THE JENNER VACCINE FOUNDATION
SUPPORTING VACCINATION

Institute for Animal Health

UNIVERSITY OF OXFORD

Jenner Vaccine Foundation News

ISSUE 03 | NOVEMBER 2010

HIGHLIGHTS

Malaria vaccine update | New Jenner Investigators appointed

Hep C – first steps for T Cell vaccines | Cancers in chickens - the role of vaccines

Flu - news from the efficacy trials answering key questions

What goes around comes around - a new marker vaccine approach for Foot-and-mouth Disease (FMD)

Dr Paul Barnett, Head of the FMD Vaccine Group, Institute for Animal Health

When I first became involved in FMD vaccine research some 30-odd years ago there was a firm belief that the next generation vaccines would be peptide orientated and largely based on the immunodominant and structurally prominent G-H loop sequence of VP1 that protrudes from the virus surface and allows cellular attachment. The early success, however, never translated itself to the target host, particularly cattle, and interest thereafter waned.

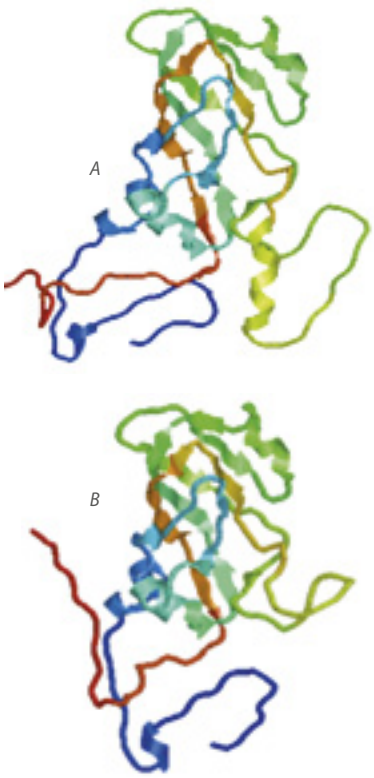
Fast-forward to now and this G-H loop sequence could play a pivotal role in the development of an FMD marker vaccine, though in a surprising way.

A major disadvantage of current FMD vaccines is their inability to elicit immunity that not only confers protection against clinical disease but prevents a sub-clinical infection and the so-called carrier state in which the virus persists. This failing, more than anything, has led to a reluctance to use vaccination to control incursions in normally disease-free countries because of the fear that vaccinated animals could still disseminate disease. Whilst this concern has not been substantiated experimentally, it nevertheless has led to improvements to the current vaccines, allowing some discrimination of vaccinated animals that become subsequently infected. Purification of the antigen component of the vaccine to remove any residual FMD virus non-structural proteins (NSPs) allows detection of antibodies against NSPs in vaccinated animals to be used as a marker for infection. However, this approach lacks the sensitivity to be used at the level of the individual animal.

With (A) and without (B), ribbon diagrams highlight the predicted structure of the G-H loop (green/yellow) of VP1 alongside the partial deletion of the VP1 G-H loop. The polypeptide chain is coloured from blue (amino-terminus) to red (carboxy-terminus).

Recent work at the Institute for Animal Health, Pirbright, has investigated the potential of an FMD virus missing a 13 amino acid portion of the G-H loop sequence of VP1 as a marker vaccine (International patent WO2009150429), based on the theory that the absence of this immune-dominant site might allow identification of vaccinated animals that become sub-clinically infected, through detection of antibodies against the G-H loop.

Preliminary studies under a PhD studentship and through a recent BBSRC-funded project show that this could be a good diagnostic approach. Significantly, with the assistance of the Transboundary Animal Diseases section at the Onderstepoort Veterinary Institute, South Africa, we have substantiated that such a vaccine will indeed protect cattle from clinical disease. The next challenge is to secure further funding to allow the construction of similar G-H loop deficient viruses representing key vaccine strains and verify these findings.



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OXFORD VACCINE GROUP

Meningitis C vaccine 'wears off in early teens'

Andrew J Pollard , Professor of Paediatric Infection & Immunity, Director of the Oxford Vaccine Group, University of Oxford

Three-quarters of children vaccinated against meningitis C lose their protection against the disease by their early teens, research led by Jenner Investigator, Professor Andrew Pollard, suggests.

