The Jenner Institute is a research partnership between the University of Oxford and The Pirbright Institute. The Institute focuses on the parallel development of human and veterinary vaccines against major global diseases – from early-stage research through to clinical trials.
Contents continued

46 Andrew Pollard  
The Oxford Vaccine Group (OVG)
48 Arturo Reyes-Sandoval  
Plasmodium vivax malaria
50 Christine Rollier  
Serogroup B Meningococcus
52 Sarah Rowland-Jones  
Immunology of HIV infections in different geographical locations
54 Quentin Sattentau  
Antigens and adjuvants for antibody vaccines
56 Adrian Smith  
Developing new vaccines and adjuvants for birds and mammals
58 Geraldine Taylor  
Vaccines for Bovine Respiratory Syncytial Virus and Peste des Petits Ruminants Virus
60 Matthew Snape  
Meningococcal, pneumococcal and influenza vaccines
62 Martin Vordermeier  
Human and bovine tuberculosis

Research Programmes and Core Facilities

66 Clinical Trial Collaborations in Africa – Malaria, HIV-1 and TB
68 Prostate Cancer Programme
69 Vaccine Delivery Programme – Sugar–membrane stabilisation of vaccines
71 MRSA and Staphylococcus Aureus
72 The Clinical Biomanufacturing Facility (CBF)
75 Transcriptomics Core Facilities (TCF)
76 Viral Vector Core Facility
78 Jenner Adjuvant Bank
79 The Jenner Insectary
81 Education Provided by the Jenner Institute
83 Finance

85 Publications

98 The Jenner Vaccine Foundation
99 Ebola – PostScript and Update

The Jenner Institute was founded in November 2005 to develop innovative vaccines against major global diseases. Uniquely, it focuses both on diseases of humans and livestock, and tests new vaccine approaches in different species in parallel. A major theme is translational research involving the rapid early–stage development and assessment of new vaccines in clinical trials. The Institute is a partnership between the University of Oxford and The Pirbright Institute, and is the successor to the former Edward Jenner Institute for Vaccine Research. The Institute is supported by the Nuffield Department of Medicine, the Jenner Vaccine Foundation (a UK registered charity), and advised by the Jenner Institute Scientific Advisory Board.

The Institute comprises the research activities of over 25 Jenner Investigators who lead research groups spanning human and veterinary vaccine research and development. Together, the Institute Investigators comprise one of the largest non-profit sector research and development activities in vaccinology. Jenner Institute Investigators, through the support of many funders, are developing new vaccine candidates against major global infectious diseases. New vaccines against malaria, tuberculosis (TB) and HIV are currently in field trials in the developing world. There has also been substantial progress on livestock vaccines against foot-and-mouth disease, bovine tuberculosis, bluetongue, avian influenza, and other major causes of economic loss.

In the last few years both malaria and tuberculosis vaccine candidates have progressed to phase IIb efficacy testing in Africa, the TB vaccine candidate being the first ever subunit vaccine to reach this milestone. A new foot-and-mouth disease vaccine that can be manufactured without the use of live virus shows considerable promise for allowing safer manufacture of this key livestock vaccine. New vaccines against outbreak pathogens, such as Ebola and Rift Valley Fever, have made rapid progress to field efficacy testing using the vectored vaccine technologies developed by the Institute. The Oxford Vaccine Group, comprising Institute scientists from the University’s Department of Paediatrics, made key contributions to the development of the recently licensed meningitis B vaccine, and to the rapid evaluation of H1N1 (swine) influenza vaccines. Finally, new horizons are being explored, with virus-like particle vaccines targeting chronic degenerative diseases such as Parkinson’s disease and exciting new T cell-inducing vaccines against cancer entering clinical trials. There have been considerable advances in assessing vaccine efficacy, through controlled human microbial infections with typhoid, paratyphoid and influenza challenge studies, adding to those regularly undertaken for malaria vaccine assessment. Finally, new technologies such as transcriptomics and virus–like particle design add to established platforms for adjuvants and viral vector generation to broaden the suite of approaches available to Jenner Investigators.

The Institute has expanded substantially in the last 10 years with several enlarging groups, strategic recruitments and a broadening base of supportive funders from four continents. The Institute’s exceptional capacity to undertake small scale first-in-human trials very rapidly was illustrated by the request from the World Health Organization to undertake, with collaborators, the first trial of a new Ebola vaccine designed for West Africa in the 2014 outbreak. Since then, no less than four new Ebola vaccines have first entered clinical testing in Oxford.

As the Jenner Institute approaches its 10th anniversary in late 2015, the global impact of vaccines and vaccination has never been greater and the scientific opportunities in vaccine development are ever increasing. So much remains to be done. Few other disciplines can offer the blend of ground-breaking science, multi-disciplinary collaboration and potential global impact that is found in vaccinology at its finest. I hope that this report conveys some of the excitement, as well as the sense of privilege, that those of us engaged and inspired by these goals are offered every day.

Adrian Hill  
Director of the Jenner Institute
JENNER LOCATIONS

Jenner Laboratories, Old Road Campus Research Building

Pirbright Institute

Clinical Biomanufacturing Facility (CBF)

Wellcome Trust Centre for Human Genetics

Centre for Clinical Vaccinology and Tropical Medicine (CCVTM)

Animal Health and Veterinary Laboratories Agency (AHVLA)

JENNER INVESTIGATORS
Vaccines against chronic diseases

A vaccine against Parkinson’s disease

Parkinson’s disease (PD) 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 being less able to direct or control their movement. Currently, there is no therapy with lasting efficacy, posing a significant challenge to the long-term treatment of patients with this neurodegenerative condition.

Overexpression of α-synuclein has been identified as a major cause for the development of Parkinson’s disease in humans. It has been noted that as little as a 1.5- to 2-fold up-regulation of α-synuclein can cause familial PD. 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 PD 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 that are able to recognize soluble oligomeric, as well as aggregated, α-synuclein.

A recently emerging possibility by which intracerebral α-synuclein levels could be reduced is vaccination against the protein for the induction of long-lived antibody responses. In recent times, mAbs as well as vaccines have reached the stage of preclinical proof-of-concept. However, the vaccine approach faces several difficulties, including generating sufficiently high antibody levels to penetrate the blood-brain barrier at relevant levels, whilst avoiding the possibility of inducing potentially harmful T cell responses. It is, therefore, essential to use a vaccine platform that induces high antibody responses in humans in the absence of relevant target-specific T cell responses. 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 cell responses. The use of next generation VLPs will avoid these issues, as strong antibody responses can be induced in the absence of an adjuvant.

My research group based in the Jenner Institute, University of Oxford is primarily interested in the development of vaccines against chronic, non-communicable diseases. The cores of these vaccines are based on virus-like particles (VLPs) that we use to display antigens of choice. I joined the Jenner Institute in 2012, after spending more than 10 years as Chief Scientific Officer at a biotech company in Zurich (Schlieren). Before this, I completed my PhD with Rolf Zinkernagel in Zurich, then spent 2 years with Pamela Ohashi in Toronto as a Post-Doc before another 2 years as a PI at the Basel Institute for Immunology. I currently divide my time between Oxford, Zurich and Doha.

My research over the last 15 years has focussed on the development of auto-vaccines in order to induce antibody responses against self-molecules involved in chronic diseases. To generate optimal antibody responses, we make use of VLPs (virus-like particles) derived from bacteriophages and, more recently, plant viruses. The technology involves the chemical linkage of VLPs to selected antigens, which we would like to neutralise via the induction of specific antibody responses.

Our current goal is to advance the development of 2 specific auto-vaccines, namely a vaccine against Parkinson’s disease and a vaccine against psoriasis. At the Jenner Institute, we also actively collaborate with other groups to apply VLP-based approaches to their targets, such as malaria antigens.

Key publications:

We have initiated a new programme for developing a vaccine against PD that employs VLPs to induce strong antibody responses against the disease-causing protein α-synuclein, launched in conjunction with Dr. Aaidd El-Turabi. Preclinical efficacy will be evaluated in collaboration with the Oxford Parkinson Centre. Provided the vaccine proves efficacious in mouse models of PD, these results will constitute preclinical proof-of-concept and will, upon adequate demonstration of preclinical safety, progress towards clinical trials.

A vaccine against psoriasis

Novel biologics for the treatment of moderate to severe psoriasis have emerged to inhibit the pro-inflammatory cytokine inter-leukin-17 (IL-17). Monoclonal antibodies (mAbs) targeting IL-17 exhibit superior efficacy over currently licensed biologics, displaying fewer adverse effects in clinical trials. However, the high cost of manufacture and frequent administration of this therapeutic agent inflicts a heavy burden on ever-stretched healthcare budgets. Vaccines based on VLPs displaying antigens of choice on their surface elicit the production of high titre antibodies against those antigens and provide excellent tolerability. As an alternative to mAb-based therapies, VLP-based vaccines represent a new generation of therapeutic strategies, shifting away from costly passive immunisation to active immunisation, instructing the body to produce its own antibodies. This approach will deliver significant cost benefits in terms of manufacture and a more favourable dosing schedule, making them extremely competitive.

The current plan aims to demonstrate that a novel VLP-based vaccine can induce high titre neutralising antibodies for IL-17 as a preclinical proof-of-concept for the proposed active immunisation therapy. If successful, our project will validate the suitability of this approach for autoimmune and inflammatory disorders, creating intellectual property and potential for further commercialisation. More importantly, it will facilitate more affordable therapies for a class of hard-to-treat conditions, favourably impacting on the quality of life of afflicted individuals, and assist in the goal of improving the overall well-being of patients.

Key publications:

We have initiated a new programme for developing a vaccine against PD that employs VLPs to induce strong antibody responses against the disease-causing protein α-synuclein, launched in conjunction with Dr. Aaidd El-Turabi. Preclinical efficacy will be evaluated in collaboration with the Oxford Parkinson Centre. Provided the vaccine proves efficacious in mouse models of PD, these results will constitute preclinical proof-of-concept and will, upon adequate demonstration of preclinical safety, progress towards clinical trials.

A vaccine against psoriasis

Novel biologics for the treatment of moderate to severe psoriasis have emerged to inhibit the pro-inflammatory cytokine inter-leukin-17 (IL-17). Monoclonal antibodies (mAbs) targeting IL-17 exhibit superior efficacy over currently licensed biologics, displaying fewer adverse effects in clinical trials. However, the high cost of manufacture and frequent administration of this therapeutic agent inflicts a heavy burden on ever-stretched healthcare budgets. Vaccines based on VLPs displaying antigens of choice on their surface elicit the production of high titre antibodies against those antigens and provide excellent tolerability. As an alternative to mAb-based therapies, VLP-based vaccines represent a new generation of therapeutic strategies, shifting away from costly passive immunisation to active immunisation, instructing the body to produce its own antibodies. This approach will deliver significant cost benefits in terms of manufacture and a more favourable dosing schedule, making them extremely competitive.

The current plan aims to demonstrate that a novel VLP-based vaccine can induce high titre neutralising antibodies for IL-17 as a preclinical proof-of-concept for the proposed active immunisation therapy. If successful, our project will validate the suitability of this approach for autoimmune and inflammatory disorders, creating intellectual property and potential for further commercialisation. More importantly, it will facilitate more affordable therapies for a class of hard-to-treat conditions, favourably impacting on the quality of life of afflicted individuals, and assist in the goal of improving the overall well-being of patients.
ELEANOR BARNES
Hepatitis C vaccines

The global burden of HCV infection is immense with 180 million people infected worldwide, and 4 million people newly infected each year. In the UK, 0.4% of the population are infected, with national prevalence rates of 10-30% elsewhere. HCV infection is associated with the development of cirrhosis and hepatocellular cancer, and is the leading cause of liver transplantation in the developed world. HCV epidemics in human immunodeficiency virus (HIV)-infected people in major European cities are a growing problem, with HCV now one of the leading causes of death in HIV-positive people on anti-retroviral therapy. New directly acting antivirals are now available that are associated with cure rates of >90%. However, these can be unaffordable even in developed countries (£30-70,000/person), and will inevitably be associated with the development of drug resistant strains. Therefore, a vaccine to prevent or treat HCV infection targeted to “at risk” populations, or more widely in high prevalence countries, would be of enormous global benefit. HCV exists globally as seven major genotypes (with 80% amino acid sequence homology between one another), and multiple subtypes that have evolved over thousands of years and which predominate in distinct geographical locations. Significant diversity may be found even within strains of the same subtype, between and within infected hosts. Within the UK, HCV exists predominantly as genotype-1 and subtype-1a infection. The very high prevalence rate of subtype-1a infection (>50%) in the UK is a unique feature of the epidemic.

HCV should be particularly susceptible to a T cell-mediated strategy, since immune-mediated viral eradication occurs spontaneously in 20% of people following primary infection. My group and others have shown that this is crucially dependent on effective T cell immunity and an appropriate host immune genetic background.

HCV vaccine approach
In recent years we have, in collaboration with others, developed highly immunogenic HCV T cell vaccines in experimental medicine studies that include both healthy volunteers and HCV-infected patients. We have used simian and human adenoviral (Ad) vectors derived from rare serotypes, in addition to Modified Vaccinia Ankara (MVA) vectors encoding all non-structural (NS) HCV proteins in heterologous prime/boost regimens. In healthy volunteers, we have shown that these vaccines are highly immunogenic, generating very high levels of functional CD8+ and CD4+ HCV-specific T cells and providing a detailed analysis of T cell function using novel CyTOF technology. Currently, these vaccines are undergoing efficacy testing in intravenous drug-taking populations in the USA and UK.

Whilst the development of a highly immunogenic T cell vaccine for HCV represents a major advance in the field, we have also shown that responses are generally attenuated in people with persistent infection and that intra-host and inter-host viral diversity, in combination with host HLA heterogeneity, may present a major challenge to the development of a successful HCV vaccine. Furthermore, recent work from the group evaluating inter-genotypic T cell immunity between HCV genotypes-1 and -3a has shown limited evidence of cross reactivity. This may have consequences for the deployment of HCV vaccines in populations where mixed genotypes circulate.

Since viral variability is an obstacle to vaccine development in several devastating infections, we are developing a generic approach for the design of genetically conserved vaccine immunogens against variable pathogens within the Jenner Institute (HIV, Dengue, and HCV). A computer algorithm has been developed to select conserved viral genomic segments, based on minimum sequence diversity within viral genomic datasets and minimum read lengths for the generation of both CD8+ and CD4+ T cell epitopes. Viral genomic segments that are conserved between genotypes, spanning both structural and NS HCV proteins, have been assimilated into a single immunogen with linker amino acids to prevent the generation of irrelevant epitopes.

Testing HCV vaccines
Moving forward, we are simian Ad vaccines that host conserved HCV genomes have been constructed (Vector Core Facility, Oxford), and immunogenicity will be compared with the current constructs in head-to-head preclinical mouse studies. Also, in collaboration with Okawa/ GlassSmithKlein and groups in Switzerland and Germany, we are assessing HCV T cell vaccines in HIV-positive people, and developing genetically adjuvanted HCV vaccines within the EU FP7 funded consortium “PEACHI” (www.peachi.eu/).

Through previous work assessing potent T cell vaccines in persistently HCV-infected people, and seeing first hand the failure to restore adaptive immunity in these patients, the group is interested in the mechanisms underpinning T cell “exhaustion” and aims to develop additional programmes of work that seek to restore immunity in experimental medicine studies in Hepatitis B virus and cancer.

Key publications:
PERSEPHONE BORROW

Understanding the immune response to HIV

There is an urgent need for vaccines to combat infection with human immunodeficiency virus type 1 (HIV-1), the virus that causes AIDS. There are currently around 35 million people living with HIV/AIDS worldwide, and about 1.5 million people die of AIDS-associated diseases each year. Combination therapy reduces viral load and delays disease progression in those who receive it, but it does not eradicate infection and is associated with many long-term problems; and even in resource-rich countries many infected individuals are not treated effectively. Importantly, the HIV-1 epidemic continues to spread, with 2.1 million people becoming infected with HIV-1 in 2013.

Understanding how T cells help the antibody response

Developing effective HIV-1 vaccines is extremely challenging, due to the variability of the virus and the many strategies it possesses for resisting and evading control by host immune responses. Together with Prof. Andrew McMichael’s group, we are working as part of the Centre for HIV/AIDS Vaccine Immunology and ImmuneSenescence Discovery (CHAVI-ID) consortium to understand innate effector responses can be harnessed to contribute to HIV prophylaxis. We are addressing the interferon-stimulated genes that mediate this activity. Natural killer (NK) cells also exert antiviral activity against HIV.

Other studies aim to identify the ligands on HIV-infected cells recognised by NK cells and explore the feasibility of developing vaccine immunogens that enhance NK cell control of HIV.

CD8+ (cytotoxic) T cells in HIV vaccines

Other immune responses can also be employed in HIV-1 vaccine design. Having previously shown that virus-specific CD8+ T cell responses are rapidly induced in primary HIV-1 infection and make an important contribution to the control of virus replication, other work in the group is addressing why the CD8+ T cell response in most infected individuals fails to contain HIV replication more completely. Mechanisms involved include viral escape from epitope-specific T cell responses, which is facilitated by focussing of the primary HIV-specific T cell response on a limited number of viral epitopes, and decline in T cell functionality following acute infection. By identifying how the specificity of the primary CD8+ T cell response to HIV is determined and how CD8+ T cell control of HIV-1 is evaded, we aim to understand how vaccines can be designed to induce optimally-effective HIV-specific CD8+ T cell responses.

The role of innate immune responses

A third objective is to determine whether innate effector responses can be harnessed to contribute to HIV prophylaxis. We are characterising the innate responses activated in acute HIV-1 infection and addressing their roles in protection and pathogenesis. Recent results show that type 1 interferons play an important role in restricting HIV-1 replication very early after transmission, and we are now addressing the interferon-stimulated genes that mediate this activity. Natural killer (NK) cells also exert antiviral activity against HIV. Other studies aim to identify the ligands on HIV-infected cells recognised by NK cells and explore the feasibility of developing vaccine immunogens that enhance NK cell control of HIV.

Key publications:


Harnessing the immune system to treat cancer, autoimmunity and infection

The principal aim of my research is to gain a better understanding of the mechanisms that control the cell–cell interplay required for optimal expansion and activation of tumour–specific T cell populations, and to apply this knowledge to the development of better treatment strategies for cancer patients. Research in my laboratory is divided into three complementary areas:

- Analysis of tumour-specific immune responses in melanoma patients and the role of the tumour microenvironment in hampering tumour-specific immune responses
- Structural, kinetic and functional analyses of invariant NKT (iNKT) cell activation
- A clinical trial vaccine programme in melanoma patients

Adjuvants and toll-like receptors enhance immune responses

Over the last three years, we have continued to characterise a range of adjuvants to enhance antigen-specific immune responses. Furthermore, we have identified novel aspects of the human toll-like receptor 7 (hTLR7) biosynthetic pathway, which is important in the innate immune response to infection, demonstrating that hTLR7 is proteolytically processed and that C-terminal fragment selectively accumulates in endocytic compartments. We have shown that hTLR7 processing occurs at neutral pH and is dependent on furin-like proprotein convertases (PCs). Furthermore, hTLR7 processing is required for its functional response to hTLR7 agonists, such as R837 or the influenza virus. Notably, pro-inflammatory and differentiation stimuli increase the expression of furin-like PCs in immune cells, suggesting a positive feedback mechanism for hTLR7 processing during infection. Because self-RNA can activate hTLR7 and trigger autoimmunity under certain conditions, our results identify furin-like PCs as a possible target to attenuate hTLR7-dependent autoimmunity and other immune pathologies.

