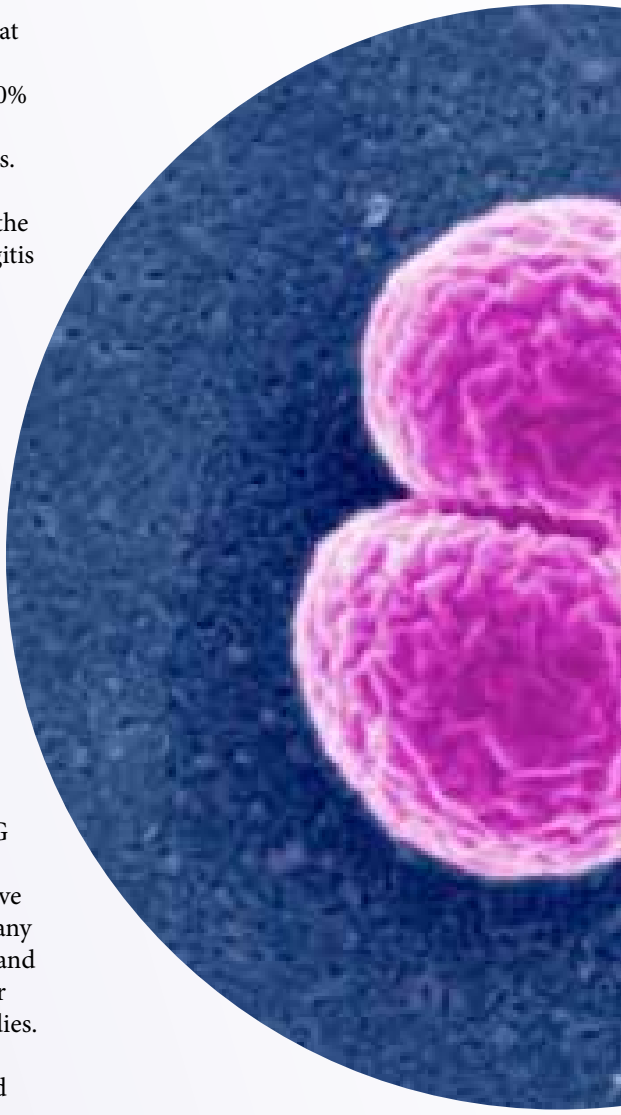
On 21st March 2014, the UK Joint Committee for Vaccines and Immunisation recommended that, subject to negotiation of a cost–effective price, a recently licensed vaccine against serogroup B meningococcus (MenB) be introduced into the UK routine infant immunisation schedule.

This represents a significant breakthrough in the fight against childhood meningitis but also a considerable achievement for the Oxford Vaccine Group, which has been extensively involved in the testing of this vaccine.

MenB is a serious cause of meningitis and septicaemia (blood poisoning) that affects about 600 - 1000 children and adults per year in England. Around 10% die and many survivors suffer long-term problems, including amputations. Since the introduction of the MenC vaccine, MenB infection has become the commonest cause of bacterial meningitis in the UK.