The Oxford team says its findings fuel calls for a booster jab to be offered to adolescents. The study of 250 children aged six to twelve, presented to the European Society for Paediatric Infectious Diseases (ESPID) recent meeting in Nice, France, looked at immunity seven years after the jab was given. UK experts agreed a booster may be needed in the future. The research was carried out by the Oxford Vaccine Group at Oxford University.

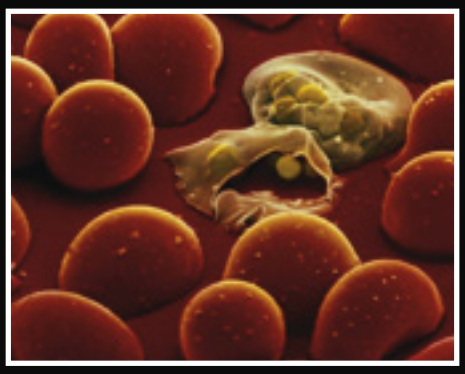
The group tested the children, who had all been vaccinated against meningitis C, for levels of antibodies against the bacteria in their bloodstream. It was found that just 25% of the children had sufficiently high levels of the antibodies to give them protection against the disease. The researchers say that British children are still protected against the potentially fatal bacteria at the moment, through the existence of herd immunity. That means that vaccination has significantly reduced the level of meningitis in the population, and so even people who are not vaccinated are also protected. But the researchers, led by Professor Andrew Pollard, say that if herd immunity starts to decline, many children will be vulnerable.

Professor Pollard said: "This study is just the latest to show that the personal protection given by meningitis C vaccines in early childhood does not last forever and several countries have now responded to these findings by introducing teenage boosters, before protection fails in the population."

Falling immunity levels against meningitis C have been reported in Greece, the Netherlands and Spain. Austria, Canada and Switzerland have already introduced booster jabs. Sue Davie, chief executive of the Meningitis Trust said: "The Oxford team's research raised significant concerns. Vaccination is the only way to prevent meningitis and save lives. We support the use of safe and effective vaccines and encourage people to receive the vaccines that are currently available. If, as a result of this research, a booster programme is introduced, we would actively encourage it."

The Malaria Vaccine Programme

Adrian Hill, Director of the Jenner Institute and Professor in Human Genetics, University of Oxford



Malaria remains one of the great global public health problems. In 2010 there will be almost a million deaths from malaria and over 100 million clinical cases. Children, particularly in sub-Saharan Africa, are the hardest hit. Although the use of traditional control measures, such as spraying and bed nets, has reduced the disease burden somewhat in recent years, an effective vaccine is urgently needed.

The Jenner Malaria Vaccine Programme is one of the closest to the goal of developing a highly effective vaccine that could save millions of lives in malarious areas. The programme is based on viral vectors that induced strong cellular and antibody immune responses by using prime-boost vaccination strategies pioneered by the Institute. This work is complementary to efforts by GSK and others to develop an antibody-inducing malaria vaccine called RTS,S.

The Jenner Programme has been in clinical development for about 10 years starting with DNA vaccines and gradually improving the performance of the vaccine candidates so that now over 50% of vaccinees showed efficacy in a recent trial.

Malaria is a remarkably difficult target for vaccine development. There are no vaccines against any parasitic disease; attenuated whole parasites don't work as malaria vaccines and natural malaria infection doesn't ever provide full immunity. So, completely new technologies have had to be developed to provide even partial protection against malaria. However, two types of malaria vaccine now show real promise and one of these has been developed mainly in Oxford.