I work at the Weatherall Institute of Molecular Medicine, Oxford. I studied Medicine at the University of Padua, Italy, specialising in Oncology, and subsequently moved to the UK to work with Professor Alain Townsend on antigen presentation. I now have a personal Chair in Immunology at the University of Oxford and I am Director of the MRC Human Immunology Unit.

Key publications:

BRYAN CHARLESTON

Foot-and-Mouth Disease and Swine Influenza

Foot-and-mouth disease (FMD)
Experimental studies in collaboration with Prof. Mark Woolhouse (Edinburgh) have determined that the infectious period of foot-and-mouth disease virus (FMDV) in cattle is shorter (mean 1.7 days) than previously realised, and that animals are not infectious until, on average, 0.5 days after clinical signs appear. These results imply that controversial pre-emptive control measures may be unnecessary for FMD and other acute viral infections of livestock and humans. Furthermore, rapid induction of CD4 T-cell independent antibody responses and the formation of virus-antibody immune complexes (IC) have been identified as key events in disease pathogenesis. IC formation triggers productive infection and killing of key immune cells called dendritic cells (DCs), alongside the induction of anti-viral proteins (type-1 interferon) from specialised cells (plasmacytoid DCs): events that correlate with the onset of clinical signs and transmission.

Persistence of non-replicating but infectious virus has been demonstrated in specific regions of lymphoid tissue in the head and neck of cattle, sheep, pigs and African buffalo. These observations have identified a role of this persisting virus in the maintenance of long-term protective antibody responses and generation of virus variation in African buffalo, the natural reservoir of foot-and-mouth disease virus in Africa.

Immunisation is said to be our society’s greatest health care achievement. The development and use of vaccines has led to the reduction or eradication of common diseases such as polio and measles. However, pathogens that cause disease and death are still common and so it is important to continue developing new vaccines.

A new FMD vaccine
In collaboration with Prof. Dave Stuart (Oxford) and Prof. Ian Jones (Reading), we have developed a new methodology to produce a vaccine for FMDV. Because the vaccine is all synthetic, made up of tiny protein shells designed to trigger an optimum immune response, it doesn’t rely on growing live virus (FMDV) in cattle is shorter (mean 1.7 days) than currently realised, and that animals are not infectious until, on average, 0.5 days after clinical signs appear. These results imply that controversial pre-emptive control measures may be unnecessary for FMD and other acute viral infections of livestock and humans. Furthermore, rapid induction of CD4 T cell independent antibody responses and the formation of virus-antibody immune complexes (IC) have been identified as key events in disease pathogenesis. IC formation triggers productive infection and killing of key immune cells called dendritic cells (DCs), alongside the induction of anti-viral proteins (type-1 interferon) from specialised cells (plasmacytoid DCs): events that correlate with the onset of clinical signs and transmission.

Persistence of non-replicating but infectious virus has been demonstrated in specific regions of lymphoid tissue in the head and neck of cattle, sheep, pigs and African buffalo. These observations have identified a role of this persisting virus in the maintenance of long-term protective antibody responses and generation of virus variation in African buffalo, the natural reservoir of foot-and-mouth disease virus in Africa.

FMDV in lymph node germinal centre

Buffalo inoculation

Two fluorescently labelled BCG bacteria (green) inside a cattle dendritic cell

Furthermore, these empty shells have been engineered to be more stable, making the vaccine much easier to store and reducing the need for a cold chain. This is important research, because it represents a big step forward in the global campaign to control FMDV in countries where the disease is endemic, and could significantly reduce the threat to countries currently free of the disease. Crucially, this new approach to making and stabilising vaccines could also impact on how viruses from the same family are fought, including polio.

Improving MVA vaccines
Modified Vaccinia Ankara (MVA) is a highly attenuated virus that is being evaluated as a vaccine delivery system. Whilst MVA is a promising vaccine platform, the development of a vaccine platform that provides strong, long lasting immunity against infectious diseases will benefit the farming industry and improve animal and human health.

After delivery through the skin, this vaccine interacts with DCs, and these in turn initiate and maintain the immune response; it is therefore important for the vaccine not to damage the function of DCs. We have previously reported that bovine DCs are seriously affected by MVA, reducing their capacity to initiate and maintain the immune response. This is because DCs recognise MVA as a foreign invader and produce lethal superoxide ions that kill the vaccine and the cell, making the vaccine ineffective. Our data show that by deleting certain genes from the MVA genome, the toxic effects observed in DC are reduced, in turn increasing the effectiveness of the vaccine.

Swine influenza
Work has just started on a new collaborative long-term study on the transmission of swine influenza. The Biotechnology and Biological Sciences Research Council (BBSRC) Swine Flu Dynamics project is a five-year study which, as well as researching virus transmission, will assess the effectiveness of different control strategies for the disease to improve animal health and help protect the UK economy.

Key publications:
African swine fever virus

ASFV is a large DNA virus that causes a haemorrhagic fever resulting in high mortality in pigs. The disease is endemic in many sub-Saharan African countries and Sardinia. Since 2007, ASF has spread from Georgia to the Russian Federation and into neighbouring Eastern European countries. The lack of a vaccine limits options for disease control.

Attenuated (non-virulent) ASFV strains are known to induce protection against challenge with related virulent viruses. We compared complete genome sequences of a naturally attenuated ASFV isolate, OURT88/3, with virulent viruses and identified a large deletion near the left end of the OURT88/3 genome. This encodes copies of multigene families MGF 360 and MGF 530/505. A further copy of MGF 360 is disrupted near the right genome end. These genes are known to be involved in suppressing the induction of a type I interferon response. Two other genes encoding membrane proteins with adhesion motifs are also disrupted in the OURT88/3 genome. Our previous work has shown that CD8+ cells are required for protection induced by OURT88/3, and that stimulation of lymphocytes from immune pigs correlates with cross-protection by different genotypes of ASFV. To identify a route for rational attenuation of other ASFV strains, we deleted similar MGF 360 and MGF 530/505 from the genome of the virulent Benin 97/1 isolate (BeninΔMGF). This deletion attenuated the Benin 97/1 isolate and induced protection against lethal challenge. Investigation of the cellular and cytokine responses induced by BeninΔMGF have identified some differences compared to those induced by OURT88/3. Future work will determine whether similar gene deletions from the genomes of other ASFV genotypes, including that circulating in Eastern Europe, can also produce candidate attenuated vaccine strains. We will also further investigate the mechanisms of protection induced by BeninΔMGF. In parallel, the effects of deleting other genes involved in inhibiting innate immune responses from virulent and attenuated ASFV strains is being evaluated. These studies currently focus on genes that suppress type I interferon or stress responses.

An alternative approach to vaccine design

Another approach for vaccine development is to identify those antigens that induce a protective response and express them from an appropriate viral vector. We have followed two approaches to identify potentially protective antigens. One involves immunising pigs by prime and boost, with pools of DNA and recombinant vaccinia virus vectors expressing individual randomly selected ASFV genes. Cellular and antibody responses to individual antigens were measured and a pool of antigens selected for further study (in collaboration with Biodesign Institute, Arizona State University). A second approach involves identifying those ASFV antigens that are recognised by immune lymphocytes from OURT88/3. A pool of 20 of the most promising antigens from both approaches are being cloned in Adenovirus vectors (Jenner Institute) and will be tested in overlapping pools in immunisation and challenge experiments in pigs.

Key publications:
LUCY DORRELL
HIV immunotherapy

I am a Senior Clinical Research Fellow, Associate Professor and Honorary Consultant in HIV medicine. I lead research programmes in HIV immunotherapy and HIV/HCV co-infection, encompassing translational immunology, imaging and vaccine trials. A major focus of my research is the identification and analysis of immunological correlates of HIV control.

**HIV vaccines used in combination with anti-HIV drugs**

Antiretroviral therapy (ART) restores health and life expectancy for HIV-infected individuals but does not provide a cure. New therapies are needed to eliminate the reservoir of CD4+ T cells in lymphoid tissue where HIV persists for years without detection. The goal of my research is to develop innovative vaccine and immunotherapy strategies to enhance immune-mediated killing of cells that harbour HIV, to be used in combination with ART and agents to reverse viral latency.

We have conducted clinical trials of HIV vaccine candidates in HIV-positive subjects treated with ART during chronic and primary infection in the UK and Spain. The vaccines comprised a conserved region immunogen, HIVconsv, delivered by replication-defective chimpanzee adenovirus and MVA vectors. These trials are among the first to evaluate latent HIV reservoirs before and after vaccination. Immunological and virological analyses will be completed in 2015.

**ImmTAVs: a novel anti-HIV therapy**

HIV is able to gain a foothold because it can rapidly evolve to escape adaptive immune responses early in the course of infection, while simultaneously seeding long-lived CD4+ T cells. In collaboration with Immixcore Ltd., Oxfordshire, we have tested novel agents, engineered immune-mobilising T cell receptors against viruses called ‘ImmTAVs’ that are designed to clear HIV-infected cells. ImmTAVs are synthetic soluble T cell receptors (TCRs) that recognise HIV epitopes with extraordinarily high affinity and are coupled to a single chain antibody targeting CD3. The ImmTAVs bind specifically to HIV-infected cells via the TCR and harnessing effector T cells via CD3 signalling, resulting in immune-mediated killing of the target cell. We studied patients on long-term ART and observed highly efficient killing of HIV reservoir cells by ImmTAV-redirected CD8+ T cells ex vivo. Importantly, ImmTAVs were able to induce killing of cells that expressed very low levels of viral proteins. Our results suggest that ImmTAVs are promising agents that could facilitate clearance of HIV reservoirs. This work has paved the way for a new project on imaging of HIV-immune cell interactions using the first ever containment level 3 high-resolution microscopy facility at the Weatherall Institute of Molecular Medicine, in collaboration with Prof. Christian Eggeling.

**Understanding how HIV vaccines work**

Only two HIV vaccines designed to elicit protective T cell responses have reached clinical efficacy testing to date, both with disappointing results. Defining the components of an HIV immunogen that could induce effective CD8+ T cell responses is therefore critical to the development of preventive and therapeutic vaccines. In collaboration with the HIV Vaccine Trials Network (HVTN) and Duke University, USA, we investigated the viral targets of CD8+ T cells that potently inhibit HIV replication in vitro, as this is highly predictive of virus control in vivo. Rare individuals whom maintain low level viremia without ART (‘viremic controllers’) showed broad and potent CD8+ T cell inhibitory activity against diverse HIV strains, in contrast to non-controller subjects. Viral inhibition was strongly correlated with the frequency of CD8+ T cells that targeted epitopes within 26 vulnerable regions in the viral proteome, which had been identified in an independent study of nearly 1,000 chronically infected individuals. These so-called ‘beneficial’ regions, while generally conserved and subdominant, would not have been predicted by bioinformatic approaches. Furthermore, vaccines encoding full-length HIV proteins, including the MRK Ad5-Gag/Pol/Nef vaccine tested in the Step trial, rarely induced responses to these regions. This observation suggests that immuno-dominance hierarchies undermine effective anti-HIV CD8+ T cell responses, and provides an explanation for the failure of conventional HIV immunogens to induce effective immune responses. Our research has thus highlighted the need for immunogens based on systematic selection of empirically defined vulnerable regions within the viral proteome, with exclusion of immunodominant decoy epitopes that are irrelevant for HIV control.

**Key publications:**


**RESEARCH REPORT**

PEACHI: preventing HCV and HIV co-infection

As HIV-positive people are living longer, prevention of comorbidities has become a priority. In 2013, we launched PEACHI, an EU FP7-funded project to develop vaccines for the prevention of hepatitis C virus (HCV) and HIV co-infections. The PEACHI consortium brings together expertise in the HIV and HCV fields, with European partners from academia (Oxford, St. James’ Hospital Dublin, Kantonsspital St. Gallen) and industry (GlanbiaPharmBio and ReThera) (www.peachi.eu): In 2014 we initiated the first phase I trial to evaluate combined vaccinations with HIV and HCV immunogens, each delivered by replication-defective chimpanzee adenovirus and MVA vectors (PEACHI 04), in healthy volunteers in Oxford. This will be followed by a phase I trial to evaluate the same HCV vaccine candidates in HIV-seropositive HCV-uninfected patients on ART in Ireland and Switzerland (PEACHI 02). In addition, ReThera has developed next generation viral vectored vaccines employing an HCV immunogen fused to the HLA class II invariant chain. We plan to take these vaccines into a first-in-human trial in 2013. These clinical studies will be complemented by comprehensive immunomonitoring using established and new laboratory assays, with the goal of identifying possible immune correlates that could be tested in future efficacy trials.

**Visualisation of ImmTAV-redirected killing of HIV-infected CD8+ T cells**

**HIV infected cell**
The development of an effective vaccine against the blood-stage malaria parasite has proved incredibly challenging. The mainstay approach in the field has focused on inducing antibodies that seek to block red blood cell invasion by the merozoite form of the parasite. This endeavour has been hindered by the antigenic variability of the parasite’s proteins, the redundancy of invasion pathways used by the parasite, and the need for extremely high titres of antibody to block this rapid and complex invasion process. Over the last 3 years, my group has sought to tackle these problems by identifying proteins within the merozoite that are conserved, essential and yet highly susceptible to vaccine-induced antibodies. In parallel, we have continued to invest significant time in the development of new and improved vaccine delivery strategies to deliver malaria antigens in a highly immunogenic manner, leading to the induction of high titer antibody responses.

In 2011, we completed a series of three Phase I/IIa clinical trials funded by the UK MRC and the European Malaria Vaccine Development Association (EMVDA). These trials sought to assess the delivery of two candidate antigens from the human malaria parasite Plasmodium falciparum (MSP1 and AMA1) using recombinant simian adenovirus (ChAd63) and MVA (modified vaccinia Ankara) viral vectors. These vaccines were shown to be safe and highly immunogenic for T cell, B cell and antibody responses in healthy adult volunteers. However, the induced responses did not protect volunteers following controlled malaria infection delivered by infectious mosquito bites. These studies did, however, provide an opportunity to better understand how vaccine-induced responses can be modulated by exposure to the malaria parasite in a controlled infection setting. This work in malaria-exposed volunteers in Oxford is complemented by similar immunological studies in individuals who are naturally exposed to malaria in Africa, through our collaboration with the KEMRI-Wellcome Institute in Kilifi, Kenya. This on-going work has a particular interest in antibody effector mechanisms against the blood-stage parasite, including neutralisation as well as antibody Fc interactions with the cellular immune system. Following on from these studies, we have undertaken a series of preclinical experiments to look at the utility of deploying protein-in-adjuvant and viral vectored vaccines in combination with immunisation regimes. This work has led to a fourth Phase Ia clinical trial using the AMA1 antigens, where we have confirmed the superior immunogenicity of the ‘adenoavirus prime – protein boost’ approach in healthy adult volunteers.

**Improved vaccine targets**

More recently, our preclinical vaccine development work has focused on the identification of improved antigen targets within the blood-stage merozoite parasite. We have spent significant time establishing new protein vaccine production platforms (based on mammalian and insect cell technologies) that, along with viral vectored delivery, are enabling the generation of a whole new range of vaccines. To date, we have identified the PRR5F antigen as the first reported target in the P. falciparum merozoite that is highly susceptible to broadly-neutralising vaccine-induced antibodies. We have shown that PRR5F is quantitatively more susceptible to vaccine-induced antibodies than the gold standards in the field (AMA1 and MSP1), with high level protective efficacy in a non-human primate challenge model. With support from the European Commission MultiMalariaVax programme, as well as the European Vaccine Initiative and UK MRC, we are currently progressing PRR5F viral vectored vaccines, as well as a protein vaccine made in Drosophila S2 cells, to Phase I/IIa clinical trials. These should initiate by mid-2015.

In parallel, we have also progressed a viral vectored vaccine candidate to Phase I clinical testing against blood-stage Plasmodium vivax. This vaccine targets the PvDTDP_RII protein, which is critically essential for red blood cell invasion by this parasite. This is the world’s first vaccine trial of a candidate for blood-stage P. vivax, and should pave the way to initiate vaccine efficacy studies in the near future.

**Future work**

Our ongoing work will now seek to make use of the valuable opportunity of having the PRR5F and PvDTDP_RII antigens in clinical testing for the first time. We will begin to explore the human antibody responses to both targets, seeking to generate panels of human monoclonal antibodies from the B cells of vaccinated volunteers. These mAbs can then be used for functional and structural analyses, and should help to guide the design of second-generation improved immunogens. In parallel, at the preclinical stage, we will continue to search for other antigens within the merozoite that are highly susceptible to vaccine-induced antibodies and suitable for inclusion in a combination vaccine with PRR5F. We are also focusing on improving the blood-stage controlled human malaria infection model, which should allow for quicker and easier efficacy testing in Phase IIa clinical trials of new candidate vaccines, including those based on PRR5F.

**Structure of RH5**

Source: Nature. 2014 Aug 17. doi: 10.1038/nature13715

**Key publications:**


TARGETING INFLUENZA AND RIFT VALLEY FEVER WITH VIRTUAL VECTOR VACCINES

New vaccines for Influenza

The main activity of my group in the last three years has been to conduct clinical trials of new influenza vaccines, which are designed to work in a different way to existing influenza vaccines and either replace or complement them. Current influenza vaccines are capable of inducing immunity to the proteins on the surface of the influenza virus, but since they constantly change from year to year, the composition of the vaccine has to be changed frequently and vaccination must be given annually. Even when the vaccine is a very good match for the influenza strains that are circulating shortly after the vaccine is given, the vaccines are not particularly effective in people aged over 65 years, which is the major target group for vaccination against influenza.

Viral vectored vaccines

My group has been using viral vectored vaccines to induce immune responses against internal regions of the influenza virus as these are not subject to frequent change. If we can induce a protective immune response against them, we can induce T cells that can recognise and kill virus-infected cells early on in the course of infection so that the virus can be prevented from spreading through the body before any illness occurs. We know that this happens when people have been infected by the influenza virus and then recover, but existing vaccines do not enhance the T cell response to influenza in adults.