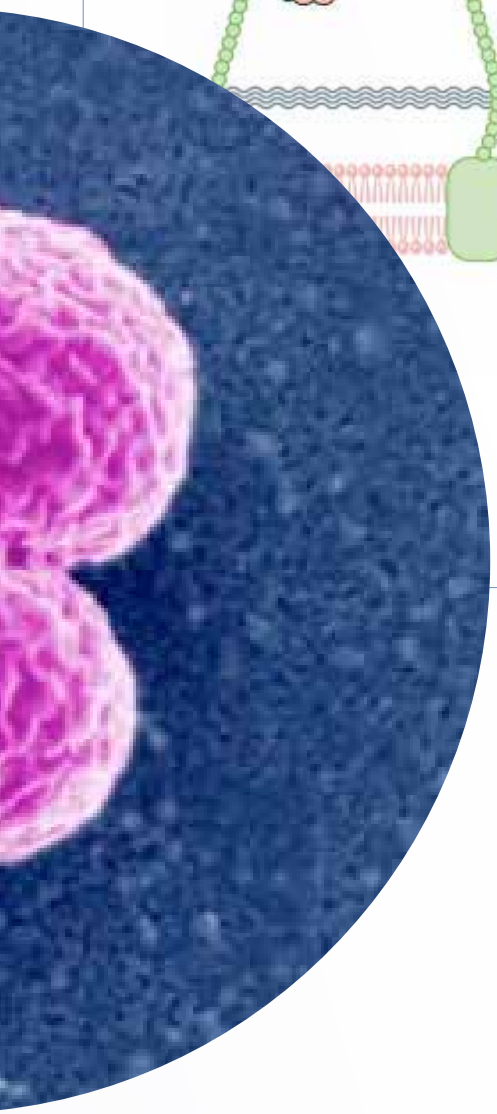
Developing a vaccine against this bacterium has required a novel approach to antigen identification, using the bacterial genome as the basis for the search for target proteins. The vaccine resulting from this search was evaluated in clinical trials conducted as an ongoing collaboration between the Oxford Vaccine Group (OVG) and Novartis Vaccines and Diagnostics.

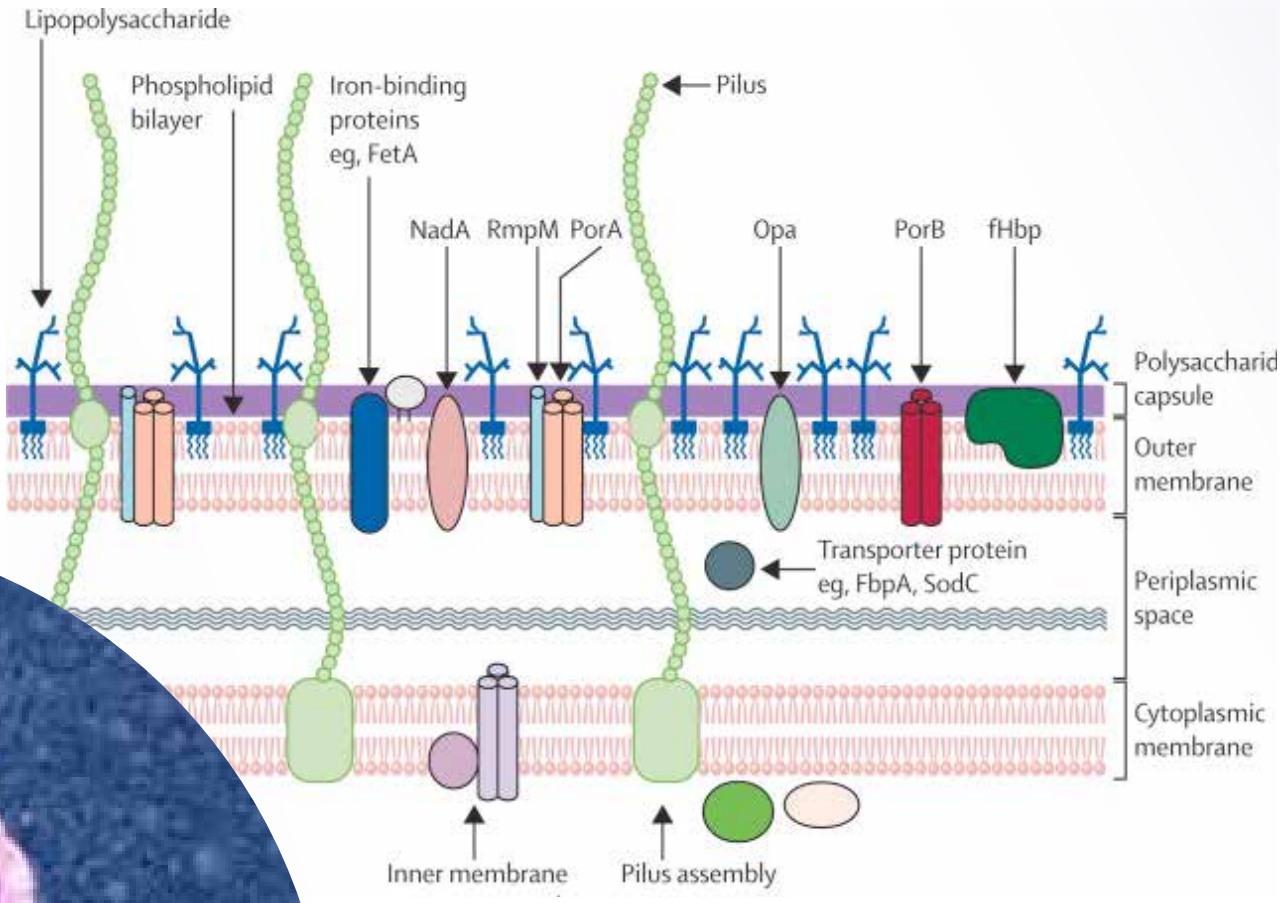
Dr Matthew Snape, Consultant Vaccinologist at the Oxford Vaccine Group explains: 'Everyone at the OVG feel very proud of this achievement. Doctors and nurses from the OVG gave the first dose of the MenB vaccine to any child anywhere in the world in 2006, and since then the group has enrolled over 1000 children and adults to these studies. The studies conducted by the Oxford Vaccine Group have directly informed