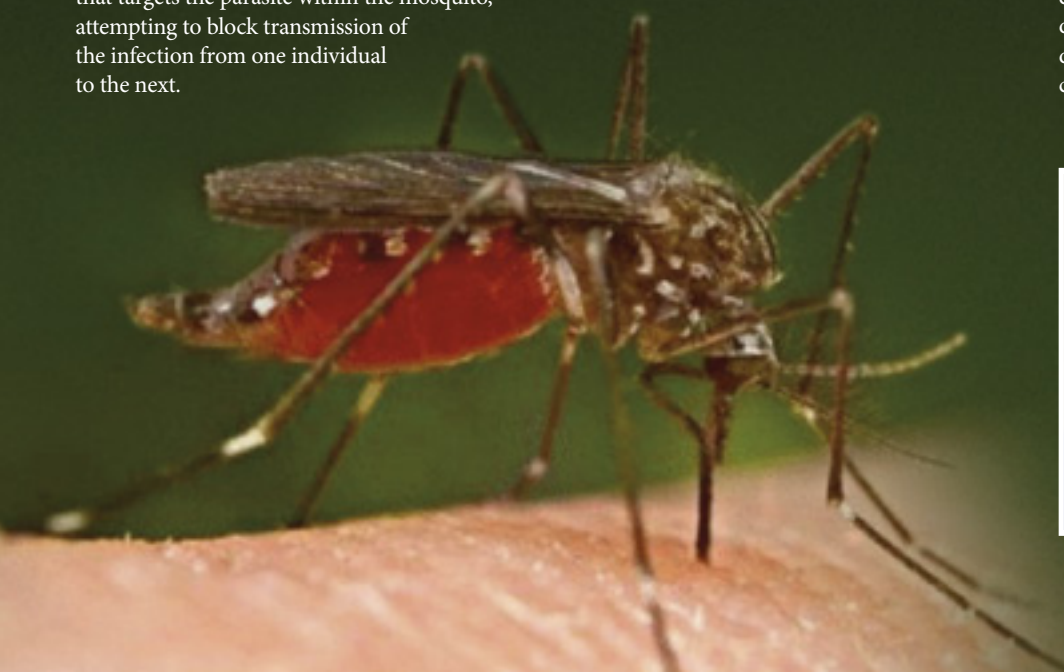
The Institute is currently developing a variety of different types of malaria vaccine. Initially the focus was on liver-stage vaccines where cellular immunity is the main requirement, but more recently vaccine candidates against blood-stage antigens have shown real promise. And very recently a new programme has started that targets the parasite within the mosquito, attempting to block transmission of the infection from one individual to the next.

The Malaria Programme is unusual in that volunteers are invited not only to be vaccinated to test various types of vaccine but many also volunteer for a so-called "challenge study" where people are infected with malaria parasites administered by the bite of laboratory reared mosquitoes. This is allowed because a drug-sensitive strain of malaria is used that can be quickly treated once parasites are seen in the blood. This challenge procedure has been key to developing the two leading malaria vaccines and the Jenner Institute is one of just two centres globally that has made extensive use of this type of challenge protocol. To date over 300 individuals from Oxford have been recruited and challenged safely, providing key information on which type of vaccine to develop further.

The Institute has been at the forefront of developing new vaccine vectors for immunisation, particularly in the malaria programmes. Adrian Hill's group did the first DNA vaccine trials in Europe and have now introduced three different viral vectors to clinical testing, most recently an attenuated adenovirus of chimpanzee origin. Using chimpanzee vectors has the advantage that the potential difficulty of the vaccine being impaired by prior natural exposure to human adenoviruses (which cause colds) is minimised.

After phase I and II testing in Oxford, promising malaria vaccine candidates progress to field testing with collaborating institutions in sub-Saharan Africa. Several trials of the malaria programme's vaccines have been undertaken in both West and East Africa. Currently trials of the new chimpanzee adenovirus vector together with a booster immunisation with an MVA vaccine are in progress at the MRC Laboratories in The Gambia which has a long record of testing new vaccines and excellent facilities for immunology. In parallel, another trial is in progress with the Kenyan Medical Research Institute in Kilifi on the Kenyan coast, as part of one of the major overseas programmes funded by the Wellcome Trust and partnered with Oxford University. All this requires substantial financial support which has been provided by several funders including the Wellcome Trust, the MRC, the UK NIHR, the European Commission, the European Vaccine Initiative, the Gates Foundation and the European and Developing Countries Clinical Trials Partnership.

Malaria vaccine development is a lengthy process, partly because of the technical challenges in making new types of vaccines, but also because documentation of safety is critical at every stage. If anyone is to provide a vaccine that can be given to tens of millions of infants in developing countries, safety of that new vaccine is paramount and this must be documented thoroughly in thousands of individuals as part of the vaccine development plan. So the Jenner malaria programme represents a huge team effort with contributions across the spectrum from vaccine design to measuring immune responses, demonstrating initial safety and efficacy in the clinic to executing larger-scale field trials.