In our first clinical trial, we demonstrated that we could achieve a significant boosting of T cell responses to conserved influenza antigens with a single dose of our vaccine, MVA-NP+M1. We went on to show that this vaccine is also highly immunogenic in older adults, and may be a better way of immunising older people who do not respond well to existing vaccines. In a proof-of-concept ‘influenza challenge’ study in which healthy young volunteers were deliberately infected with influenza virus, we saw that fewer vaccinated than unvaccinated volunteers became ill with symptoms of influenza.

We have also found that if we give our influenza vaccine, MVA-NP+M1, at the same time as the licensed trivalent inactivated vaccine (TIV) which is normally given to adults, it not only boosts T cell responses to influenza but also increases the antibody response to the TIV vaccine. This is expected to considerably improve the efficacy of TIV in older adults, and we hope to conduct a much larger study of this approach starting in 2015.

A novel viral vector vaccine with increased potency

Work on viral vectors at the Jenner Institute has led to the development of a new simian adenovirus vector ChAdOx1. We know that replication-deficient adenoviruses are potent vaccine vectors when tested in animals, but if we use a human adenovirus to make a vaccine vector to use in humans, the response is reduced because of naturally-acquired human immunity to the adenovirus vector. This problem is avoided if we use an adenovirus normally found in chimpanzees to make a vaccine vector. Following the initial development of ChAdOx1 in the lab, we introduced two conserved antigens from influenza and made a vaccine that has now been tested in clinical trials. As with MVA-NP+M1, the new vaccine boosts T cell responses to influenza and, when both vaccines are used one after the other, the response is even stronger. We are now continuing with a clinical trial using both novel vaccines with the aim of determining the optimum approach to vaccination.

Rift Valley Fever

Work led by George Warimwe using adenoviral vectors to vaccinate sheep, goats, and cattle against Rift Valley Fever virus is showing great promise. A single immunisation induces high titre antibodies, and the vaccine that is being developed could be used in humans as well as livestock — perhaps the ultimate example of a One Health vaccine. This vaccine programme is developing rapidly, with plans to vaccinate camels in the next few months, since they can be infected with Rift Valley Fever virus and have been implicated in spreading the virus following an outbreak.
I completed my PhD at The University of St Andrews, UK. In 1994, I took up a post-doctoral position in the lab of Prof. Sir Andrew McMichael at the University of Oxford. With the establishment of the Medical Research Council (MRC) Human Immunology Unit in 1996, I started my own group and, five years later, obtained an MRC Career Development Programme. I lead the HIV-1 Vaccine Development Programme in collaboration with other experts in the field, we explore novel approaches and emerging technologies to induce protective T cell and neutralising antibody responses. The vaccine development programme covers conception, construction and stepwise improvements of new vaccine candidates in an iterative process from mouse to non-human primate models, followed by clinical studies in humans.

Designing an effective vaccine against HIV-1 is a long and laborious task. The HIV-1 virus is highly mutable and thus highly variable, and evolves to evade the adaptive arms of the immune system. Furthermore, during HIV-1 infection, immune responses are dominated by those targeting the most variable parts of proteins. These variable regions serve as decoys, which attract most of the attention of the immune response, but easily change under their selective pressure. Mutated, unrecognised viruses then rapidly overgrow the targeted strains and replace them.

Scientists have employed a range of innovative solutions to combat these challenges. After being initially ignored, the problem of variability was tackled by creating immunogen cocktails from different HIV-1 isolates or amino acid average sequences. Efforts to make use of the growing HIV-1 sequence database and the advent of increasing computing power has led Dr Bette Korber’s team at Los Alamos National Laboratory, USA, to develop mosaic proteins. As artificial proteins assembled from all HIV-1 sequence variants in the database, these immunogens are computed over every HIV-1 protein to provoke HIV-1-specific responses, and thus the insertion of an HIV-1 derived immunogen into the scheduled BCG vaccine for TB, delivered soon after birth, could provoke HIV-1 specific responses, and thus potentially decrease mother-to-child HIV-1 transmission through breastfeeding. In 2010, I led randomised clinical trials that involved administering a candidate HIV-1 vaccine to 20-week-old infants born to HIV-1-negative mothers in The Gambia, and HIV-1-positive mothers in Kenya. Promisingly, and similarly to the other published infant trials, the study demonstrated that it is feasible to test candidate HIV-1 vaccines in high-risk African infants. Furthermore, the results supported the use of MVA as a boosting vector within heterologous prime-boost vaccine strategies in the under-1-year age group.

Key collaborators: Our key collaborators are: Prof. Lucy Dorrell, Prof. Sir Andrew McMichael and Dr Andrew Ogg, King’s College London; Prof. Christian Brandt and Dr Bettina Koep, University of Oxford; Prof. Walter Jaako, University of Nairobi, Kenya; Dr Bette Korber, Los Alamos National Laboratory, USA; The International AIDS Vaccine Initiative; Dr Katie Flanagan, formerly MRC Laboratories, The Gambia; Prof. Grace John-Stewart, University of Washington, USA; Prof. Marie Reilly, Karolinska Institute, Sweden; Prof. Sir Mark Pepys, University College London; Prof. Christian Brandt and Dr Beatrice Mota, Irsicaixa AIDS Research Institute HIVACAT, Spain; Dr Sarah Didier, Imperial College London and Dr Joan Josepeh, Hospital Clinic Barcelona, Spain.

Key publications:
GLYN HEWINSON
Bovine tuberculosis vaccine programme

Development of TB vaccines for Cattle
Bovine TB is currently one of the greatest challenges that the farming industry faces in the UK, especially in the southwest of England and Wales. The most cost-effective control measure for infectious disease is vaccination, and used alongside existing bovine TB control measures, vaccination could reduce disease severity and prevalence. The development of vaccines for cattle forms part of the Government’s comprehensive eradication strategy for bovine TB.

The development of an effective vaccination strategy for TB is compromised in humans and cattle by two major problems. The first is that the protection conferred by the currently available vaccine, BCG, is variable at both the individual and population level and host responses to vaccination are unpredictable. Thus one arm of our vaccination programme is to exploit this variability in cattle to identify correlates of protective immunity and in doing so identify the underlying reasons for the variability in protective efficacy of BCG. The comparison of transcriptome and RNAseq profiles of vaccinated cattle that are protected from infection with those that are not protected is helping us to identify useful immune markers that predict the outcome of vaccination (for more details please see the section from my colleague Martin Vordermeier). Along with Adrian Hill and John Fazakerley, I am joint holder of the Wellcome Trust Strategic Award that supports the Transcripomics Core Facility at the Jenner Institute and this facility helps underpin the collaborative work on TB between myself, Helen McShane and Martin Vordermeier.

Diagnosis of TB
The second problem that we face is that since BCG is not 100% effective, a diagnostic test is required to differentiate vaccinated from infected individuals (a so-called DIVA test) so that disease control programmes may continue in the face of vaccination. Unfortunately BCG vaccination interferes with the statutory diagnostic skin (tuberculin or PPID) test. This problem has been, to a certain extent, alleviated for humans in prosperous countries by the development of blood-based DIVA diagnostic tests that predict the outcome of vaccination, but these are expensive and inappropriate for the developing world and as cost-effective livestock tests. Cost benefit analysis of cattle vaccination suggests that the optimal combination of vaccine and diagnostic test would be either a vaccine with an associated skin test DIVA that could replace the existing comparative tuberculin skin test, or a vaccine that does not sensitize vaccinated animals to the current tuberculin skin test. At present our research programme aims to address both these problems.

Key publications:

Testing vaccine efficacy in field trials
One of the difficulties we encounter in developing vaccines against bovine tuberculosis is deciding when vaccines are ready to enter clinical field trials. The stringent challenge model used to assess the efficacy of TB vaccines in cattle consists of an endobronchial challenge with a single dose of approximately 1,000 cfu of M. bovis grown in artificial culture media. In the field, vaccination must protect against natural challenge comprising of multiple exposures to M. bovis that may express different antigens than those expressed in artificial culture of varying dose over the lifetime of the animal. For this reason we have developed a natural transmission model for bovine TB that allows us to test vaccine efficacy in a natural transmission setting. The recent award of a 5 year grant funded under the ZELS (Zoonoses and Emerging Livestock Systems) research initiative (www.bbsrc.ac.uk/funding/opportunities/2012/zoonses-emerging-livestock-systems.aspx) will allow us to maintain and develop this model.
ADRIAN HILL

Pre-erythrocytic malaria

A vaccine for pre-erythrocytic malaria

My group’s work has focused on the development of a vaccine against Plasmodium falciparum malaria, specifically against the early sporozoite and liver stages of this parasite. We designed and developed vaccine candidates that, uniquely, show efficacy in clinical trials associated with the induction of cellular immunity, in particular CD8+ T cells. This has been achieved by the iterative development of so-called heterologous prime-boost regimes, where one viral vector is used to prime the immune response and another as a booster immunisation. This leads to the induction of exceptional levels of CD8+ T cells in animals and humans, and has demonstrated high levels of immunogenicity and protection of human vaccines against infection using a liver-stage malarial protein, known as TRAP, expressed from particular recombinant viral vectors. These viruses act as highly efficient delivery mechanisms to target genes encoding malarial protein(s) into human cells, via natural cellular infection pathways; the foreign protein, in this case P. falciparum TRAP, is expressed inside the infected cells leading to the generation of a powerful cellular immune response. The optimal immunisation regime uses adenovirus vectors as priming agents and MVA (modified Vaccinia Ankara) as a boosting agent, and we discovered that simian adenovirus vectors are excellent priming vaccines clinically, probably as there is no pre-existing immunity to these chimpanzee vectors in humans, thereby avoiding any neutralisation of the adenovirus vaccine.

Partial efficacy with the P. falciparum TRAP-vectorised vaccines was initially demonstrated through the use of a standardised controlled human malaria infection model. This entails volunteers agreeing not just to be immunised with new vaccines but to undergo a controlled infection with mosquito bites to allow the vaccine’s efficacy to be assessed. Oxford is one of the leading centres globally for this “challenge model” with over 20 such studies conducted. In the last 3 years, African field trials in adults, children and infants have been completed using Chimpanzee Adenovirus (ChAd) strain 63 encoding the ME-TRAP antigen as an initial priming vaccination, and MVA-MU-TRAP as the secondary boost. Data has demonstrated good safety and immunogenicity profiles of this vaccination regime for malaria in all populations tested, now totalling over 10,000 vaccinees. In a recent efficacy trial in Kenyan adults, 47% efficacy was found against malaria infection in a short two month trial using new PCR-based monitoring techniques.

New malaria vaccine approaches

Complete protection of humans against infection has yet to be achieved, so we have taken a number of approaches to increase the effectiveness of malaria vaccines. We have generated new simian adenovirus vectors (called ChAdOx1 and ChAdOx2), and also improved the effectiveness of existing adenovirus and MVA viral vectors by the addition of a ‘molecular adjuvant’ related to the CD74 invariant chain, which increases the presentation of foreign proteins to the immune system leading to an enhanced immune response. This work was funded by a major grant from the Bill and Melinda Gates Foundation, addressing one of the Grand Challenges in Global Health. We have carried out an extensive screen for new liver-stage antigens/proteins which would either make effective vaccines on their own, or could be combined with other antigens, including TRAP. This screen has identified two very promising candidates, known as LSA1 and LSAP, which confer complete protection against infection in a novel rodent model for malaria, which was developed in collaboration with Leiden University.

As a complementary approach to virally vectored vaccines, we have developed a virus-like-particle vaccine by fusing a segment of the P.falciparum circumsporozoite protein to the Hepatitis B surface antigen protein, which spontaneously forms particles containing numerous copies of the protein and is used as a vaccine against the Hepatitis virus. This malaria vaccine, called R21, is similar to the RTS,S vaccine produced by GSK which protects up to 50% of individuals in a vaccinated population. One hypothesis being tested is that R21 will generate a greater malaria-specific immune response as it contains a higher proportion of the circumsporozoite protein relative to hepatitis protein.

It has proved extremely challenging to produce a completely effective vaccine against malaria, as Plasmodium is a complex parasite with several different life stages in mosquito and human hosts; many of its genes are highly polymorphic and there is redundancy in many of its functions, meaning that if one protein is targeted by a vaccine, others can take its place. It is therefore possible that in order to protect 100% of a population we will need to combine different vaccines, probably against different stages of the parasite’s life cycle. We are coordinating a European consortium (MultiMalVax), which has received funding to test a combination of vaccines, either viral vectors expressing antigens from different life stages, or viral vectors in combination with the R21 virus-like particle. Very encouraging clinical data has already been obtained from a challenge trial in UK adults testing this approach, combining GSK’s RTS,S vaccine and viral vectors containing ME-TRAP.

Key publications:
PAUL KLENERMAN
Vaccines for Hepatitis C Virus and Respiratory Syncytial Virus

My group has been involved in studies of T cell responses to viruses, and our work over the last 3 years has focused on two areas—hepatitis C virus (HCV) and respiratory syncytial virus (RSV).

Hepatitis C Virus
HCV is a major cause of liver disease globally and no vaccine is currently licensed. Some HCV-infected people clear the virus spontaneously, i.e. through effective innate and adaptive immunity. The relevant immunity appears to be mediated by T cells, and by generating a vaccine that induces T cells it has been shown in proof-of-concept preclinical studies that this can accelerate immune control. We collaborated with Okairos to test T cell vaccines for HCV. The first of these trials (HCV001) using two different adenoviral constructs, one based on a newly described adenovirus (ChAd3), showed good immunogenicity. Ellie Barnes has taken this work forward in further trials using these vectors as immunotherapy (in patients already infected with HCV) and also with an improved boosting regimen with a modified vaccinia virus (MVA) vaccine, in HCV003. This latter strategy appears to produce the highest levels of immune response and has been taken into Phase II trials by Okairos in the US.

Respiratory syncytial virus
RSV is a major cause of respiratory disease in infants and is increasingly recognised as a problem in the elderly, potentially on a scale similar to influenza. No vaccine exists, partly as a result of failed vaccine trials in the past, where there was enhanced immune-mediated pathology in infants. Improved immunogenicity for B and T cells based on adenoviral and MVA vectors is being assessed in a Phase I trial with Andrew Pollard’s group. This trial has been completed in healthy young adults and it is hoped that it will soon move on to paediatric populations, as well as older adults.

Key publications:
I originally trained as a microbiologist at the University of Reading, followed by a molecular genetics and biochemistry PhD at the University of Cambridge, after which I worked at the National Institute for Biological Standardisation and control for 9 years on various aspects of bacterial vaccines. I moved to the University of Oxford as a Wellcome Trust Senior Fellow in 1997 and, since 2004, have been Professor of Molecular Epidemiology and a Fellow of Hertford College. In 2010, I was elected a Fellow of the Royal College of Pathologists.

Vaccines against meningococcus
We are interested in the design and implementation of vaccines against the encapsulated bacterium Neisseria meningitidis, otherwise known as the meningococcus, a much feared cause of both meningitis and septicaemia worldwide. We use an explicitly multidisciplinary and collaborative approach, based on understanding the ecology and evolution of this enigmatic pathogen which, paradoxically for such a notorious cause of severe disease, is found to harmlessly colonise the upper respiratory tract of many people.

Understanding meningococcal diversity
We are involved in a ground-breaking initiative to make the latest genomic data on meningococcal genomes from England and Wales available on-line in near real time (http://www.meningitis.org/current-projects/genome). We also work to curate and maintain catalogues of diversity in vaccines, such as the newly licensed Novartis vaccine Bexsero© (http://PubMLST.org/neisseria). We have developed easy to use, publicly available tools for the resolution of epidemics caused by highly variable pathogens such as the meningococcus. Our own approach to the development of a novel meningitis vaccine, MenPF, is based on two major outer membrane proteins, PorA and FetA, and comprises a carefully composed combination of variants of these proteins. MenPF1, a first generation realisation of this concept, has recently completed a successful phase I trial in collaboration with Prof. Ian Pollard (Department of Paediatrics, Oxford), Prof. Andrew Feavers (National Institute for Biological Standards and Control), Prof. Jeremy Derrick (University of Manchester) and Prof. Andrew Pollard (Department of Paediatrics, Oxford).

At the time of writing, we are embarking on a major survey of meningococcal carriage in the UK (UKMenCar4) that will sample 18,000 teenagers to generate a large dataset of carried meningococci collected at the present time, a period of very low meningococcal disease incidence. This data will complement the disease isolate data from the MRF-MGL and the carriage surveys conducted by us at the time of the introduction of the meningococcal C conjugate polysaccharides 15 years ago, a period of high meningococcal disease incidence. The data generated will provide unparalleled opportunities in understanding the highly variable and inherently unpredictable epidemiology of meningococcal disease, and hopefully lead to novel approaches to vaccination.

Understanding meningococcal disease
We are involved in a ground-breaking initiative to make the latest genomic data on meningococcal genomes from England and Wales available on-line in near real time (http://www.meningitis.org/current-projects/genome). We also work to curate and maintain catalogues of diversity in vaccines, such as the newly licensed Novartis vaccine Bexsero© (http://PubMLST.org/neisseria). We have developed easy to use, publicly available tools for the resolution of epidemics caused by highly variable pathogens such as the meningococcus. Our own approach to the development of a novel meningitis vaccine, MenPF, is based on two major outer membrane proteins, PorA and FetA, and comprises a carefully composed combination of variants of these proteins. MenPF1, a first generation realisation of this concept, has recently completed a successful phase I trial in collaboration with Prof. Ian Pollard (Department of Paediatrics, Oxford), Prof. Andrew Feavers (National Institute for Biological Standards and Control), Prof. Jeremy Derrick (University of Manchester) and Prof. Andrew Pollard (Department of Paediatrics, Oxford). At the time of writing, we are embarking on a major survey of meningococcal carriage in the UK (UKMenCar4) that will sample 18,000 teenagers to generate a large dataset of carried meningococci collected at the present time, a period of very low meningococcal disease incidence. This data will complement the disease isolate data from the MRF-MGL and the carriage surveys conducted by us at the time of the introduction of the meningococcal C conjugate polysaccharides 15 years ago, a period of high meningococcal disease incidence. The data generated will provide unparalleled opportunities in understanding the highly variable and inherently unpredictable epidemiology of meningococcal disease, and hopefully lead to novel approaches to vaccination.

Key publications:
I was Director of the MRC Human Immunology Unit from 1998-2010, Director of the Weatherall Institute of Molecular Medicine from 2000-2012 and I am currently Professor of Molecular Medicine. I have worked on T cell immunity to viruses, particularly influenza and HIV, showing how HLA molecules present influenza virus and HIV peptide epitopes and how HIV-1 escapes T cell recognition. I am very active in HIV-1 vaccine development and have worked with the Jenner Institute since it moved to Oxford.

We have four main projects:

1. Identification of ligands for the stimulatory killer cell immunoglobulin-like receptors (KIR) on natural killer (NK) cells and T cells. The ligand for KIR3DS1 is elusive. We have expressed soluble KIR3DS1 protein and are searching for its ligands using HLA (human leukocyte antigen) arrays, peptide-HLA tetramers, virus-infected cells and yeast cells expressing HLA class I molecules with random peptides. So far no ligand has been identified. It is possible that there is no specific ligand in most cells, but that NK cells bearing KIR3DS1 are slightly more activated than those bearing the inhibitory allelic forms (KIR3DL1).