Neisseria meningitidis (large gram-negative diplococci), a prevalent cause of bacterial meningitidis. When bacterial meningitis is caused by this bacteria, it usually occurs when the bacteria from an upper respiratory infection enters the blood stream. This type of bacterial meningitis is highly contagious and can be seen as epidemics in community living situations. (6) A culture of the cerebral spinal fluid can be taken and then gram stained. A gram stain of the culture would show paired cocci (spherical shaped bacterial cell). Neisseria meningitidis is gram negative, therefore it will not take in the crystal violet dye of the gram stain test, but it will be stained pink after it is washed with alcohol.
(source: http://sitemaker.umich.edu/mc13/bacterial_meningitis_causative_organism)

Illustration of the surface structures of Neisseria meningitidis





The recently licensed MenB vaccine is based on the outer membrane proteins factor H binding protein (fHbp), Neisserial adhesion antigen (NadA), Neisserial Heparin Binding Antigen (NHBA, not shown) and outer membrane vesicles containing PorA.

Reprinted from Sadarangani RV & Pollard AJ, 2010, Serogroup B meningococcal vaccines—an unfinished story, Lancet Infect Dis 10: 112–24, with permission from Elsevier.

the recent decision by the UK Joint Committee for Vaccines and Immunisation (JCVI) as they have provided information on the vaccine's immunogenicity in children of ages 2 months to 5 years, as well as the side effect profile and persistence of the immune response to the vaccine through childhood. An important additional question is whether use of the vaccine in adolescents and young adults is likely to induce herd immunity through a reduction in the asymptomatic carriage of the meningococcus bacterium in the throat. This was evaluated in a study conducted in 2010 which revealed an impact on some, but not all meningococcal serogroups, and this is an area that the JCVI have rightly identified requires further study.

Professor Andrew Pollard, chairman of the JCVI, Director of Oxford Vaccine Group and Jenner Investigator stated: 'MenB disproportionately affects babies and young children and can be devastating. Routine use of the MenB vaccine is expected to make an important contribution to the health of our population.'

The work of the OVG in studying this vaccine is ongoing, with a further trial commencing shortly that will evaluate the immune response to MenB immunisation in 2 month to 4 month old babies at a genetic level. This 'gene expression' study has been funded by an EU grant (EUCLIDS) and is expected to start recruitment in Spring 2014. ■

OXFORD VACCINOLOGY PROGRAMME
Courses in 2014

The Oxford Vaccinology Programme offers training opportunities in vaccinology through a five-day Human and Veterinary Vaccinology course and a four-day course in Clinical Vaccine Development and Vaccine Biomanufacturing.