Hepatitis C Virus:
First steps for T cell vaccines

Paul Klenerman, Senior Research Fellow and Practicing Clinician, Oxford
Ellie Barnes, MRC Clinician Scientist and Honorary Consultant in Hepatology, Oxford

Hepatitis C virus (HCV) is thought to infect nearly 200 million people globally and is a major cause of liver disease. The virus is able to set up chronic infections in the majority of those exposed, and although typically the early disease is silent, over time it can cause liver failure and also liver cancer. Although antiviral treatment has improved substantially since the virus was first discovered two decades ago, it is still based on injectable interferons and so is costly, toxic and still only partially effective.

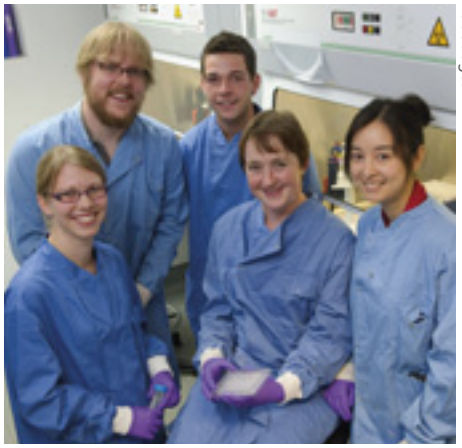
HCV is spread globally largely through infected blood products and intravenous drug use, with smaller amounts spread sexually or from mother to child. Much progress has been made in blood product safety in those countries which can afford it, but the virus continues to spread in at-risk groups and in certain high-prevalence areas such as Egypt. Given the burden of disease and the difficulty of treatment, a vaccine would be a worthy goal. Additionally, as well as potentially providing protective immunity, such a vaccine might also act as an adjunct to therapy. So is it possible?

Immunity to HCV – without a vaccine

For those exploring a vaccine against HCV, there is a very good starting point –a proportion of those infected naturally (typically around 25%) can contain the virus "spontaneously". Unlike hepatitis B virus (HBV), where a successful vaccine already exists, the humoral response is not a good correlate of protection. Neutralizing antibodies are made and target the viral envelope, but due to the ability of HCV – which is RNA based – to generate extensive mutations in vivo, there is rapid escape. Both CD4+ and CD8+ T cell responses are more closely associated with resolution of infection. There is no one specific response which can be regarded as "protective" but the general features of such responses are that they should be at high levels, show broad specificity against different viral proteins (often non-structural (NS) proteins), be sustained over time and maintain functions such as interferon-gamma release and proliferation. From these kinds of data, the idea of a T cell based vaccine for HCV has emerged.

Generating T cells against HCV

A group originally at Merck and now at Okairos was among the first to take the T cell vaccine idea forward in a paper by Antonella Folgori and colleagues in 2006. In a preclinical challenge model, they were able to generate T cells against HCV NS proteins using DNA and recombinant adenovirus vaccinations, which showed efficacy in vivo. The viral vector used – based on human adenovirus 6 (HuAd6) is suitable for man as the serotype of adenovirus is rare compared to HuAd5, which was used in the STEP trial of HIV. The current human trials taking place in Oxford, have used this or a very similar vector generated by the same group (based on Chimpanzee adenovirus 3), aiming to reproduce the high levels of T cell response seen in preclinical models. Is this achievable in man?



Rob Judges

Prevention and cure?

The first trial of a T cell based vaccine to protect against HCV (HCV001) has now nearly finished in Oxford and Birmingham. This Phase I trial uses the two adenoviral vectors expressing HCV NS proteins in a dose escalation approach, where one vector is used to prime and the other to boost. To date we have seen extremely strong responses to these vectors, with long lasting, broad and functional T cell reactivity in several volunteers. Since these are equal to or greater than those seen in people who can clear the virus spontaneously, we are hopeful this could provide the basis of protective immunity. A second approach – starting shortly – is to try and use a different vector (Modified Vaccinia Ankara or MVA) to provide even better boosting and coverage.

In the meanwhile, we have started to test the idea in a second trial (HCV002) that in those who fail to clear the virus, improving T cell responses through therapeutic vaccination might allow them to regain control. Here the challenges are even greater than in a protective vaccine as the virus will have adapted to the host through mutation and the T cell responses may over time have become "exhausted". However, using a similar approach to HCV001, we are now starting to examine the responses obtained after vaccination (with or without concurrent interferon treatment) - early signs of immunogenicity are very encouraging, and this will be examined further using the MVA vector in HCV003.

The end of the beginning?