2. Investigating the epitope specificity of HIV-1 envelope-specific CD4 T cells. We have shown that HIV-1 unexposed and uninfected donors have naïve and memory T cells in their blood that are HIV-1-specific. We are exploring the hypothesis that the latter are primed by cross-reactive antigens, including bacteria of the gut and skin microbiome.

3. Optimisation of a conserved vaccine to stimulate cytotoxic CD8 T cells that are specific for conserved epitopes of HIV-1. In collaboration with Tomaš Hanke (Jenner Institute) and Bette Korber (Los Alamos National Laboratory), we have designed a second generation conserved region HIV-1 vaccine that is a two stranded mosaic. This has better coverage of HIV-1 variability than the HIVconsv vaccine, which has shown excellent immunogenicity in a phase one trial. The new vaccine perfectly matches more than 80% of all conserved nonamer epitopes present in all the major clades of HIV-1. This vaccine is currently in preclinical development and will be used for prophylactic and therapeutic immunisations. It should enable the recipients to make T cell responses that are much less likely to select virus escape mutants than the natural primary T cell responses in acute HIV-1 infection.

4. Searching for HLA class II and HLA-E-restricted HIV-1-specific CD8 T cells. These T cells have been shown by Picker et al. to be associated with T cell responses that can eradicate Simian Immunodeficiency Virus infection in rhesus monkeys. If these unusual T cells can be shown to exist in humans, vaccines could be designed to stimulate them.

Our group, together with that of Dr Persephone Borrow in Oxford, leads the T cell and innate cell programmes of the CHAVI-ID consortium, under the overall direction of Dr Bart Haynes at Duke University.

Key publications:


HELEN McSHANE
Tuberculosis vaccine programme

I have lead a TB vaccine research group at the University of Oxford since 2001. My research interests include TB immunology, preclinical animal models, translational clinical trials, human mycobacterial challenge models and mucosal immunisation. I have published over 100 research articles and have an H-index of 30. I was appointed Professor of Vaccinology at the University of Oxford in 2009. I am a member of the Wellcome Trust Clinical Interview Committee and the GLOBVAC Board. I am also an honorary consultant physician in HIV/GU medicine, and the Academic Foundation Programme lead for academic junior doctor supervision.

Tuberculosis (TB), a disease caused by Mycobacterium tuberculosis (M. tb), has been around since the Pharaohs, and remains a very significant cause of disease and death throughout the world in the 21st Century. In 2012, there were 8.6 million new cases of TB and 1.3 million deaths. The emergence of drug resistant strains of M. tb and the geographical overlap with the HIV epidemic have compounded the challenges facing our ability to control TB worldwide, and there is an urgent need for improved tools for TB control. The most cost-effective way to control any infectious disease epidemic is with an effective vaccine. The only licensed vaccine against TB is an attenuated strain of Mycobacterium bovis, Bacille Calmette Guerin (BCG). When administered at birth, BCG confers consistent and reproducible protection against disseminated disease, particularly TB meningitis, in the first ten years of life. However, the protection conferred against lung disease is much more variable and is lowest in TB high burden countries. We therefore need a more effective vaccine.

Towards an improved TB vaccine

Strategies to develop an improved TB vaccine regimen include replacing BCG with a recombinant strain of BCG, or attenuated strain of M.tb; and/or developing a subunit booster vaccine, where only one or a few proteins from M.tb are used, to be administered after BCG either in infancy or in adolescence. I lead a research group developing subunit booster vaccines. One of the vaccines that we developed was the first new TB vaccine to enter into clinical trials, MVA85A, a recombinant strain of modified vaccinia Ankara expressing the mycobacterial antigen 85A. This vaccine has been evaluated in many phase I and IIa clinical trials in the UK and several countries in Africa, and was the first vaccine to enter into phase IIb efficacy testing in BCG-vaccinated South African infants in 2009. An efficacy trial in HIV infected adults is ongoing. Current work in the group includes identifying methods of optimising the immunogenicity of new TB vaccines. One promising strategy is to administer the vaccine directly into the airways, which is the route by which M.tb enters the body. Data from our first phase I study using this route are very promising, and we have just commenced our second clinical trial to evaluate this route of immunisation further. Other ongoing trials include combination studies where recombinant adenoviral vectors, which are potent at inducing CD8+ T cells, are combined with MVA vectors, which are potent at inducing CD4+ T cells. Current opinion is that an optimal new TB vaccine would induce both T cell subsets. Other areas of work include developing a human mycobacterial challenge model with which to test new vaccine candidates, and new methods of immune-monitoring in TB vaccine trials including functional mycobacterial growth inhibition assays. Ongoing overseas trials in Uganda will evaluate the effect of helminth co-infection on TB vaccine immunogenicity, and in South Africa will evaluate safety of new TB vaccines in BCG naive infants.

Key publications:
PETER MERTENS
Bluetongue and African horse sickness viruses

Phylogenetic studies of Bluetongue virus (BTV) and related orbiviruses

The Arbovirus Molecular Research Group has established, continues to maintain and is expanding a reference collection of bluetongue and other related orbivirus isolates from around the world (http://www.reoviridae.org/dsRNA_virus_proteins/ReoID//virus–not-by–country.htm). This has provided a basis for full genome sequencing studies and phylogenetic analyses that have revealed the extent of serological and geographic variation within the Bluetongue virus genome and antigens. The collection has provided virus isolates for other research groups, and vaccine production companies.

These sequence analyses have allowed us to develop and update a suite of novel diagnostic and typing assays that are more sensitive, more rapid and more reliable than the conventional serological assays, and which now represent the primary basis for Bluetongue virus serotype detection and identification around the world. As part of these studies, we actively track the movement and can identify the origins of individual virus lineages that threaten or emerge in Europe or elsewhere, showing that new strains of the virus have entered Europe (usually in the Mediterranean region) every year since 1998. This database has played a vital role in the identification of novel serotypes of BTV (BTV-24 from Switzerland and BTV-26 from Kuwait). We have also recently established reverse genetics technologies for Bluetongue viruses that have allowed us to identify the individual viral genes of BTV-26 that restrict its infection or replication in cells of Culicoides vector species (biting midges).

In 2014, a novel virulent strain of BTV-4 was identified that emerged in Greece and Bulgaria, causing severe disease in local breeds of sheep. Full genome analyses showed that this virus is related to earlier strains that were circulating in the eastern Mediterranean region, particularly in North Africa. Genome segment exchange (re-assortment) has generated a novel combination of the ten viral genes, potentially leading to its enhanced transmission and virulence characteristics.

Vaccine development for BTV and AHSV

Studies of BTV and AHSV outer capsid protein VP2 (which is involved in cell attachment and interaction with neutralising antibodies) expressed by bacteria, plants, baculoviruses or modified Vaccinia Ankara have led to the development of subunit vaccine candidates. Unlike the previous live or inactivated vaccines, these are compatible with assays to distinguish vaccinated from infected animals (DIVA compatible). In particular, the modified Vaccinia Ankara strains expressing VP2 from different AHSV serotypes appear to be effective vaccine candidates.

Intracellular studies of BTV replication have shown that infection can cause cell cycle arrest in mammalian cells (BHK 21 cells), linked to the disruption of spindle formation during mitosis. Fluorescence microscopy studies have implicated BTV protein NS2 in this mechanism, and may provide a partial explanation for the anti-tumour activity previously reported for BTV.

Other orbiviruses

We have extended our full genome sequencing studies to include all of the 22 known Orbivirus species, including several other significant pathogens of livestock (such as palyam viruses, equine encephalosis virus, Peruvian horse sickness virus and epizootic haemorrhagic disease viruses). These studies have not only provided information concerning potential protective antigens against these viruses, but also provide a basis for virus identification and diagnostic assay development, and have identified seven additional species of Orbivirus.

Key publications:


Haemophilus influenzae, Meningococcus and

RICHARD MOXON

Meningococcus and Haemophilus influenzae

Key publications:


4. In collaboration with Marco Oggioni of Leicester University, I am investigating the pathogenesis of pneumococcal bacteremia (in a mouse model) to better understand the early phases in the infection. Previous research in the past 2 years has shown that pneumococcal bacteremia, initiated following challenge with millions of bacteria, is founded by a single surviving bacterial clone. Further, we have identified adaptive mutations in ex vivo organisms obtained from blood during the bacteremic phase. Our future research aims to identify the details of the profound population bottleneck of pneumococci, the role of host factors in clearance and the host-adaptive mechanisms of the pathogen.

In my capacity as a scientific adviser to Novartis Vaccines, I have been deeply involved with the research leading up to the licensure of the MenB vaccine (Bexsero) and the subsequent post-licensure events leading to the recommendation that the vaccine, if cost-effective, should be introduced into the routine infant immunisation programme in the UK. As a member of the Scientific Council of Institut Pasteur, I am active in supporting a new initiative that aims to bring about a major programme in vaccinology spearheaded by the Director General, Christian Brecho. I continue to be active in teaching, for example as a member of the faculty of the annual Advanced Course In Vaccinology (held in Annecy, France), where I lecture and participate in workshops and discussion groups.

I remain active in original research on bacterial pathogens with emphasis on how this knowledge can facilitate prevention of bacterial infections in childhood through immunisation. In the past three years, my research has included:

1. The development of a model of otitis media caused by capsule-deficient H. influenzae (Hi). Scientists at Harwell have identified a mutant mouse line (Junbo) that is susceptible to nasopharyngeal colonisation and ascending bacterial infection with Hi resulting in otitis media. This has opened the door to investigations of the pathogenesis, treatment and prevention of this important infection of childhood. In collaboration with Derek Hood and other Harwell Scientists, we have demonstrated the importance of a profound population bottleneck during the establishment of otitis media and the feasibility of the model to investigate the protective effect of candidate Hi antigens, identified through whole genome sequencing.

2. Subsequent to the licensure of a vaccine against the B strain of meningococcus (MenB), I am collaborating with the research group of Martin Maiden (Zoology Department) to use whole genome sequences of large collections of MenB carriage and disease isolates to describe their genetic diversity, especially with respect to variations in the vaccine antigens over time, before and after the introduction of Bexsero into the UK routine immunisation programme.

3. In conjunction with Professor Andrew Pollard and the Oxford Vaccine Group, we have evaluated the adjuvant effect of a modified lipopolysaccharide in native outer membrane vesicles (nOMVs) on immune responses to vaccination with the recombinant meningococcal protein, rPorA, tetanus toxoid, or meningococcal serogroup C capsular polysaccharide. These results highlight the potential importance of considering not just the antigens that result in priming and boosting B cell responses, but the pathogen-specific molecular determinants that underpin interactions with the innate immune response in obtaining optimal protection and long-lasting immunity following immunisation.

I was Action Research Professor of Paediatrics from 1982-2008, Head of the Molecular Infectious Diseases Group in the Weatherall Institute of Medicine (1988-2008), founded the Oxford Vaccine Group in 1994 and was the principal investigator and lead scientist for funding and establishing the Centre for Clinical Vaccinology and Tropical Medicine (CCVTM) (1999 – 2008). I am currently an Emeritus Professor of Paediatrics in the Medical Sciences Division, a member of the Scientific Council for Institut Pasteur and the Advisory Boards of the Wellcome Trust, Novartis Vaccines and GlycoVaxyn. My research has been on the molecular basis of bacterial infections of childhood, especially meningitis and septicaemia caused by Haemophilus influenzae type b and the meningococcus, with a major interest in their prevention by immunisation.
VENUGOPAL NAIR OBE
Avian viral diseases programme

I obtained my veterinary qualification and doctorate degree in Veterinary Medicine from India. I have over 25 years experience in veterinary virology and avian diseases, have published more than 100 scientific publications and book chapters, and also served as one of the Associate Editors of the 13th Edition of Diseases of Poultry. In recognition of my contributions to Avian Medicine, I was inducted to the World Veterinary Poultry Association Hall of Honour in 2013. I also hold honorary Visiting Professorships at Imperial College London and The University of Liverpool, and I am an Adjunct Fellow at Linacre College, Oxford.

Marek’s Disease
My laboratory (www.research.pirbright.ac.uk/viralloncogenesis/) currently focuses on Marek’s disease virus (MDV), a highly contagious neoplastic disease of poultry caused by the Marek’s disease virus (MDV). My group is one of the two World Reference Laboratories on MD for the World Organisation for Animal Health (OIE). As a major disease of poultry, causing estimated annual economic losses of up to $2,000 million to the poultry industry worldwide, understanding the molecular determinants and mechanisms of the disease is crucial to develop novel control strategies.

We have identified a number of major viral determinants directly associated with the induction of T cell lymphomas utilising: a) highly efficient reverse genetics systems with bacterial artificial chromosome (BAC) clones of the full-length genomes of a number of pathogenic and vaccine strains of MDV; and b) excellent models of the disease in genetically defined susceptible chicken hosts. These include the major virus-encoded oncopogene Meq, a basic leucine zipper-containing transcription factor, as well as miR-M4, a virus-encoded homologue of the oncogenic microRNA gga-miR-155. For further elucidation of the molecular pathways of oncogenesis, we are currently examining the global Meq “interactome” (the set of proteins that interact with Meq), and miR-M4 “targetome” in transformed tumour cells. More recently, we have also determined the global changes in DNA methylation in MDV induced lymphomas, in order to demonstrate that these epigenetic changes also contribute to oncogenicity.

Key publications:

Vaccines for Marek’s Disease
MD is a good-natural model for virus-induced lymphomas, and is the first example of a cancer that can be prevented by vaccination. Although vaccines have been immensely successful in preventing the disease during the last 40 years, the current trend of continuing virulence of MDV strains is threatening the sustainability of the vaccination strategy. Our recent studies suggest that the inability of the current vaccines to prevent virus replication and transmission (as opposed to preventing disease) is contributing to this increased virulence, which is caused by viral mutation. Novel strategies that can reduce virus transmission are required to stop this current trend. Recombinant vaccine vectors, such as herpesvirus of turkeys (HVT), expressing MDV proteins are now widely deployed as an alternative vaccination strategy, which can prevent not only disease but also transmission between birds, and so control the viral evolution that leads to increased virulence. BAC clones of the genomes of HVT and other vaccine strains also provide us with the opportunity to develop novel recombinant vectors.
I lead the Vaccine Differentiation Group in the Livestock Viral Disease Programme at The Pirbright Institute, UK, which carries out applied research that will help to control foot-and-mouth disease (FMD) and peste des petits ruminants (PPR). I am an adjunct Professor to Murdoch University, Australia, and an Investigator at the Jenner Institute, University of Oxford. I recently joined the National Institute of Animal Biotechnology (NIAB), Hyderabad, India, as a Visiting Faculty in the infectious disease programme.

**Ongoing work on foot-and-mouth disease and peste des petits ruminants**

My group is focussed on the development and validation of marker vaccines and associated diagnostics for FMD and PPR, with three lines of investigation: (1) improving our understanding of the aspects of the immune response that are important in the protection of vaccinated animals against acute and persistent infection; (2) developing alternative means of detecting infection in vaccinated animals; and (3) developing and evaluating improved marker vaccines (DIVA vaccines) for FMD and PPR. Marker vaccines allow differentiation between infected and vaccinated subjects, which is particularly important for the control of disease epidemics affecting livestock.

During the last four years, our work has focussed on these areas:

**FMD vaccine development**

1. Determining the immunogenic potential of 2 recombinant viral vector vaccines (rSeV/FMD and rAdV/FMD), and obtaining data on the ability of these vaccine candidates to block FMDV (foot-and-mouth disease virus) infection through the intranasal route. Both vaccines were immunogenic in a homologous prime-boost parenteral vaccination strategy, and protected cattle against virulent FMDV challenge delivered using a nebuliser and mask. Intranasal vaccination of cattle with one vaccine alone (rSeV/FMD), but not the other, also provided full protection against FMDV challenge.

2. Improving existing inactivated FMD vaccines: 8 new adjuvants, Abisco300, CPG, ISA206, Poly I:C, Iniquimod, MPLA, liposome and ISA70, were tested with FMD antigen + ISA206 in cattle. Two of them improved the immunogenicity of the existing vaccine and provided complete protection upon challenge with virulent FMD virus.

3. The widest diversity of FMD viruses circulates in East Africa, with four serotypes found in livestock, and few tailor-made vaccine strains are currently available. We have serologically characterised field isolates and vaccine strains for serotypes A and O. The genes encoding the virion proteins of these viruses have been sequenced, and the serological and genetic data have been synthesized to determine genetic determinants of their antigenic phenotypes. Collaborating with Glasgow University, we are currently involved in developing a sequence-based method for determining antigenic similarity, and using this to develop a method for vaccine strain selection for emerging foot-and-mouth disease virus outbreaks in enzootic countries, through analysis of the antigenic characteristics of recently circulating viruses.

4. We have developed and validated confirmatory antibody tests against non-structural proteins that could differentiate infection in vaccinated animals (DIVA). Also we have developed a mucosal antibody test (Iga) for O, A, and Asia1 serotypes that could detect persistently FMDV virus infected ruminants.

**PPR vaccine development**

5. Development of a recombinant PPR marker vaccine: Reverse genetic techniques have been established for the PPR virus, and a live attenuated recombinant marker vaccine for PPR Nigeria 75/1 has been developed and evaluated in goats, which provides complete protection.

6. For the first time, we have sequenced the complete genome of Lineage III PPR virus and the complete genome of 6 other PPR viruses. Using these full genome sequences, we have studied the evolution and worldwide emergence of the PPR virus.
BRIAN PERRY OBE
Global disease control and health initiatives

I am a veterinarian and epidemiologist specialised in assessing the impacts of livestock diseases and their control in developing country settings, where I have widespread experience in many countries of Africa, Asia and Latin America. In recent years, I have led many independent evaluations of public funding investments in agricultural and health development programmes by international and bilateral agencies. I hold honorary visiting Professorships at the Universities of Oxford, Edinburgh and Pretoria, and Chair the Scientific Advisory Board of the Wellcome Trust-funded One Health research consortium ‘Afrique One’.

Foot-and-mouth disease research
Following many years of exploring the contributions of foot-and-mouth disease (FMD) control to development and poverty reduction, I convened a global consultation in India in 2007 on the need for research into the better control of FMD in endemic settings of the world. Following on from this, I embarked on a two year process of leading the design of research to address FMD in endemic settings, and seeking funding for its support. Many of the concepts presented have now been funded by the Wellcome Trust and others, including a new strategic award obtained by the Jenner Institute.

Human resource and institutional capacity building in the health sciences Afrique One.
Since 2009, I have been Chairman of the Scientific Advisory Board of Afrique One, an Africa-wide consortium of eleven universities and research institutions undertaking research on zoonotic diseases at the human, animal and environmental interface in Africa. This is supported by funding from the Wellcome Trust under its African Institutions Initiative.