The courses are aimed at participants from both business, academic, clinical and veterinary backgrounds, including research scientists, programme managers, clinical trial co-ordinators, nurses, physicians and veterinarians. The courses are accessible to people already working in the field and to those who wish to enter the field.

Clinical Vaccine Development and Biomanufacturing
(21 - 24 October 2014)

Human and Veterinary Vaccinology
(17 - 21 November 2014)

The Programme provides state-of-the-art teaching in both veterinary and human vaccinology. Lecturers are drawn from the Jenner Institute, Oxford University, The Pirbright Institute and our partners in industry to provide training in areas related to vaccine design and construction, including: immunology and molecular biology; manufacturing; clinical trial design; immunomonitoring; regulatory strategy; post-marketing surveillance; vaccine financing; and the ethics of vaccination.

Jenner Investigators - May 2014:

JENNER INVESTIGATORS		AFFILIATION	PRINCIPAL AREAS OF INTEREST
Prof	Martin Bachmann	OXFORD	Parkinson's Disease vaccines
Dr	Ellie Barnes	OXFORD	Hepatitis C vaccines
Dr	Persephone Borrow	OXFORD	HIV immunity
Prof	Vincenzo Cerundolo	OXFORD	Cancer vaccines
Dr	Bryan Charleston	PIRBRIGHT	FMDV vaccines
Dr	Linda Dixon	PIRBRIGHT	African swine fever virus
Dr	Lucy Dorrell	OXFORD	HIV vaccines
Dr	Simon Draper	OXFORD	Malaria vaccines
Prof	Sarah Gilbert	OXFORD	Influenza & malaria vaccines
Prof	Tomáš Hanke	OXFORD	HIV vaccines
Prof	Glyn Hewinson	AHVLA	Bovine TB vaccines
Prof	Adrian Hill	OXFORD	Malaria vaccines
Prof	Paul Klenerman	OXFORD	Hepatitis C vaccines
Prof	Martin Maiden	OXFORD	Meningitis vaccines
Prof	Andrew McMichael	OXFORD	HIV immunity & vaccines
Prof	Helen McShane	OXFORD	TB vaccines
Prof	Peter Mertens	PIRBRIGHT	Arborovirus vaccines
Prof	Richard Moxon	OXFORD	Paediatric vaccines
Prof	Venugopal Nair	PIRBRIGHT	Poultry vaccines
Dr	Satya Parida	PIRBRIGHT	FMDV vaccines
Prof	David Paton	PIRBRIGHT	FMDV vaccines & diagnostics
Prof	Brian Perry	OXFORD	Tropical veterinary medicine
Prof	Andrew Pollard	OXFORD	Paediatric vaccines
Dr	Arturo Reyes-Sandoval	OXFORD	Malaria Vivax & dengue vaccines
Prof	Sarah Rowland-Jones	OXFORD	HIV immunity
Prof	Quentin Sattentau	OXFORD	HIV vaccines
Dr	Adrian Smith	OXFORD	Coccidiosis immunity
Dr	Geraldine Taylor	PIRBRIGHT	Respiratory syncytial virus vaccines
Dr	Martin Vordermeier	AHVLA	Bovine TB vaccines

Oxford: University of Oxford Pirbright: The Pirbright Institute AHVLA: Animal Health & Veterinary Laboratories Agency

Call for Volunteers to Participate in Clinical Trials

The Centre for Clinical Vaccinology and Tropical Medicine (CCVTM) on the Headington campus of the University of Oxford conducts clinical vaccine trials for diseases of global importance and impact. If you would like to learn more about the clinical trial process, what it entails and how to volunteer to participate, please contact the Volunteer Coordinator via email or telephone, or visit the Jenner Institute website.

Email: VaccineTrials@ndm.ox.ac.uk
Tel: +44 (0)1865 857406
www.jenner.ac.uk/clinicaltrials

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