There are a number of major issues to overcome in the HCV vaccine field. Probably the most important of these is the huge genetic diversity of the virus, which has evolved in human populations for thousands of years. So far we are focusing on just one of six separate genotypes and we do not yet know how much cross-reactivity and cross-protection will be observed. However, with the current wave of vectors and the new knowledge obtained from the first trials, we are looking forward with optimism to exploring and overcoming these issues in future. HCV T cell vaccines have been given an enormous boost by the experience of the Jenner Institute in malaria and TB studies. We have also received generous support from the European Union, the Medical Research council (UK) and the Oxford NIHR Biomedical Research Centre. We hope to be able to repay these programmes with the new knowledge we generate in the ongoing series of studies.

IAH Scientist Featured On BBC News Item – E. coli explained

In April a BBC website reporter visited Compton to film Mark Stevens describing E. coli O157. The idea is that the short (a couple of minutes) film will be linked to from within web articles covering any future outbreaks amongst people of E. coli O157. The media clip can be viewed at http://news.bbc.co.uk/1/hi/health/8649910.stm

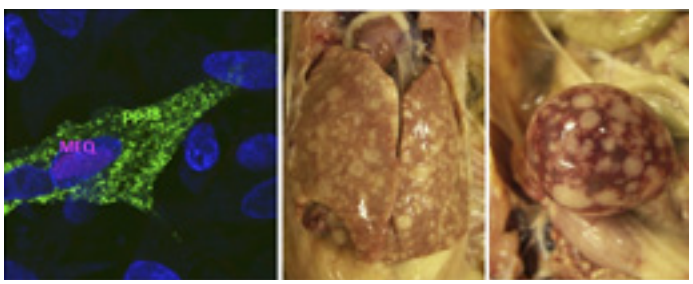
Cancers in chickens

Prof. Venugopal Nair, Head, Avian Infectious Disease Programme
Institute for Animal Health

IAH

Cancer is one of the major challenges facing modern Human Medicine, and is a disease that undoubtedly creates fear in all of us. Many of us are unaware that cancer is also a major threat for animal health, particularly for chickens. Unlike in humans, where more than 80% of the cancers are of non-infectious origin, the vast majority of the neoplastic diseases of poultry are caused by viruses, which form a major threat to the 55 000 million chickens produced annually in the world. The two major groups of viruses associated with cancer in chickens are the retroviruses and herpesviruses. Avian retrovirus diseases have played major historical roles in contributing to the understanding of a number of molecular mechanisms of cancer. These include the demonstration of transmissible tumours by Peyton Rous in 1911 and the discovery of oncogenes by Michael Bishop and Harold Varmus in 1984. Major cancers associated with avian retroviruses such as lymphoid, myeloid or erythroid leukosis and reticuloendotheliosis remain a major challenge to avian health in many countries.

Marek's disease (MD) is a rapid-onset T-cell lymphoma caused by the highly contagious Marek's disease herpesvirus (MDV). MD is present in all poultry-raising countries and is estimated to cause economic losses of up to $2 000 million annually. MDV spreads by inhalation of the poultry house dust contaminated by shedding of the virus from the feather follicle epithelium of infected birds. MDV can persist for long periods in the poultry houses as well as in a latent form for life in infected birds, making eradication of this disease extremely difficult. Vaccination with live avirulent herpesviruses has been the cornerstone of MD control programme for the last 40 years. With over 22 000 million doses used annually, MD is one of the first and best examples of the widespread use of effective anticancer vaccines. Although very effective in preventing the onset of cancer, vaccines have not been able to prevent the evolution of the virus towards increasing virulence. Current research at IAH is focused on identifying the molecular mechanisms of MD and to develop more effective vaccines for sustainable control.



IAH

Marek's disease virus-infected cell showing viral antigens MEQ and pp38.

Marek's disease virus-infected bird showing lymphoma in liver and spleen.

Edward Jenner Museum
The country home of a gentleman of science

Sarah Parker, Director, Edward Jenner Museum

The Museum

The Edward Jenner Museum was established in 1968 to preserve the life and legacy of Dr Edward Jenner. Jenner's most notable contribution to mankind was vaccination against smallpox which eventually led to its world-wide eradication in 1980.

The museum, a Queen Anne Grade II* listed house, is based in Berkeley, rural Gloucestershire. It was here that Jenner was born, lived and worked for most of his life, pioneering vaccination against smallpox in May 1796. He died here in 1823. The Chantry is a national treasure, an important part of history in its own right, as are Jenner's garden and vinery, Temple of Vaccinia and Old Cyder House. As an independent museum and charity, we work hard to ensure the site is preserved for our many visitors worldwide as well as for future generations.