Zoonosis and Emerging Livestock Systems Initiative (ZELSI).
In 2013, I was invited to Chair the Development Relevance Panel Review Committee in the evaluation of research proposals submitted to the Biotechnology and Biological Sciences Research Council (BBSRC), for the £19 million investment in the Zoonosis and Emerging Livestock Systems Initiative (ZELSI) by the Department for International Development (DFID).

Strategic analytical contributions to global opportunities in livestock research and development and animal health Livestock disease control and processes of poverty reduction.
It is now 10 years since I led a DFID initiative to develop a prioritisation of research needs and opportunities for the better control of livestock diseases affecting poorer sectors of society in Africa and Asia. I have continued to play an active research role in this field, updating earlier work on disease impacts and exploring other mechanisms for contributions of disease control to economic growth.

Global livestock disease dynamics.
I was invited by the Food and Agriculture Organisation (FAO) to be the team member responsible for animal health in the development of the FAO’s annual publication on livestock entitled “The State of Food and Agriculture”; the special edition was entitled “Livestock in the Balance”. From this work, a publication emerged in the Proceedings of the National Academy of Science entitled “Current drivers and future directions of global livestock disease dynamics”.

Global livestock research imperatives and responses by the Centres of the Consultative Group on International Agricultural Research (CGIAR).
In 2013, I was invited by the Independent Science and Partnership Council (ISPC) of the CGIAR to develop a strategic overview of the current priorities for global livestock research, the comparative advantage of the CGIAR, and the responses made by the 15 research centres through the formation of the CGIAR Research Programmes (CRPs), designed to build and enhance partnerships between centres and disciplines and to be largely undertaken in the context of specified ecoregions. The final report was published as a white paper in early 2014 and appears on the ISPC website. As part of the Sustainable Livestock Initiative, I have also been invited to organise, operate and facilitate international panel discussions involving multiple stakeholders.

Leadership of independent evaluations of public funding investments in agriculture and health
Since 2009, I have led nine independent evaluations of the effectiveness and impact of public funding investments in agriculture and health in different countries and regions of the world.

These have included the global real-time evaluation of the FAO’s programmes in highly pathogenic avian influenza, the performance of the United Nation’s programmes in agriculture in Ethiopia and, in late 2013, I participated in an evaluation of the decentralisation process of the FAO in Asia and the Pacific, in which I led the review of all of the FAO’s work on animal health and production in the region.

Other activities
I have been involved in assessing the impact of the World Bank’s investment in avian flu control in Nigeria. In a different field, I have undertaken a study of the effect of changing trade agreements on the benefits to different stakeholders engaged in the export of fresh flowers from Kenya and Ethiopia, in particular to Norwegian markets.

Key publications:
My research group, the Oxford Vaccine Group (OVG), includes over 70 clinical trials and scientific staff, who enrolled more than 10,000 participants to research studies and published over 100 scientific papers in the past 5 years. Studies conducted by the group have impacted on the licensing or deployment of many of the vaccines currently recommended for use in the paediatric immunisation schedule, and were also instrumental in providing safety data allowing the use of the Influenza A H1N1 ‘swine flu’ vaccines in response to the recent pandemic and the evaluation of vaccines in response to the Ebola outbreak in 2014.

Meningitis and encephalitis

I have been investigating immunity to meningococcal disease following infection and vaccination for 20 years, bringing this focus to the work of the Oxford Vaccine Group since 2001. Neisseria meningitidis causes approximately 100,000 cases of invasive meningococcal disease (meningitis and septicaemia) every year. OVG has had a broad programme of meningitis vaccine development and evaluation, spanning from preclinical development to clinical trials and post-licence studies.

- Respiratory syncytial virus (RSV) infection usually produces widespread bronchiolitis and interstitial pneumonia which may sometimes be associated with giant cells. This image shows a non-specific encephalitis in early 2015 funded by the Wellcome Trust. Our central aim was to design, initiate and utilise a human model of typhoid infection to make major advances in our understanding of host-pathogen interactions and the development of protective immune responses. While providing novel insights into S. typhi pathogenesis, we have also directly applied the model to assess and validate novel diagnostics and vaccines. Experience gained in performing human challenge studies has led to the field introduction and testing of novel approaches to typhoid diagnostics and interventions.

Since completion in 2012 of the largest single randomised control trial using human challenge to assess vaccine efficacy, the enteric fever programme has expanded to encompass the development of a paratyphoid challenge model, work exploring immunological responses following re-challenge, and funding aimed to introduce a new generation of diagnostics and vaccines to those most at need.

Respiratory Syncytial Virus

Respiratory Syncytial Virus (RSV) is the single greatest burden to paediatric hospital resources every winter in industrialised nations. Two thirds of infants have an RSV infection in the first year of life, with 2-3% requiring admission to hospital, and approximately 6% of these needing management on dedicated paediatric intensive care units (PICU). Worldwide, RSV disease in hospitalised <5 years accounts for 33.8 million lower respiratory infections, 1.4 million hospitalisations and 66,000-199,000 deaths annually, second only to malaria in all-cause post-neonatal infant mortality. Estimates in the elderly population suggest that RSV causes a burden of death and disease comparable to seasonal flu.

Despite decades of research effort, there remains no licensed RSV vaccine to mitigate the enormous human and financial cost of the worldwide annual RSV epidemic. OVG are currently conducting a phase 1 adult study of a novel RSV vaccine, using viral vectors to deliver key RSV protein antigens.

Enteric Fever

Enteric fever, the systemic illness caused by bacteria including Salmonella typhi and Paratyphi A, continues to be a major cause of illness and death globally, particularly in children living in impoverished surroundings.

In 2009, a programme to accelerate the progress being made in the control of enteric fever was initiated, with major funding provided by the Wellcome Trust. Our central aim was to design, initiate and utilise a human model of typhoid infection to make major advances in our understanding of host-pathogen interactions and the development of protective immune responses. While providing novel insights into S. typhi pathogenesis, we have also directly applied the model to assess and validate novel diagnostics and vaccines. Experience gained in performing human challenge studies has led to the field introduction and testing of novel approaches to typhoid diagnostics and interventions.

Since completion in 2012 of the largest single randomised control trial using human challenge to assess vaccine efficacy, the enteric fever programme has expanded to encompass the development of a paratyphoid challenge model, work exploring immunological responses following re-challenge, and funding aimed to introduce a new generation of diagnostics and vaccines to those most at need.

B cells and antibodies

While the kinetics of antibody responses following vaccination against pneumococcus, meningococcus and H. influenzae type b capsular polysaccharides have been studied extensively, little is known about the specific B cell responses that underlie the production of antibody. We have investigated B cell responses using various approaches to explore the mechanisms of protection through use of both plain polysaccharide and protein-polysaccharide conjugate vaccines.

Our work focuses on the effect of capsular antigens on the frequencies of antigen-specific IgM memory B cells, innate B1 cells and plasma cells. Maturisation of B cell response at the molecular level is being studied using high-throughput sequencing technology and novel bioinformatics algorithms in order to investigate B cell receptor repertoire following vaccines against meningococci, H. influenzae, S. pneumoniae and Hepatitis B. These methods have the potential to identify antigens specific B-cell sequences and determine patterns of B-cell subset activation.

Childhood infections in Nepal

In 2011, GAVI (Global Alliance for Vaccines and Immunisation) funded a 4-year programme of research to investigate the impact of the introduction of pneumococcal conjugate vaccines in the Nepal infant immunisation schedule. This programme of research, led by OVG, is being undertaken jointly with the International Vaccine Access Centre (IVAC) at Johns Hopkins School of Public Health and the Agence de Médecine Préventive (AMP), and continues a collaboration with Patan Hospital Department of Paediatrics that commenced in 2005. This collaboration has allowed the epidemiology of bacterial pneumonia and meningitis to be defined in Nepali children funded by PneumoADIP and WHO, together with large-scale studies of the carriage of Haemophilus influenzae type b and Streptococcus pneumoniae, which are the most important causative pathogens. In addition, a recently completed clinical trial of a novel pneumococcal conjugate vaccine (PCV10) has supported the planned introduction of this vaccine in Nepal in 2014/15.

Highlights include:

- Leadership of phase II and III clinical trials supporting development and evaluation of capsular group B meningococcal vaccines and quadrivalent capsular group A, C, W and Y meningococcal vaccines.
- Delivery of a large European project to identify genetic factors underlying the reactogenicity and immunogenicity of a recently licensed MenB vaccine.
- Key studies in the development of pneumococcal conjugate vaccines for the UK programme.
- Study of the impact of smoking in different age-groups on meningococcal disease.
- Investigation of capsular group X meningococcal serological responses in Africa and preclinical characterisation of the structure and vaccine potential of the X polysaccharide.
- Improvement of the outer membrane vesicle components of MenB vaccines through several research projects, one of which has included the creation of a proof of concept vaccine characterised in preclinical models, which was recently evaluated in a first-in-man phase I clinical trial.
- Creation of a novel capsular group B meningococcal (MenB) vaccine, which will enter phase I clinical trials in 2015.

In 40-50% of meningitis and encephalitis cases the cause is unknown. We are now undertaking the largest prospective study of paediatric meningitis and encephalitis in Europe to identify the causes of these infections, develop better diagnostics and describe outcomes, and plan to initiate a clinical trial of intravenous immunoglobulin for the treatment of encephalitis in early 2015 funded by the National Institute for Health Research.

Respiratory Syncytial Virus (RSV) infection usually produces widespread bronchiolitis and interstitial pneumonia which may sometimes be associated with giant cells. This image shows a non-specific encephalitis in early 2015 funded by the Wellcome Trust. Our central aim was to design, initiate and utilise a human model of typhoid infection to make major advances in our understanding of host-pathogen interactions and the development of protective immune responses. While providing novel insights into S. typhi pathogenesis, we have also directly applied the model to assess and validate novel diagnostics and vaccines. Experience gained in performing human challenge studies has led to the field introduction and testing of novel approaches to typhoid diagnostics and interventions.

Since completion in 2012 of the largest single randomised control trial using human challenge to assess vaccine efficacy, the enteric fever programme has expanded to encompass the development of a paratyphoid challenge model, work exploring immunological responses following re-challenge, and funding aimed to introduce a new generation of diagnostics and vaccines to those most at need.

B cells and antibodies

While the kinetics of antibody responses following vaccination against pneumococcus, meningococcus and H. influenzae type b capsular polysaccharides have been studied extensively, little is known about the specific B cell responses that underlie the production of antibody. We have investigated B cell responses using various approaches to explore the mechanisms of protection through use of both plain polysaccharide and protein-polysaccharide conjugate vaccines.

Our work focuses on the effect of capsular antigens on the frequencies of antigen-specific IgM memory B cells, innate B1 cells and plasma cells. Maturisation of the B cell response at the molecular level is being studied using high-throughput sequencing technology and novel bioinformatics algorithms in order to investigate B cell receptor repertoire following vaccines against meningococci, H. influenzae, S. pneumoniae and Hepatitis B. These methods have the potential to identify antigens specific B-cell sequences and determine patterns of B-cell subset activation.

Childhood infections in Nepal

In 2011, GAVI (Global Alliance for Vaccines and Immunisation) funded a 4-year programme of research to investigate the impact of the introduction of pneumococcal conjugate vaccines in the Nepal infant immunisation schedule. This programme of research, led by OVG, is being undertaken jointly with the International Vaccine Access Centre (IVAC) at Johns Hopkins School of Public Health and the Agence de Médecine Préventive (AMP), and continues a collaboration with Patan Hospital Department of Paediatrics that commenced in 2005. This collaboration has allowed the epidemiology of bacterial pneumonia and meningitis to be defined in Nepali children funded by PneumoADIP and WHO, together with large-scale studies of the carriage of Haemophilus influenzae type b and Streptococcus pneumoniae, which are the most important causative pathogens. In addition, a recently completed clinical trial of a novel pneumococcal conjugate vaccine (PCV10) has supported the planned introduction of this vaccine in Nepal in 2014/15.
ARTURO REYES-SANDOVAL
Plasmodium vivax malaria

Vaccines against Plasmodium vivax malaria

The fight against malaria is becoming of central importance to the global health agenda, following the initial commitment in 1969 by the World Health Organization to eradicate this disease. Such momentum has been driven by the growing appreciation of the humanitarian and economic issues in malaria-endemic populations, the development of novel tools to fight the disease and increased investment by funding organisations.

Of the two malaria parasites with the greatest prevalence, Plasmodium vivax is the most difficult to eliminate from endemic areas because of its ability to remain dormant as hypnozoites in the liver of an infected person for weeks, months or years, later reactivating and continuing with the transmission cycle. The presence of a parasite with the ability to hide for years constitutes a formidable challenge to its elimination from densely populated areas of Asia and Latin America, where it threatens nearly 40% of the worldwide human population and is responsible for an estimated 132-391 million cases of malaria each year.

There is currently no licensed vaccine for malaria, and vaccine development for P. vivax has been a particularly slow process, with only two candidates reaching clinical trials, that confer only modest protection against infection. Fortunately, modern technology should permit faster future progression towards the development of novel vaccine candidates.

P. falciparum malaria.

In recent years, I have contributed to the development of one of the leading vaccine candidates for P. falciparum malaria that targets the parasite in the liver, where it stops and multiplies before entering the blood (this is known as a pre-erythrocytic or liver-stage vaccine). This strategy uses novel recombinant viral vectors (ChAd63 and modified Vaccinia Ankara, MVA) expressing the recombinant antigen TRAP. By exploiting their extraordinary ability to stimulate both arms of the adaptive immune response, i.e. both antibodies and T cells, we can elicit immune responses able to provide outstanding protection in a sporozoite challenge model that mimics the infection process by which a mosquito inoculates parasites into a mammalian host. My research has contributed to the understanding of the mechanisms responsible for the extraordinary protective efficacy of recombinant viral vectors, forming the basis for their use as malaria vaccines, including the following examples:

• The first description of a single vaccination with a chimpanzee adenoviral vector malaria vaccine, and its ability to induce complete, sterile protection against a sporozoite challenge using the P.berghei malaria parasite;
• Demonstration that Ad-MVA prime-boost vaccination regimens elicit long-term protection against malaria and enhance the functionality of CD8+ T cells;
• Identification of correlates of protection for T cell-inducing vaccines in pre-erythrocytic malaria;
• Demonstration of the potential of viral-vectored vaccination for pre-erythrocytic malaria in non human primates and humans;
• Various methods to enhance the immunogenicity and protective efficacy of viral vectors against malaria.

Ongoing research

My ongoing research focuses on the development of a novel malaria vaccine against P. vivax, using recombinant viral vectors expressing pre-erythrocytic antigens. Through the support of the Wellcome Trust, I aim to develop and investigate the following:

• A novel P. vivax vaccine using recombinant viral vectors expressing pre-erythrocytic antigens;
• Development of novel transgenic P.berghei parasites expressing P. vivax transgenes, which would permit the assessment of new vaccine candidates;
• The ability of viral-vectored vaccines to target the hypnozoites from P. vivax;
• Design, production and purification of proteins from P. vivax to be used for research and vaccine development.

An additional research interest focuses on the development of vaccines for Dengue Fever using recombinant viral vectors.

Key publications:

CHRISTINE ROLLIER (OXFORD VACCINE GROUP)

Serogroup B Meningococcus

Neisseria meningitidis causes around 500,000 cases of meningitis and septicaemia every year, disproportionately affecting children under 2 years. The case-fatality rate is 10% in resource-rich settings, and has not decreased significantly since the 1950s. 30% of survivors suffer severe long-term disability including deafness, amputation and cognitive impairment.

Vaccination is the optimal way to reduce the mortality and morbidity from this disease. Our objective is to develop a new vaccine against capsular group-B meningococcal disease (MenB), in order to address the need for an improved and more cost-effective vaccine which has lower manufacturing costs, higher immunogenicity, longer duration of protection and requires a single injection to protect infants, as compared to the currently available vaccines. Two vaccine candidates have recently been licensed, but they do not provide complete protection against MenB, especially in infants, who are at most risk of this devastating disease. Furthermore, these vaccines require multiple doses which increases the cost of vaccine implementation. Development of alternative vaccines is therefore required.

Improvement of Outer Membrane Vesicle vaccines

N. meningitidis produces non-infectious outer membrane vesicles (OMVs), which contain many subcapsular antigens during growth in liquid culture and in vivo. OMVs have been used successfully as vaccines during outbreaks of MenB and are also included in the multicomponent MenB vaccine Bexsero, which was licensed in Europe in 2013. However OMVs have considerable limitations: the immune responses are weak, strain-specific and short-lived. Therefore improving their immunogenicity may contribute to the design of more potent MenB vaccines or vaccine components. N. meningitidis has developed complex mechanisms to evade the immune system and especially the Complement cascade, in particular by binding human factor H (hFH), an inhibitor of the Alternative Complement Pathway (AP). By binding Complement inhibitors to turn off Complement activation, the bacteria or vaccine becomes less visible to the immune system. This is likely to have an impact on the immunogenicity of vaccine candidates such as OMVs containing such Complement-inhibitor binding proteins. Therefore the aim of this project is to create OMVs unable to bind hFH and thus able to activate the Complement AP, and test the hypothesis that these modified OMVs would raise a higher host immune response when compared to the wild-type counterpart. The objectives were to engineer a capsular group B N. meningitidis strain lacking the ability to bind hFH, to produce an OMV vaccine from this strain and to compare its immunogenicity to a wild-type counterpart in pre-clinical mouse models.

Development of novel MenB vaccines

We are investigating the potential of an alternative type of vaccine technology for the development of a new vaccine against MenB. The research group has developed proprietary vaccine candidates, through a method that is safe and effective at triggering an immune response. We have investigated this new approach for several antigens and have demonstrated that while all of the prototypes are able to induce strong antibody responses, these antibodies are not always able to kill the bacteria to a sufficient extent. Exploring the reasons behind these results allowed us to develop a novel and successful prototype vaccine, which is currently being optimised to progress to phase 1 clinical trial in 2016.

Key publications:
SARAH ROWLAND-JONES

Immunology of HIV infections in different geographical locations

In Zimbabwe, we are collaborating with epidemiologists and clinicians in Harare who have recently shown that a substantial proportion of older children and adolescents (up to 50% in hospital, 15-20% in primary care) are presenting with previously undiagnosed and hence untreated HIV infection, which they acquired in infancy. These young people have frequently developed life-threatening complications, including severe chronic lung disease and heart problems, predominantly cardiomyopathy. We are investigating the mechanisms underlying these unusual clinical complications and looking at protective immunity in the small proportion of long-term survivors with perinatal HIV infection who remain well and have evidence of viral control in the absence of anti-retroviral therapy (ART). Together with investigators from Zimbabwe, Malawi and South Africa, we will be taking part in a multi-centre clinical trial of Azithromycin in older HIV+ children with chronic lung disease, funded by the Research Council of Norway (Globvac programme).

In China, we are working with clinical researchers providing care for villagers who acquired HIV during participation in an illegal plasma donor scheme. These subjects were infected with a very similar viral strain through the same route at approximately the same time, and had limited access to anti-retroviral therapy (ART) during the first decade of infection. We are investigating how different components of the immune response have shaped viral evolution from an almost identical starting point, which may provide evidence for the relative importance of these different immune components to viral control.

In Nairobi (Kenya), we are also studying viral evolution using samples collected 15-20 years ago, from infants who acquired HIV infection from their mothers. The course of infant HIV infection is very different from that in adults; whereas in adults the immune system rapidly brings down the blood viral load following acute infection, the viral load in infected babies is extremely high and falls very little in the first year of life. We are looking at how HIV changes over time using samples collected over the first 2 years of life, in order to estimate when the immune system firsts starts to exert selection pressure on the virus: these studies should provide insights into when the infant immune system is first able to respond effectively to HIV, important for deciding on the optimal timing for the deployment of candidate HIV vaccines in early childhood.

HIV-2: For over 20 years, our group has studied HIV-2, the second strain of HIV that has remained relatively limited to West Africa. Although some HIV-2 infected people progress to HIV disease and death in a manner very similar to AIDS caused by HIV-1, a substantial proportion (35-40% in the Caio community cohort in Guinea-Bissau) of HIV-2 infected patients spontaneously control the virus without anti-retroviral drugs for a decade or more, effectively experiencing what is now termed a “functional cure”. We are working with researchers in Guinea-Bissau and London to investigate mechanisms of HIV control in such people.

In Kilifi (Kenya) and Malawi, we are also studying the immune response to vaccines and infections in uninfected infants exposed to HIV (HEU, HIV exposed uninfected) from their infected mothers. Although the roll-out of effective measures to prevent mother-to-child transmission of HIV has provided huge benefits in terms of many fewer HIV+ children in countries with high HIV prevalence, HEU children often show immune system abnormalities and stunted growth: they are 2-3 times more likely to die than unexposed children, and are much more likely to develop severe infections in the first year of life. Working with investigators in Kilifi and Malawi, we are studying how HEU children respond to vaccines given in early life and looking at possible mechanisms that may underlie their increased susceptibility to infection.
My recent work has focussed principally on developing antigens and adjuvants for use in antibody-based HIV-1 and other vaccines, which are designed to trigger neutralising antibody responses. HIV-1 is a difficult virus for vaccine development, largely because it has evolved multiple antibody evasion strategies. Of these, glycan coverage, antigen instability and amino acid variation are major challenges to be overcome. My laboratory has explored the modification of glycosylation, the stabilisation of antigen conformational flexibility and enhanced B cell targeting of highly conserved regions of the viral envelope glycoproteins (Env) as strategies to overcome these challenges. Recently, we demonstrated that cross-linking of soluble forms of HIV-1 Env enhances their stability, leading to increased titres and breadth of neutralising antibodies.

**New vaccine adjuvants**
Over the past 4 years, my laboratory has developed carbopol as a potent Th1-biased adjuvant that elicits robust antibody and T cell responses, and can be combined with oil-in-water adjuvants such as MF59 to elicit unusually strong antibody responses. A second adjuvant discovered by our laboratory is polyethyleneimine (PEI). PEI has strong mucosal and systemic adjuvant activity and drives a balanced Th1/Th2 biased T cell response. It may have particular utility in the protection of mucosal surfaces from viral infections. Future studies in these areas will involve pre-clinical and clinical assessment of PEI adjuvanticity, and preclinical analysis of cross-linked HIV-1 Env for potential use in man.

**Additional research into anti-HIV immunity and allergy**
Non-neutralising antibodies may also contribute to vaccine-elicited protection, and we have investigated Fc-mediated killing by innate immune cells of HIV-1-infected T cells (Fc mediated killing is triggered by binding of antibodies to ‘Fc receptors’ on the surface of various cytotoxic immune cells). We will continue to study this using vaccine and patient samples. Additional vaccine-related work in the laboratory relates to how HIV-1 uses cell-to-cell spread between contacting immune cells to evade neutralising antibodies. A final area of work concerns the contribution of oxidative modifications made to proteins in driving allergies and immune hypersensitivity. We are attempting to understand the molecular basis of this induction of aberrant immune responses.

**Key publications:**


ADRIAN SMITH
Developing new vaccines and adjuvants for birds and mammals

Improving immunity in young animals
Researchers in my group work on the immunology of birds and mammals, with a focus on developing vaccines and on improving the immune system of young animals. In the past few years, we have had notable success in developing strategies for determining which antigens are protective in antigenically complex pathogens (especially bacteria and parasites). We have employed two novel antigen discovery platforms to identify protective antigens, one based upon parasite genetics and the other based upon analysis of the T cell receptor repertoire (Protecta Technology). Both of these methods have the capacity to differentiate between responses that are generated against protective or irrelevant antigens, and both indicate that with complex pathogens most of the response is directed against antigens that are not protective. This point is important, since it is of little use to focus vaccine development on non-protective antigens, and the methods are currently being used to identify new protective antigens for inclusion into vaccines.

We have recently developed a range of tools to analyse the repertoire of the adaptive immune response in a range of different vertebrate species including rodents, humans and chickens. Our studies of T cell and B cell receptor repertoire are currently focused on defining how different patterns of response or degrees of clonality arise during infection or vaccination, and how these influence the effectiveness of the response. By studying these processes in different vertebrate hosts, vaccination schedules and infection models, we aim to determine conserved and species distinct characteristics of the response. For example, how do the number of available variable gene segments affect the diversity of the responses seen in different animal species, and how relevant are these to developing vaccines?

Pattern recognition in the immune system
The other main thrust of our research programme is the comparative biology of pattern recognition, in particular the ways that different animals respond to molecules that might be included in vaccine adjuvants. In this area, we have recently published work on the nature of chicken Toll like Receptor 15 which is present in birds (and reptiles) but not mammals. This type of work may lead to species-specific adjuvants for use in livestock. Many of the projects have relevance to better understand the evolution of immunological processes and infectious disease.

My research group is based in the Department of Zoology, University of Oxford, where we explore a variety of topics including immunology and vaccine development against a variety of diseases of birds and mammals. I joined the Department in 2008 after spending 10 years at the Institute for Animal Health, Compton Laboratory, leading a group focused on enteric immunology. Prior to this, I spent 4 years as a postdoctoral associate with Professor Adrian Hayday at Yale University in Connecticut, USA.
Meningococcal, pneumococcal and influenza vaccines

Meningococcal disease

The European licensing of a vaccine against capsular group B meningococcal disease in 2013 represented a major breakthrough in the prevention of childhood meningitis. In the seven years prior to this the Oxford Vaccine Group (OVG) enrolled over 10,000 children and adults in clinical trials of this vaccine, and published seven manuscripts reporting clinical trial data critical for this vaccine’s licensure. Research continues post-licensure, with an ongoing clinical trial studying the vaccine’s immunogenicity in ‘at-risk’ children with complement deficiencies, and splicing dysfunction, and another European Union funded study evaluating gene expression in infants following immunisation with this vaccine. In March 2015 it was announced that this vaccine will be administered to all UK infants at 2, 4 and 12 months of age from late 2015.

The OVG has also recruited over 780 infants and adults to clinical trials evaluating the immunogenicity of a recently licensed capsular group A, C, W and Y meningococcal vaccine (MenACWY). Over the last year there has been a dramatic increase in the incidence of serogroup W meningococcal disease in the UK, such that this serogroup now accounts for a quarter of all invasive meningococcal disease in England and Wales. In response to this increase, it was announced in 2015 that the MenACWY vaccine would be incorporated into the routine adolescent immunisation programme later in this year.

The OVG has also been extensively involved in studies informing vaccine protection against capsular group C meningococcal (MenC) disease, conducting the only clinical trials of a combination Hib-MenC vaccine used as a 12-month booster dose in the UK schedule. Further studies demonstrating waning of vaccine induced antibodies through school years and into adolescence directly informed the introduction of a routine adolescent booster dose of MenC vaccine in 2014, thus providing both direct protection against this devastating illness and maintaining herd immunity for younger children.

Pneumococcal Disease

The introduction of pneumococcal glycoconjugate vaccines over the past decade has had a dramatic impact on this major cause of childhood meningitis and septicaemia. A 13-valent pneumococcal conjugate vaccine was introduced into the United Kingdom routine immunisation schedule in 2010, replacing the 7-valent vaccine. The Oxford Vaccine Group was the lead site for the clinical trials informing the use of this vaccine in the UK immunisation schedule, as part of an ongoing European Union funded study providing vital information on the persistence of the vaccine induced antibodies through pre-school years and response to a booster dose administered at that time.

Serogroup B streptococcus

Serogroup B streptococcus is a major cause of neonatal meningitis, affecting approximately 1 in 2000 births in the United Kingdom. The peak incidence of this disease is in the first week of life, therefore prevention through infant immunisation is not feasible. An alternative strategy is immunisation of pregnant women to induce trans-placental transfer of antibodies to the unborn child, thereby providing them with ‘passive immunity’ in their first few months of life. Vaccines for this purpose are currently in development, however the acceptability of such an intervention is uncertain. The Oxford Vaccine Group therefore obtained funding from Meningitis Now to conduct a qualitative study of pregnant women and health care professionals involved in their care. Results from an online survey have already been published, while individual interviews and focus group discussions have informed a questionnaire survey currently being conducted across 7 sites in the United Kingdom.

Influenza

In 2009/2010 the Oxford Vaccine Group was the lead site for an expedited multi-centre study providing ‘a head to head’ comparison of the two influenza A H1N1 ‘swine flu’ vaccines available to respond to the influenza pandemic. Over 940 children were recruited in 3 weeks, 270 of whom were recruited by Oxford. The early provision of reactogenicity data to the Department of Health directly informed the decision to offer these vaccines to all children under 5 years of age in the winter of 2009/2010, while a ‘follow-on’ study conducted in 2010/11 provided novel data demonstrating a clear difference in persistence of protective antibody response between the two vaccines studied.

Subsequent work has compared the gene expression profile of 1 to 2 year olds immunised with either an adjuvanted or un-adjuvanted vaccine in 2012/2013, and supported development of ‘quadrivalent’ influenza vaccines (containing four rather than the traditional three influenza vaccine strains).

Over the last two influenza vaccine seasons the OVG has participated in clinical trials of the intra-nasal influenza vaccine in egg allergic children. This live attenuated vaccine is routinely recommended for all children aged 2 to 4 years, however it contains small amounts of egg albumin. Accordingly, the vaccine was initially contra-indicated for children with egg allergy, who comprise approximately 3% of the paediatric population in the United Kingdom. The safety data accrued through conduct of these national, multi-centre studies has now provided reassurance that this vaccine can be given in a primary care setting to children suffering non-anaphylactic egg allergy, thus removing this potential obstacle to immunisation.

Key publications:


I am Head of the Vaccinology group at The Pirbright Institute. My research interests are directed at developing new and improved vaccines against respiratory syncytial virus, and vaccines against African swine fever virus (ASFV), in collaboration with Linda Dixon’s group at Pirbright Institute. My research group at The Pirbright Institute, have shown that a single intranasal vaccination induced pneumonic lesions. Despite having reduced ability to replicate in the lungs of calves, virus lacking SH appeared to be immunogenic and effective in inducing resistance to viral infection challenge 6 months later. Furthermore, a single intranasal vaccination induced protection even when given to calves with MDA. These findings suggest that BRSV/SASH may be an ideal live attenuated virus vaccine candidate for calves, combining safety with a high level of immunogenicity.

Human respiratory syncytial virus
BRSV is closely related to Human (H)RSV, which is a major cause of respiratory disease in infants throughout the world, causing severe disease in an estimated 14 million children under the age of 1 years, every year. Annual epidemics of RSV infection occur during the winter and early spring, causing most severe disease in infants less than 6 months of age. Nearly all children have been infected with HRSV by 2 years of age and the virus readily re-infects throughout life, even with closely related virus strains. The burden of RSV disease in the elderly is comparable to that of seasonal influenza, while the economic impact of RSV disease in adults is even greater. There is no effective HRSV vaccine, and progress in vaccine development has been hampered by a vaccine programme in the 1960s involving an inactivated viral vaccine that enhanced disease following RSV infection, rather than preventing it, in children not previously exposed to the virus. There is a need for a safe and effective RSV vaccine not only to protect infants, but also to boost immunity in adults and the elderly, thereby reducing the circulation of RSV in the community. My group, in collaboration with ReThera (previously Okairos), has used a new approach to induce protective immunity. A replication-defective chimpanzee adenovirus (ChAd) vector, to which there is limited pre-existing immunity in man, and an attenuated parvovirus vector, MAV, expressing a string of conserved RSV proteins, were evaluated for their ability to protect calves against bovine (B) RSV. Studies in calves showed that intranasal vaccination with ChAd/RSV, followed by intramuscular boosting with MAV/RSV, induced antibodies able to neutralise RSV as well as T cells that help to clear the virus. This novel vaccine was safe and induced complete protection against BRSV infection in calves. The vaccine is now in Phase I clinical trials in the UK. The exploitation of BRSV infection in the natural host, calves, to evaluate an RSV vaccine being developed for use in man, highlights the value of the One Health approach of uniting research in veterinary and human medicine in the development of vaccines.
I am a cellular immunologist with more than 24 years’ experience of working on tuberculosis (TB), both human and bovine. At present, I lead a work group at the Animal Health and Veterinary Laboratories Agency (AHVLA) engaged in vaccine development for cattle TB vaccines, immunodiagnostic development and biomarker studies looking at correlates of protection and disease development.

MARTIN VORDERMEIER
Human and bovine tuberculosis

I am interested in host responses to mycobacterial infections, in particular Mycobacterium bovis, in cattle. Most of my work is geared towards developing better vaccines or vaccine strategies that improve on BCG, and the development of associated vaccine-strategy compatible immune-diagnostics reagents not compromised in their specificity by vaccination (so-called DIVA reagents). Underpinning both of these applications are studies to understand the mechanisms of protective immunity, and in particular why vaccination fails in a proportion of vaccinated individuals. These biomarker studies are therefore aimed at generating robust stage gating parameters, whose application would accelerate vaccine development by reducing the reliance on expensive and resource-intensive large animal CL3 accommodation. Our approaches are closely linked and harmonised as much as possible with the effort to produce better human vaccines, in particular with Prof. McShane’s group at the Jenner Institute.

Vaccines against bovine TB, Mycobacterium bovis

Over the last few years we have concentrated on vaccination strategies that combine BCG priming with heterologous boosting, using recombinant viral vectors such as MVA and human adenovirus type 5. We have demonstrated that a strategy of combining BCG with Ad5 expressing the protective antigen Ag85A can significantly improve vaccine efficacy measured in an experimental challenge model, compared to BCG vaccination alone. Using samples generated from these experiments, we have also undertaken biomarker discovery studies applying both hypothesis and data-driven approaches. For example, we have shown that memory ‘T cells measured by cultured ELISPOT correlated with protection and the duration of immunity when measured after vaccination but before infection, using the outcome of infection measured at post-mortem as a relevant clinical endpoint.

Data-driven approaches have concentrated on a host (cattle) RNASeq methodology, which identified a number of immune markers that predicted the outcome of vaccination, such as IL17A and IL22. The validation of these markers in a larger sample set is a priority for the future. We will also expand our biomarker repertoire by conducting, for example, more in-depth RNASeq studies, and including parameters such as micro-RNA expression to study gene regulation. We are in the process of characterising the cells that are being measured in the cultured ELISPOT, and those that are producing IL-22, with a view to gaining more insights into the biology of these populations and to design simpler biomarker assays more amenable to routine testing.

Animal transmission model for bovine TB

We have established a transmission model in Ethiopia that allows us to test vaccine (BCG) efficacy in a natural transmission setting. We are also interested in antigen discovery, and have recently begun to look at antigens recognised by non-conventional immune cell populations such as natural killer T cells, by mining antigens based on lipids and glycolipids. This will form a main area of our future research, in particular to determine whether such antigens contribute to immunity and whether they can be used as additional subunit vaccines against bovine TB.

Key publications:
RESEARCH PROGRAMMES AND CORE FACILITIES
CLINICAL TRIAL COLLABORATIONS IN AFRICA
Malaria, HIV–1 and TB

Over the last few years, the Jenner Institute’s activities in Africa have been guided by its strategy of translational research, specifically in progressing candidate vaccines for the prevention of malaria, TB and HIV–1 from initial Phase I/II clinical trials in Europe to Phase I/IIb clinical trials in target populations in Africa. Transitioning these vaccines into African clinical trials requires satisfactory safety, immunogenicity and in some cases efficacy data from the Oxford vaccine trials. This has resulted in several collaborations with old and new partners, either directly or as part of an international consortium of partners (Table 1). Major clinical trial consortia involving Jenner Institute staff/scientists include the Malaria Vectored Vaccines Consortium (MVVC/MVVC2) for malaria, PedVacc 001 and PedVacc 002, and HIV-CORE004 for HIV, as well as several collaborations enabling the assessment of the TB vaccine MVA85A in different populations (Table 1). These collaborations have ensured the performance of clinical trials to international standards at African trial sites and provided invaluable clinical trial data for these vaccine fields.

Malaria vaccine trials

Within the period 2011-2013, four malaria vaccine trials were initiated in Africa. These vaccine trials tested the prime-boost combination of viral vectors expressing the antigen ME-TRAP (CAAl63 ME-TRAP and MVA ME-TRAP), which targets the liver-stage life cycle of P. falciparum malaria. VAC042 (2011-2013) was a safety and immunogenicity clinical trial in infants aged either 10 weeks or 5-12 months. VAC046 and VAC047 (2012-2013) were efficacy, safety and immunogenicity clinical trial in adults in Kenya and Senegal, respectively. Both of these clinical trials involved an intensive study design that required the administration of the study vaccines, clearance of malaria parasites using anti-malaria drug combination therapy, and follow-up for the detection of malaria parasitaemia by PCR over a two-month period. VAC050 (2012-2014) is a safety, immunogenicity and efficacy clinical trial in children aged 5-17 months in Burkina Faso. Interwoven with clinical trial performance, staff at the Jenner Institute has been involved with capacity building and infrastructure/laboratory upgrades at African clinical trial institutions. Aside from assistance with the purchasing of state-of-the-art laboratory equipment and training on the conduct of immunoassays and Polymerase Chain Reaction (PCR) molecular biology techniques, Jenner staff have ensured that the quality assurance processes at these African laboratories meet the required international standards for on-going and future studies. This was mainly achieved by on-the-job training, combined with laboratory and clinical trial staff exchange visits with the specific clinical trial sites. These staff training and exchange visits have resulted in better quality data from assays conducted in laboratories in Africa.