2010 marks the 30th World Health Organization's anniversary of the eradication of smallpox; it also marks the Royal Society's 350th anniversary. As Jenner was a Fellow of the Royal Society, we are proud to be celebrating both with various activities and events throughout the year. It is also the museum's 25th anniversary in The Chantry. To mark it, we have launched a Friends of the Museum project.

The work of the Edward Jenner Museum

Located in the stunning period-setting of Jenner's former home, The Chantry, the museum puts Jenner's life into historical context, illustrating the life of a country doctor and gentleman in the late 18th/early 19th century Gloucestershire.

It is an engaging source of education, entertainment and research for visitors of all ages and interests who wish to explore Jenner's scientific practices and discoveries and the impact they had on the world. They include his ground-breaking work in medicine, air-ballooning, natural history - including bird migration and hibernation - and geology.

2010 has been a busy year for many reasons and 2011 is set to continue in this vain. Next year marks the 45th anniversary of the decision of the World Health Assembly to embark on a global smallpox eradication programme. We will also be officially unveiling a newly restored and re-thatched Jenner's Temple of Vaccinia, where he vaccinated the local people for free.

Contact Details

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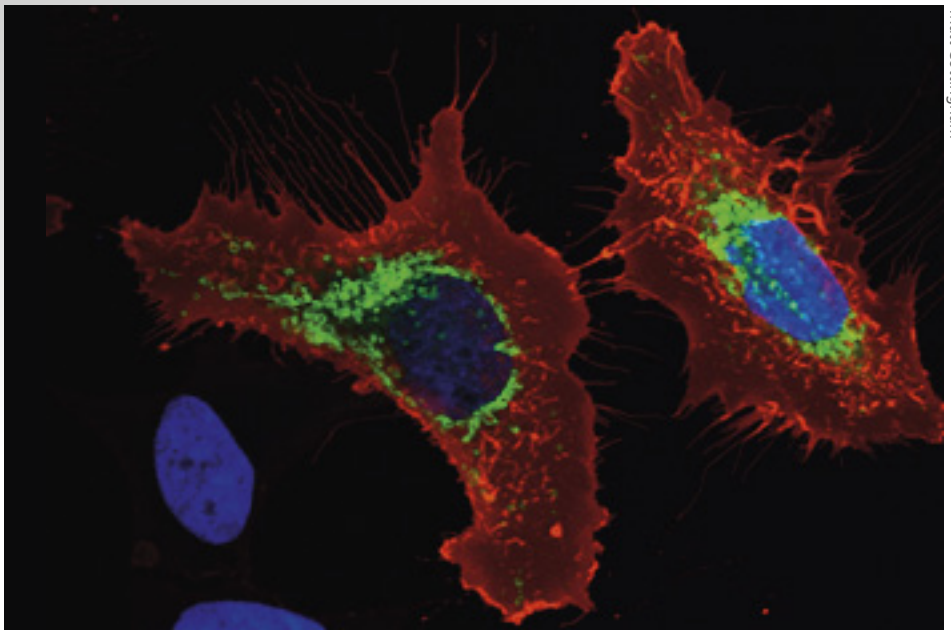
Viral Vector Core Facility of the Jenner Institute

The Viral Vector Core Facility was established in October 2008 as a centralised facility for the production of novel, recombinant Modified Vaccinia Ankara (MVA), Fowlpox and Adenovirus vectors. The three vector backbones are all established in the fields of veterinary and human vaccinology and have well documented safety profiles.



Matt Cottingham

HeLa cells infected with a simian adenoviral vector expressing a GFP fusion protein (green) and the co-stimulatory ligand CD70 (red), with nuclei stained in blue.

The Core Facility uses standard protocols and adheres to strict working practices to produce the viral vectors, thus ensuring quality of production. However we are continually striving to improve all aspects of the production processes, including capacity, efficiency and quality control. Due to recent advances we have made in various areas of the production process, we are currently able to produce new vectors in as little as five weeks.

The vaccines we produce are designed to express novel recombinant proteins that target Jenner Institute priority research areas (Malaria, Tuberculosis (Human and Bovine), Influenza (Human and Avian), HIV and Foot-and-mouth Disease) for use by Jenner Investigators. In addition to this we also produce viral vectors for Jenner Investigators interested in targeting other research areas and vectors for external collaborators.