HIV–1 vaccine trials

Three HIV–1 vaccine trials have been carried out since 2011. The EDCTP (European and Developing Countries Clinical Trials Partnership) funded project entitled “Building capacity of African HIV–1 Vaccine Clinical Trial Centres in Nairobi, Kenya and Fajara, The Gambia”, with the acronym “PedVacc”, ran from 2008 to 2012. As part of the study, facilities were substantially refurbished and redesigned, significantly increasing capacity and efficiency. Staff were trained in many activities (laboratory, GCP, data management, project management) and six Masters and PhD students were supported. Another EDCTP and International AIDS Vaccine Initiative funded study, HIV-CORE 004, is currently underway in Nairobi and is designed to evaluate the safety and immunogenicity of different delivery regimens using three novel HIV–1 vaccine candidates: a) pSG2 HIVconv DNA with and without electroporation; b) adenovirus Ad5–GRIN; and c) poxvirus MVA HIVconv administered in heterologous prime-boost regimens.

TB vaccine trials

For the TB group, this period saw the first efficacy trial of a new TB vaccine in infants in 40 years, with the TB020 phase IIB double-blind, placebo controlled efficacy trial of MVA85A at SATVI, South Africa. 2797 BCG vaccinated infants were enrolled at 4-6 months of age, and followed up every 3 months for up to 37 months. MVA85A has also been in trial in HIV-infected adults in Cape Town (UCT) and Dakar (CHU Le Dantec). During both these trials, significant capacity building has been achieved at the clinical sites in terms of clinical and laboratory facilities, as well as staff training, substantially improving these sites for future clinical trial capabilities. Additionally, during this period MVA85A has been in trial TB029, a phase II randomised controlled trial to evaluate the safety and immunogenicity of MVA85A prime and delayed BCG boost vaccination in HIV-exposed infants in South Africa. More recently, in 2014, an exciting new collaboration with UVRI Uganda was initiated using MVA85A to investigate the effect of Schistosoma mansoni infection on immune responses to vaccination in Ugandan adolescents. This is the first IMP trial for this Ugandan team, and the sharing of clinical trial expertise from the Oxford team has provided invaluable capacity building. All these collaborations with our African partners have been crucial in moving the TB vaccine field forwards.

Training and technology development

An important reality in conducting research in Africa is the difficulty African scientists face in attending training at institutions outside their regions of origin. Recognising this, the Jenner Institute initiated the five day Masters level “Vaccinology in Africa” course in September 2013. More detail is given in the Education section (p81). Finally, in addition to new vaccines that will enter the Jenner Institute vaccine portfolio in the near future, we recognise the urgent need for transfer of technology enabling the development of pre-clinical vaccinology and vaccine design to institutions in Africa. This includes the ability to set up vaccine manufacturing capacity in African countries. This is a huge task, but funds permitting we hope that we will be able to initiate the process in incremental steps over the next few years.
The prostate cancer vaccine programme was launched in 2012, building on the success of heterologous viral-vectorised vaccination employing adenovirus and MVA vectors in various infectious disease settings. The programme is led by Dr. Irina Redchenko.

Prostate cancer is the most prevalent non-cutaneous malignancy, and the second most common cause of cancer-related death among men in developed countries. The treatment options for advanced prostate cancer are limited, with immunotherapy one of the few options. The only licensed vaccine for the therapeutic treatment of prostate cancer, Sipuleucel-T, is an individualised treatment that costs over $50,000 per patient and provides a modest survival benefit of 4.5 months. A more efficacious and affordable vaccine is clearly needed.

A therapeutic vaccine for prostate cancer
The development of a vaccine against cancer is a challenge because tumours originate from normal tissues that are invisible to the immune system. Our work has started by selecting several prostate tissue associated antigens (PAP, PSCA, STEAP and PSMA) and expressing them from simian adenovirus (ChAdOx1) and MVA virus vectors in a mouse model, in order to break immunological tolerance to these self-antigens. Following on from the immunogenicity studies, we have demonstrated that a T cell immune response induced against some of these antigens is modestly protective in a mouse tumour challenge model. The on-going preclinical studies are focused on improving the vaccine’s tumour protective efficacy, by countering the suppressive tumour microenvironment with monoclonal antibodies against immune checkpoint inhibitors (PD-1 and PDL-1 mAbs).

In parallel, with support from a recently awarded European Commission grant, we are currently progressing a heterologous viral vector-based vaccination strategy into clinical trials in prostate cancer. A Phase I clinical trial in early stage prostate cancer patients deploying ChAdOx1 and MVA vectors targeting a ‘pan-tumour’ antigen, ST4 (previously evaluated in the clinic in a homologous MVA vaccination setting) should initiate in the first quarter of 2015, followed by a Phase II efficacy study one year later.

VACCINE DELIVERY PROGRAMME
Sugar–membrane stabilisation of vaccines
In both developed countries and the developing world there is an urgent need for vaccines that are thermostable. The impact of vaccination is compromised significantly by the need to maintain a cold chain for vaccine distribution and administration. Huge numbers of vaccine doses are consequently lost, thereby vaccination is more expensive, fewer individuals are effectively immunised and lives are lost.

Introducing thermostable vaccines into vaccination programmes for developing countries would reduce, and could eventually eliminate, the need for the cold chain. The advantages of such a breakthrough are well known and documented: maintaining the cold chain for vaccine distribution and administration. Huge numbers of vaccine doses are consequently lost, thereby vaccination is more expensive, fewer individuals are effectively immunised and lives are lost.

How the technology works
As with other approaches to stable vaccine formulation, sugar-membrane stabilisation technology adheres to the basic principle that macromolecules require water to perform physiological activities and to retain their structural integrity. The simple principle of removing water from a molecule’s environment can inhibit its intrinsic activity, keep it immobile and thus enhance its shelf life. We have explored the ability of disaccharides, in particular trehalose and sucrose, to form inert glasses on specific membranes after dehydration to less than 1% water content. A sugar glass is an infinitely viscous anhydrous liquid in which molecules, including proteins and viral particles, can be immobilised and remain stable for long periods of time. A crucial component of the technology is the use of membranes composed of thin fibres, to provide a large surface area that can be thinly coated or intercalated with sugar glass containing vaccine. Impregnated membranes can potentially be stored at ambient temperatures for long periods of time, and the vaccines can be rapidly reconstituted in a liquid buffer phase with very little loss of active material. The sugar-membrane technology was originally developed as a collaboration with Cambridge Biostability from 2005–2009, as part of the Gates Grand Challenges in Global Health programme.

Successful vaccine stabilisation
We have stabilised a range of different vaccines at temperatures of 25–55°C over weeks, and in some cases many months, including: a) live attenuated viral vectors (Adenovirus and modified vaccinia virus Ankara, MVA) that are in Phase II clinical development for diseases such as malaria and HIV; b) a live attenuated virus vaccine (measles); and c) recombinant protein particles (hepatitis B and human papilloma virus) formulated with and without different adjuvants. We have worked in collaboration with a biopharmaceutical company to stabilise one of their vaccine products.

How the technology works
As with other approaches to stable vaccine formulation, sugar-membrane stabilisation technology adheres to the basic principle that macromolecules require water to perform physiological activities and to retain their structural integrity. The simple principle of removing water from a molecule’s environment can inhibit its intrinsic activity, keep it immobile and thus enhance its shelf life. We have explored the ability of disaccharides, in particular trehalose and sucrose, to form inert glasses on specific membranes after dehydration to less than 1% water content. A sugar glass is an infinitely viscous anhydrous liquid in which molecules, including proteins and viral particles, can be immobilised and remain stable for long periods of time. A crucial component of the technology is the use of membranes composed of thin fibres, to provide a large surface area that can be thinly coated or intercalated with sugar glass containing vaccine. Impregnated membranes can potentially be stored at ambient temperatures for long periods of time, and the vaccines can be rapidly reconstituted in a liquid buffer phase with very little loss of active material. The sugar-membrane technology was originally developed as a collaboration with Cambridge Biostability from 2005–2009, as part of the Gates Grand Challenges in Global Health programme.

Successful vaccine stabilisation
We have stabilised a range of different vaccines at temperatures of 25–55°C over weeks, and in some cases many months, including: a) live attenuated viral vectors (Adenovirus and modified vaccinia virus Ankara, MVA) that are in Phase II clinical development for diseases such as malaria and HIV; b) a live attenuated virus vaccine (measles); and c) recombinant protein particles (hepatitis B and human papilloma virus) formulated with and without different adjuvants. We have worked in collaboration with a biopharmaceutical company to stabilise one of their vaccine products.

How the technology works
As with other approaches to stable vaccine formulation, sugar-membrane stabilisation technology adheres to the basic principle that macromolecules require water to perform physiological activities and to retain their structural integrity. The simple principle of removing water from a molecule’s environment can inhibit its intrinsic activity, keep it immobile and thus enhance its shelf life. We have explored the ability of disaccharides, in particular trehalose and sucrose, to form inert glasses on specific membranes after dehydration to less than 1% water content. A sugar glass is an infinitely viscous anhydrous liquid in which molecules, including proteins and viral particles, can be immobilised and remain stable for long periods of time. A crucial component of the technology is the use of membranes composed of thin fibres, to provide a large surface area that can be thinly coated or intercalated with sugar glass containing vaccine. Impregnated membranes can potentially be stored at ambient temperatures for long periods of time, and the vaccines can be rapidly reconstituted in a liquid buffer phase with very little loss of active material. The sugar-membrane technology was originally developed as a collaboration with Cambridge Biostability from 2005–2009, as part of the Gates Grand Challenges in Global Health programme.

Successful vaccine stabilisation
We have stabilised a range of different vaccines at temperatures of 25–55°C over weeks, and in some cases many months, including: a) live attenuated viral vectors (Adenovirus and modified vaccinia virus Ankara, MVA) that are in Phase II clinical development for diseases such as malaria and HIV; b) a live attenuated virus vaccine (measles); and c) recombinant protein particles (hepatitis B and human papilloma virus) formulated with and without different adjuvants. We have worked in collaboration with a biopharmaceutical company to stabilise one of their vaccine products.
Staphylococcus aureus is one of the most important human pathogens, of which MRSA (meticillin-resistant Staphylococcus aureus) species are resistant variants. Common disease manifestations include skin abscesses (boils), with less common but more serious disease including wound infections (sometimes after surgery), bone infections, joint infections (septic arthritis) and heart infection (endocarditis). Disease is caused both in the community, and in hospitals, where it is estimated that about half of all infections are due to Staphylococcus aureus. The organism is also found in farm animals, including cows and pigs.

S. aureus vaccine development is complicated by an incomplete understanding of both the mechanisms of disease pathogenesis, and the mechanisms by which the host protects itself from S. aureus. This was illustrated by a recent Phase III efficacy trial (the V710 trial) in which a vaccine against a cell-surface protein appeared to be immunogenic in man, but increased the severity of disease and did not offer significant protection.

Viral vectors developed in the Jenner Institute allow us to generate potent immune responses against a wide range of antigens, including those from S. aureus. We have identified a cell-surface lipoprotein that appears to have some efficacy as a vaccine; the protective responses appear associated with high levels of T cells against this antigen. This is in keeping with data published by other groups suggesting that T cell action, as well as the induction of antibodies, may be very important in S. aureus protection. Because of this data, we are currently working as part of an EU-funded programme (www.bellerophon-project.eu/about-bellerophon) to generate S. aureus vaccines eliciting both T and B cell responses, using vectored vaccines. A multi-antigen vaccine is being evaluated, with a view to possible phase I assessment later in the programme. We are also working on an antigen-discovery programme, which is supported by a bacterial RNA profiling project.
Since 1995, the Clinical BioManufacturing Facility (www.cbf.ox.ac.uk) has had an unrivalled track record in bringing novel products to the clinic for both medical researchers and some commercial collaborators. The CBF enables academic-lead translational research in Oxford to progress effectively, both in terms of numbers of products it has succeeded in manufacturing, and also the speed of progress from the research lab to the manufacture of novel first-in-class products for phase I first-in-man clinical trials.

In 2004, the CBF became the first (and for a while the only) university facility to hold a Medicines and Healthcare products Regulatory Agency (MHRA): Manufacturing Authorisation, permitting it to manufacture Investigational Medicinal Products (IMPs) for phase I, II, and III clinical trials. This authorisation permits it to manufacture a broad range of cutting-edge biotechnology products for clinical application, including more complex Advanced Therapy Medicinal Products (ATMPs). Products include: viral vaccines, adjuvants, gene therapy products, cellular therapies, viral therapies, proteins, and monoclonal antibodies. Over the last 19 years, the facility has proved itself as a key asset for the translational research programmes of the University of Oxford, facilitating cost-effective and rapid translation of basic research to clinical trials in research areas for which there is no or limited GMP (good manufacturing practice)-compatible manufacturing methodology or history, because they are ground breaking, highly novel in nature or possibly even a ‘disruptive technology’. The CBF opened in 1995 as the Therapeutic Antibody Centre (TAC), and for 11 years manufactured monoclonal antibodies and other related biologicals that have been used worldwide in clinical trials involving more than 5,000 patients. With the maturing of monoclonal antibody manufacturing technologies, the facility moved from the Sir William Dunn School of Pathology to the Jenner Institute in the Nuffield Department of Medicine, and started manufacturing viral vectors for use as novel vaccines and gene-based therapeutics. In October 2007, the first clinical trial volunteer was immunised with a novel malaria vaccine manufactured by the CBF (AdCh63 ME-TRAP). Since then, over 1000 volunteers have been immunised with this vaccine in more than 15 clinical trials. In total, over 1400 volunteers have received eleven different CBF-manufactured vaccine vectors since 2007.

Manufacturing at the CBF
Manufacturing IMPs (investigational medicinal products) to GMP standards for clinical trials on the Churchill Hospital site is a major enabling factor for translational research in the Jenner Institute, and also helps strengthen the Biomedical Research Centres partnership between the Oxford University Hospitals Trust and the broader University of Oxford. It also enables close interaction between the research workers (located in the ORCRB) and the clinical team (located at the CCVTM), and thus considerably speeds up the translation pathway from fundamental scientific advances into clinical research with the ultimate aim of benefiting patients by providing new and better treatments.

Manufacturing and Process Development

| AdCh63 ME-TRAP (large batch) | Malaria Vaccine | CBF | CBF | N/A | CBF (2011) | University of Birmingham |
| AdINRM | Cancer Therapy | CBF | CBF | CBF | CBF (2012) |
| ChAdOx1 NP + M1 | Malaria Vaccine | CBF | CBF | CBF | CBF (2012) |
| ColoMSV | Cancer Therapy | CBF (2012) | CBF | Ark | Ark Finland |
| ChAdOx1 pDNA | Malaria Vaccine | CBF | CBF | CBF | CBF (2019) |
| ChAdD1 | T B Vaccines | CBF | CBF | CBF | CBF (2019) |
| ChAdOx1 Rry | Malaria Vaccine | CBF (2013) | Okaros/GSK | Okaros | Advant Italy |

Clinical Trial Labelling and Certification
Before a product can be used in a clinical trial, it has to be certified by a Qualified Person (QP) and labelled according to the European Clinical Trials Directive (2004). The CBF not only releases its own products to trial, but also assists clinical researchers with the importation, QP certification and labelling of IMPs from within and outside the European Union (EU). Between 2011 and mid-2014, 11 new batches of CBF products and 29 batches of external IMPs (imported from the US and EU countries) were certified for 27 different vaccine trials, two of which took place in endemic areas. As part of the importation process, several manufacturing sites in the US, Italy, Sweden, Norway and the Netherlands were audited by our QPs to ensure that the investigational medicinal products (IMPs) were manufactured to EU GMP.

<table>
<thead>
<tr>
<th>Disease Area</th>
<th>Number of certified/labelled CBF batches</th>
<th>Number of certified/labelled non-CBF batches</th>
<th>Number of clinical trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria</td>
<td>3</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Influenza</td>
<td>1</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>1</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>HIV</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>other (HCV, choroideremia, prostate cancer)</td>
<td>5</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td>29</td>
<td>27</td>
</tr>
</tbody>
</table>
Transcriptomics is the measurement of the expression of thousands of genes simultaneously by quantifying RNA levels, to create a global picture of cellular function and examine differences between samples, for example blood lymphocytes isolated from vaccinated or diseased individuals compared to controls. The Transcriptomics Core Facility (TCF) was established in late 2013, with the support of a Wellcome Trust Strategic Award, and consists of two bioinformaticians and a wet lab scientist. The purpose of this facility is to support Jenner Investigators in identifying correlates of immunogenicity and efficacy for a broad range of human and veterinary vaccines, and to evaluate new immunomodulatory molecules suggested by transcriptomics data.

The Jenner Institute has pioneered the development of many novel vaccine candidates. Clinical trial data from some of these candidates are encouraging, although there are often variations in immunogenicity and efficacy between individuals in a given trial. We can also use transcriptomics to understand why some vaccinees are not protected when challenged with infectious agents, while others are protected. Understanding these differences can lead to new ideas for developing improved vaccines.

Dr Adaikalavan Ramasamy is Head of the Transcriptomics Facility and Senior Leadership Fellow in Bioinformatics. Adai joined the Jenner Institute in December 2013.

Services offered by the facility
The TCF provides: (1) funding for consumables; (2) wet lab services; and (3) bioinformatics analysis. The TCF can fund a maximum of 50% of the study lab consumables costs for Jenner Investigators. The standard wet lab services include the following RNA processing steps: extraction, globin clearing, amplification, hybridisation onto microarray chips and quality assessment after each step. As of July 2014, the TCF has provided partial funding amounting to £72,175, and wet lab services to generate transcriptomics data using Illumina HT12-v4 microarray chips for 2,513 samples from 10 different vaccine trials (including malaria, TB, influenza, RSV001, meningococcal disease, and Hepatitis B and C).

Bioinformatics, statistical and other analytical services are available at no cost to Jenner investigators. These include design, data management, quality control and analyses as well as re-using publicly available datasets for replication or meta-analyses with their own datasets. We also have experience of analysing RNA-sequencing, ChIP-Seq and eQTL datasets.

To date, we have conducted a preliminary analysis of transcriptomics data from two malaria vaccine trials that have been generated in-house. In addition, we have also analysed existing data from a Kenyan malaria challenge trial and from the IDEA consortium, a large European Commission 7th Framework Programme (FP7), to look at genes related to malaria and TB in the presence and absence of worm infection.
The majority of new vaccine candidates developed by Jenner Investigators have been viral vectors, which have the capacity to induce strong protective T cell responses against pathogens. For example, the Institute’s Malaria Vaccine Programme has taken MVA, fowlpox (FP9) and simian adenoviral vectors to clinical trials using a prime-boost approach (adenovirus or FP9 priming and MVA boosting). Using adenovirus vectors as the priming immunisation results in strong antibodies as well as T cell responses, extending the range of applications for this technology.

Services provided by the facility
Once a candidate antigen has been identified, DNA is synthesised and cloned into a suitable shuttle vector by an Institute scientist. VVCF production commences with the introduction of this shuttle vector into a suitable cell culture system to generate recombinant viral vectors. These vectors are amplified and purified using standardised protocols to produce individual batches of vector, which are subjected to Quality control (QC) tests that assay infectivity and sterility, and also confirm that the inserted DNA sequence is in place.

Until recently, all vectors made by VVCF were Adenovirus, MVA or fowlpox vectors modified at a single site in the vector backbone. The VVCF has now begun production of Adenoviral and MVA vectors expressing proteins at two different sites, and these dual expressing constructs allow the delivery of multiple antigens within a single batch of viral vector.

The majority of viral constructs produced are used in preclinical studies to identify the most promising vaccine candidates. Where a successful vaccine candidate has been identified, the VVCF can produce a preclinical batch of virus, using methods approved by the MHRA, which can be used as an input for clinical manufacture (the VVCF itself is not a GMP production facility).
An adjuvant (from the Latin adjuvare, meaning “to help”) can be any compound or vaccine additive used to enhance the immune response to a vaccine antigen. Simple adjuvants, such as aluminium salts, have been employed to enhance vaccine efficacy for nearly a century. More recently, advances in our understanding of the innate immune system have given rise to new vaccine adjuvants, able to induce a stronger as well as more targeted immune response to the vaccine antigen, opening up possibilities for developing vaccines against more complex infectious diseases such as malaria or HIV. The Jenner Adjuvant Bank currently holds over 50 different adjuvants with immunostimulatory and/or antigen delivery properties, from oil and water emulsions, liposomes, TLR agonists and polymers, to more complex multicomponent adjuvants such as saponin and lipid-based Immunostimulating Complexes (ISCOMs). In terms of novel adjuvants, particular focus has been placed on proprietary pilot research compounds obtained through material transfer agreements. For selected preclinical applications, we have been successful in negotiating access to adjuvants with proven safety and efficacy, licensed for human use. More recently, the Bank has been granted access to adjuvants through the TRANSVAC infrastructure funded by the European Commission FP7 programme, and coordinated by the European Vaccine Initiative (EVI). This involves access to biosimilars of established potent adjuvants, formulated and tested by the Vaccine Formulation Laboratory (VFL), a WHO Collaborating Centre in Lausanne.

Preclinical and clinical testing of adjuvants
Experimental assessment of adjuvants from the Bank has been carried out with vaccines against malaria (liver, blood and transmission stage), influenza, tuberculosis (TB), Streptococcus pyogenes, Meningitis B and prostate cancer. Good protective efficacy with our leading liver-stage malaria vaccine, tested with a range of adjuvants in preclinical challenge models, led to a Phase 1 clinical trial of the vaccine combined with Matrix M, an ISCOM adjuvant, which showed a good safety profile. Veterinary applications to date include Rift Valley Fever Virus in preclinical (mice) and clinical (sheep) settings, as well as the evaluation of adjuvants in combination with a Foot-and-Mouth Disease Virus (FMDV) vaccine in cattle, and E. coli infection in turkeys. Two manuscripts resulting from the preclinical work above have been published, and three more are currently in preparation. An internal Adjuvant Workshop was held in January 2013 on past and current use of adjuvants within the Institute. Our work on adjuvants has led to a patent application on “Viral Vector Immunogenic Compositions”, filed by Isis Innovation Ltd. in September 2011.

We welcome opportunities for collaboration or business partnership; enquiries can be directed to Dr. Anita Milicic: anita.milicic@ndm.ox.ac.uk

The Jenner Institute Insectary is used for the rearing of mosquitoes. Researchers then use these mosquitoes to test vaccines against malaria, a disease caused by Plasmodium parasites that are transmitted from one person to another by female Anopheles mosquitoes. Our colony of Anopheles stephensi mosquitoes are reared in state-of-the-art temperature and humidity-controlled incubators. The female mosquito lays her eggs in water, where they hatch after a few days. These aquatic larvae feed and develop through four stages, or instars, before pupation and emergence into adulthood. It takes two weeks after hatching for the mosquitoes to become adults.

The mosquitoes are used to produce sporozoites, which grow inside the mosquito salivary gland and are infective to the vertebrate host. We use sporozoites to test vaccines targeting the liver and blood stages of malaria infection.

The facility is also used to test transmission-blocking malaria vaccines that aim to halt the sexual development of the malaria parasite in the mosquito. The mosquitoes are kept in highly secure cabinets for the time required for the parasites to develop within the midgut and then dissected. Effective vaccines block the appearance of sporozoite-producing oocysts in the midgut.
Scientists working in the advanced animal health laboratories of ILRI, in Nairobi, Kenya (photo credit ILRI David White)

The Jenner Institute encourages students to apply for DPhil (PhD) and Masters degrees, and also welcomes undergraduate students carrying out short research projects. Students are enrolled either at the Jenner Institute in Oxford (University of Oxford) or at the Pirbright Institute. During 2011–2013, 15 students working at the Jenner in the Old Road Campus Research Building were awarded DPhil degrees; approximately 50% of the students were British in nationality, with other students coming from a wide range of countries including China, India, Nigeria and Thailand. The Jenner Institute also regularly participates in public engagement events to keep members of the public informed about our activities, and ways in which they can become involved, for example through volunteering to participate in a clinical trial.

The Pirbright Institute has a vigorous postgraduate student programme. This has a three-fold purpose: to produce excellent research scientists in animal health; to make the unique facilities in the Institute available more widely; and to strengthen the links between the Institute and the Universities. The Pirbright Institute has recently formed partnerships with a number of academic and commercial bodies to offer studentships in viral diseases of livestock. These include: the Universities of Oxford, Cambridge, Warwick and Oxford Brookes; Oxford Expression Technologies; and Pfizer Animal Health Europe.

Vaccinology in Africa Course

The Jenner Institute initiated the five-day Masters level “Vaccinology in Africa” Course in September 2013. This course, jointly organised by the Jenner Institute, Fondation Mériteux and the African host institution, is aimed at students, researchers and professionals who are resident in Africa. The course covers the main aspects of vaccinology, the vaccine development process, biomanufacturing, regulatory and ethical issues. It is unique in that it is held in Africa. The course provides an opportunity to gain academic and industrial experience. The programme is led and organised by the research scientists in animal health; to make the unique facilities in the Institute available more widely; and to strengthen the links between the Institute and the Universities. The Pirbright Institute has recently formed partnerships with a number of academic and commercial bodies to offer studentships in viral diseases of livestock. These include: the Universities of Oxford, Cambridge, Warwick and Oxford Brookes; Oxford Expression Technologies; and Pfizer Animal Health Europe.

Vaccinology in Africa Course

The Jenner Institute initiated the five-day Masters level “Vaccinology in Africa” Course in September 2013. This course, jointly organised by the Jenner Institute, Fondation Mériteux and the African host institution, is aimed at students, researchers and professionals who are resident in Africa. The course covers the main aspects of vaccinology, the vaccine development process, biomanufacturing, regulatory and ethical issues. It is unique in that it is held in Africa. The course provides an opportunity to gain academic and industrial experience. The programme is led and organised by the research scientists in animal health; to make the unique facilities in the Institute available more widely; and to strengthen the links between the Institute and the Universities. The Pirbright Institute has recently formed partnerships with a number of academic and commercial bodies to offer studentships in viral diseases of livestock. These include: the Universities of Oxford, Cambridge, Warwick and Oxford Brookes; Oxford Expression Technologies; and Pfizer Animal Health Europe.

The Jenner Institute provides a three-fold purpose: to produce excellent research scientists in animal health; to make the unique facilities in the Institute available more widely; and to strengthen the links between the Institute and the Universities. The Pirbright Institute has recently formed partnerships with a number of academic and commercial bodies to offer studentships in viral diseases of livestock. These include: the Universities of Oxford, Cambridge, Warwick and Oxford Brookes; Oxford Expression Technologies; and Pfizer Animal Health Europe.

Vaccinology in Africa Course

The Jenner Institute initiated the five-day Masters level “Vaccinology in Africa” Course in September 2013. This course, jointly organised by the Jenner Institute, Fondation Mériteux and the African host institution, is aimed at students, researchers and professionals who are resident in Africa. The course covers the main aspects of vaccinology, the vaccine development process, biomanufacturing, regulatory and ethical issues. It is unique in that it is held in Africa. The course provides an opportunity to gain academic and industrial experience. The programme is led and organised by the research scientists in animal health; to make the unique facilities in the Institute available more widely; and to strengthen the links between the Institute and the Universities. The Pirbright Institute has recently formed partnerships with a number of academic and commercial bodies to offer studentships in viral diseases of livestock. These include: the Universities of Oxford, Cambridge, Warwick and Oxford Brookes; Oxford Expression Technologies; and Pfizer Animal Health Europe.

Vaccinology in Africa Course

The Jenner Institute initiated the five-day Masters level “Vaccinology in Africa” Course in September 2013. This course, jointly organised by the Jenner Institute, Fondation Mériteux and the African host institution, is aimed at students, researchers and professionals who are resident in Africa. The course covers the main aspects of vaccinology, the vaccine development process, biomanufacturing, regulatory and ethical issues. It is unique in that it is held in Africa. The course provides an opportunity to gain academic and industrial experience. The programme is led and organised by the research scientists in animal health; to make the unique facilities in the Institute available more widely; and to strengthen the links between the Institute and the Universities. The Pirbright Institute has recently formed partnerships with a number of academic and commercial bodies to offer studentships in viral diseases of livestock. These include: the Universities of Oxford, Cambridge, Warwick and Oxford Brookes; Oxford Expression Technologies; and Pfizer Animal Health Europe.

The Jenner Institute provides a three-fold purpose: to produce excellent research scientists in animal health; to make the unique facilities in the Institute available more widely; and to strengthen the links between the Institute and the Universities. The Pirbright Institute has recently formed partnerships with a number of academic and commercial bodies to offer studentships in viral diseases of livestock. These include: the Universities of Oxford, Cambridge, Warwick and Oxford Brookes; Oxford Expression Technologies; and Pfizer Animal Health Europe.
FINANCE

Jenner Laboratories at the Churchill Hospital site receive funding from a variety of sources.

The breakdown of more than 30 million pounds of funding for the 2011–2013 period is shown below.
PUBLICATIONS
Publications

Martin Bachmann


Persephone Borrow


Elle Barnes


Linda Dixon


Bryan Charleston


immunization with ChAd63 and MVA ME-TRAP from malaria naive to Plasmodium chabaudi AS Apical Membrane Antigen 1: Mechanisms
Duncan and Draper. Controlled human blood stage malaria infection: Forbes et al. T cell responses induced by adenoviral vectored vaccines
Douglas et al. Comparison of Modeling Methods to Determine Liver- Sheehy et al. Challenges of assessing the clinical efficacy of asexual
reduces intensity of Plasmodium berghei infection in mosquitoes. Int J Williams et al. Immunisation against a serine protease inhibitor
Publications

Glyn Hewison


Adrian Hill

Hodgson et al. Evaluation of the efficacy of ChAd63-MVA vectored vaccines, ChAd63 ME-TRAP and MVA ME-TRAP, in healthy Gambian

Bradley et al. Exploring the use of molecular epidemiology to track TB spread and contain epidemics in an area of high TB incidence in India.


in HIV and/or Mycobacterium tuberculosis-infected adults. Am J
Reyes-Sandoval et al. Mixed vector immunization with recombinant tuberculosis using Mycobacterium bovis bacille Calmette-Guerin. J
Lillie et al. Distinguishing malaria and influenza: early clinical features
Publications

Elias et al. Assessment of immune interference, antagonism, and
Grossman et al. Identifying recent adaptations in large-scale genomic
Publications

Daugla et al. Effect of a serogroup A meningococcal conjugate vaccine on meningococcal carriage: an observer-blind, phase 3 randomised
Read et al. Effect of a quadrivalent meningococcal ACWY polysaccharide vaccine on carriage of meningococcal serogroups C, W135, and Y.
Martin Maiden
Daugla et al. Effect of a meningococcal C-polysaccharide conjugate vaccine on carriage of Neisseria meningitidis serogroup C: a randomized controlled
Martin Maiden
Daugla et al. Effect of a meningococcal C-polysaccharide conjugate vaccine on carriage of Neisseria meningitidis serogroup C: a randomized controlled
Helen McShane


Mertens et al. Full genome sequence of a western reference strain of New Member of the Umatilla virus Species. PLoS One 2011; 6: e23605.


Sanchez et al. BCG vaccination protects against severe V. cholerae infection in mice with small intestinal villous atrophy. J Immunol 2013; 191: 2657-65.


Shaw et al. BCG-induced redistribution of lymphoid tissue is associated with higher BCG efficacy. Vaccine 2014; 32: 3462-68.


Publications

Andrew Pollard, Christine Rollier, Matthew Snape and the Oxford Vaccine Group


Publications


DeMaster et al. Vaccine design to prevent against tuberculosis subversion may aid the establishment of novel vaccine vectors for the development of novel vaccine vectors. Vaccine 2012; 30: 6294-6300.


Martin Vordermeier


DeMaster et al. Vaccine design to prevent against tuberculosis subversion may aid the establishment of novel vaccine vectors for the development of novel vaccine vectors. Vaccine 2012; 30: 6294-6300.

DeMaster et al. Vaccine design to prevent against tuberculosis subversion may aid the establishment of novel vaccine vectors for the development of novel vaccine vectors. Vaccine 2012; 30: 6294-6300.

DeMaster et al. Vaccine design to prevent against tuberculosis subversion may aid the establishment of novel vaccine vectors for the development of novel vaccine vectors. Vaccine 2012; 30: 6294-6300.

DeMaster et al. Vaccine design to prevent against tuberculosis subversion may aid the establishment of novel vaccine vectors for the development of novel vaccine vectors. Vaccine 2012; 30: 6294-6300.
The Foundation seeks to enhance philanthropic support of vaccinology and is currently evaluating options for enhanced fundraising activities. The Foundation currently supports vaccine research and development through the Jenner Institute. The Foundation Board appoints the Director of the Institute, elects Jenner Investigators and has funded space and facilities for vaccine research and development.

The Foundation actively supports enhanced collaborative interactions between researchers at the Pirbright Institute working on veterinary vaccines and those at the University of Oxford developing new vaccines for human use. The Foundation has also provided support for scientists from the former Edward Jenner Institute for Vaccine Research to continue their work as part of the Jenner Institute. The Foundation draws Trustees from both the University of Oxford and the Pirbright Institute, and has an external chair and three further independent trustees.

## Trustees
- Prof David Salisbury CBE (Chairman)
  Director of Immunisation, UK Department of Health (until end 2013)
- Dr Norman Bagg
  VP and Chief Medical Officer, GSK Biologicals
- Prof John Fazakerley
  Director, The Pirbright Institute
- Prof Paul Fine
  Professor of Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine
- Prof Sir Andrew McMichael FRS
  Professor of Molecular Medicine and Group Head
- Dr Bryan Charleston
  Head of Livestock Viral Diseases Programme, The Pirbright Institute
- Prof Andrew Pollard
  Director of the Oxford Vaccine Group, University of Oxford
- Dr Ian Tarpey
  Head Global Poultry / Discovery and Technology, MSD Animal Health, Netherlands

## Scientific Advisory Board

The aim of the Scientific Advisory Board is to advise The Jenner Institute on both specific vaccine programmes and the overall strategy and organisational structure of the Institute's activities.

### Board Members
- Prof Jonathan Heeney (Chair)
  University of Cambridge
- Prof Ivan Morrison (Vice-Chair)
  University of Edinburgh
- Dr Rene Aerts
  Independent Consultant, Veterinary Vaccines
- Dr Jeffrey Almond
  Visiting Professor, University of Oxford
- Dr Steve Chaitfield
  Independent Consultant, Human Vaccines
- Dr Tim Dool
  Independent Consultant, Veterinary Vaccines
- Prof Bruno M Goddeeris
  University of Louvain
- Prof Margaret Liu
  Karolinska Institute, Stockholm
- Dr Bonnie Mathieson
  NIAID, Bethesda
- Dr James Merson
  Pfizer, San Diego
- Dr Alfredo Nicosia
  ReThera, Rome
- Prof Albert Osterhaus
  Erasmus University, Rotterdam
- Dr Allan Saul
  Novartis Global Health Vaccines Institute, Siena

## Company Secretary
- Mr Gary Strickland
  Business Manager, Nuffield Department of Medicine

## EBOLA PostScript and Update

The declaration of the West African Ebola outbreak in August 2014 as a public health emergency of international concern by the World Health Organization (WHO), set in train an ambitious and unprecedented attempt to develop a new vaccine and test it for efficacy in clinical trials during the course of the outbreak. The Jenner Institute was invited to test the first vaccine destined for use in West Africa. This was a chimpanzee adenovirus, ChAd3, encoding the surface glycoprotein of the strain of Ebola causing the outbreak. The vaccine candidate had been developed and tested by Okairos, a biotechnology company and the Institute’s longstanding collaborator on adenovirus vectors, and the National Institutes of Health (NIH) which has undertaken promising non-human primate studies.

Following a request from the WHO in August 2014, it proved possible to start a phase I first-in-human trial of this vaccine in 60 subjects with full approvals by mid-September. This allowed a phase I trial to start in early October in Mali, and by the end of the year sufficient safety and immunogenicity data was available to proceed to start a phase II efficacy trial in Liberia in January 2015.

Oxford played the key role in accelerating the initiation and conduct of the phase I trials, with support from the Wellcome Trust, Department for International Development and the Medical Research Council. The same grant awarded both the manufacture of tens of thousands of vaccine doses, and also a booster trial of an MVA vector, to determine whether better immunogenicity could be achieved, similar to that found to be protective in non-human primates. This goal too was achieved by mid-December, providing a vaccination regime that appears highly promising. In addition, Oxford led an initiative to manufacture tens of thousands of doses of a new MVA vector using an immortalised cell line, allowing future manufacture of much larger batches of MVA than conventional processes. The whole programme entailed close collaboration with GlaxoSmithKline, who had acquired Okairos, the WHO, the NIH and several other clinical trial sites.

By December 2014, Johnston and Jonston had developed a related prime-boost regime using an Ad26 adenoviral vector, again with MVA. They too chose Oxford for their first-in-human trial. This time, Matthew Snape led a study conducted by the Oxford Vaccine Group that rapidly enrolled the required 87 subjects and this vaccine is progressing to further larger scale trials at the Oxford Vaccine Group, in France and in West Africa.

The accelerated delivery of phase I Ebola vaccine trials in the UK has been dependent upon the prioritisation of regulatory and ethical review, aided by frequent and open dialogue between investigators, manufacturers, trial sponsors and senior staff in the reviewing agencies. Regulatory approval for ChAd3-EBOZ was granted in four working days by the Medicines and Healthcare Regulatory Agency (MHRA) and within a week by the Research Ethics Committee. Jenner researchers have benefited from critical support across the relevant Government departments, and from extensive experience with phase I trials of live viral vectors as investigational vaccines for many disease indications.