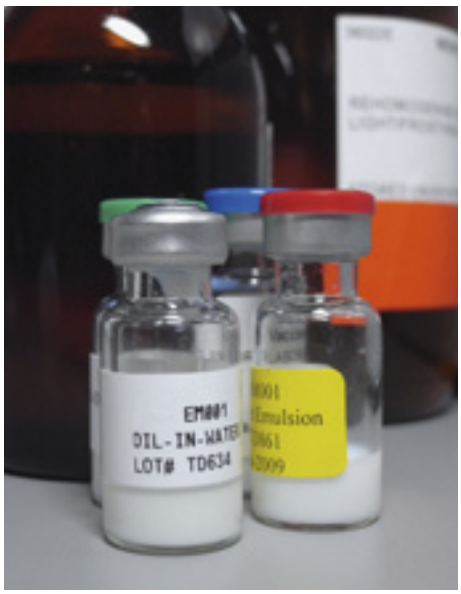
In the two years we have been running, the Core Facility has generated approximately 110 new adenoviral vectors, 90 novel MVA vectors, 5 Fowlpox vectors and prepared approximately 100 new batches of vectors from existing stocks as have been required. We provide viral vectors in batches ranging in size from those sufficient for small, preliminary testing to those for much larger experiments.

Any enquiries regarding vaccine production can be sent to ali.turner@ndm.ox.ac.uk.

Adjuvant Bank - a Core Facility at the Jenner Institute

Adjuvants (from the Latin *adiuvare*, meaning "to help") have been used to enhance the protective efficacy of vaccines for over 80 years. Historically, many diverse compounds – from breadcrumbs to live tuberculosis bacteria - have been tried as vaccine adjuvants. More recently, the advances in our understanding of the innate immune system have given rise to new vaccine adjuvants, able to induce stronger as well as more targeted immune response to the vaccine antigen, opening the possibilities for developing vaccines against more complex infectious diseases, such as malaria or HIV.

Over past decades, development of these new, more potent, adjuvants has been the prerogative of major pharmaceutical companies, with very limited access for public sector research, in which the Jenner Institute is positioned. To remedy this, and to build in-house capacity for adjuvant application, optimisation and evaluation, the Jenner Adjuvant Bank was established through a Wellcome Trust Strategic Award. The Jenner Adjuvant Bank currently holds nearly 40 adjuvants from various commercial and academic sources, and continues to search for new compounds. The particular focus is on pilot research adjuvants, which are often supplied in small quantities for an initial evaluation and can require a negotiation of complex material transfer agreements with the source institution. The strategic aim of the adjuvant core facility is to access a large range of promising adjuvants and enable Jenner researchers to evaluate these in veterinary and pre-clinical settings. An early experimental assessment of the adjuvants from the Bank in combination with a model protein antigen highlighted the differences in their ability to induce humoral and cellular immunogenicity. In collaboration with the Institute of Animal Health (IAH, Pirbright, UK) and Indian Immunologicals Ltd. (Hyderabad, India), selected adjuvants from the Jenner Bank were recently tested in combination with the vaccine against Foot-and-mouth Disease Virus (FMDV) in a cattle challenge trial. Pre-clinical studies of adjuvants in combination with our candidate vaccines in disease models of malaria, flu and TB are currently underway. For some of the adjuvants that have already shown good results, in-licensing discussions are in progress and we aim to test one of these in a clinical trial by 2012.



Anita Milicic

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

Core Flow Sorting Facility - at the Jenner Institute

At the Jenner Institute we have a facility with a number of dedicated instruments for analysing or sorting cells based on how they have been tagged with antibodies labelled with fluorescent molecular probes. This process, called flow cytometry, allows simultaneous measurement of certain characteristics of a cell, based on light signals generated, as they flow in single file within a stream of salt solution, through one or more laser beams. Using colour differentiated fluorescent probes allows researchers to look at a range of cell markers at the same time. Prime examples of cell characteristics that can be analysed in this way, include cell size, differentiation markers that indicate the cell type being looked at, and markers that indicate the activation state of that cell.

Flow sorting, using an instrument like the MoFlo, extends the process of flow cytometry to the collection of up to four subsets of analysed cells, in a purified form ready for further study, by the electrostatic deflection of the cells of interest away from the main flow stream and into one of four separate tubes. Alternatively, single cells can be separated and sorted into individual wells on a 96-well plate.

During a vaccine trial, prepared blood samples are run on the LSRII flow analyser to study the immune cells of trial participants. This allows researchers at the Jenner labs to monitor how well the trial vaccine is working.

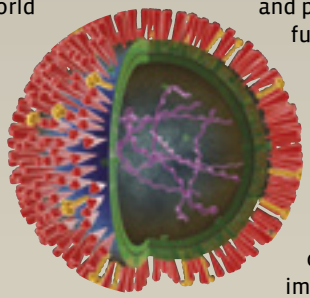
Anita Milicic

News of the efficacy flu trials answering key questions

Dr Sarah Gilbert, Reader in Vaccinology, Jenner Institute.

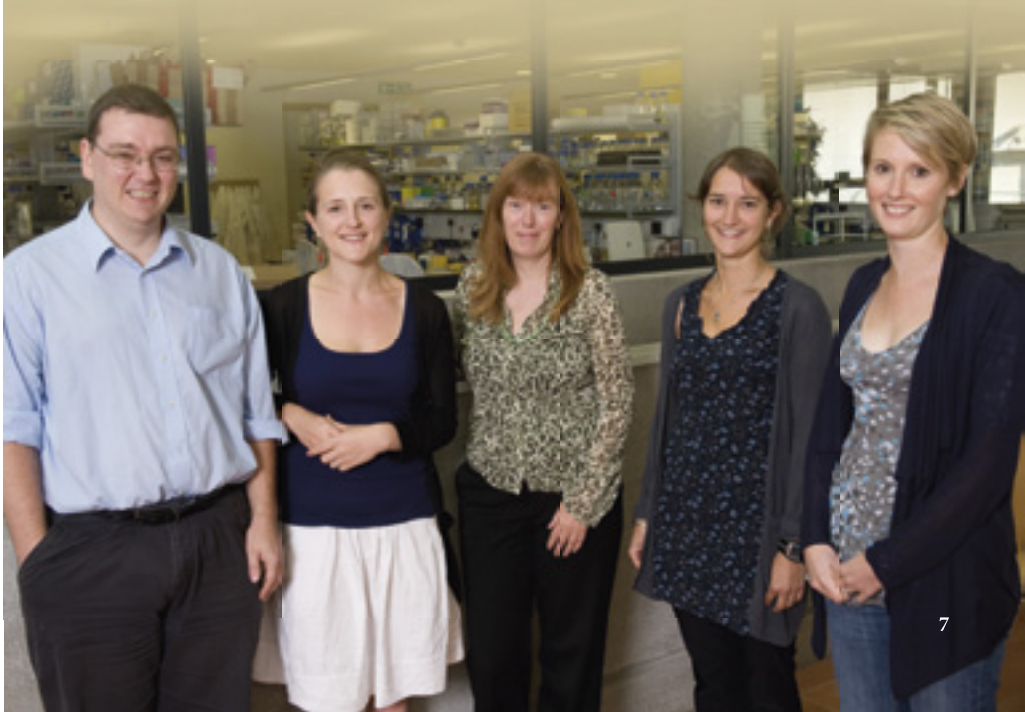
The H1N1 influenza pandemic of 2009/2010 spread rapidly around the world, with no countries unaffected. The initial estimates of the severity of the disease and high mortality rates reported from Mexico fortunately proved to have been overstated, and the impact of the pandemic on global health was considerably less than first feared. Scientists from around the world collaborated to develop a pandemic influenza vaccine, but despite a huge effort it took six months from the identification of the new virus to the availability of the first doses of the vaccine. If the pandemic virus had resulted in a higher mortality rate, the delay in producing a vaccine would have allowed many more deaths to take place.

The influenza vaccines that are in use at present rely on knowing precisely which variants of influenza are causing infections in people and then making a new vaccine consisting of the correct haemagglutinin protein variant. Haemagglutinin, or HA, is the most abundant protein on the surface of the virus, and can be recognized by antibodies that then prevent the virus from causing an infection, but only if the antibodies are an extremely good match for the HA protein. Scientists at the Jenner Institute are taking a different approach to influenza vaccine development which could mean making a single vaccine to protect against any influenza A virus that infects humans. This is possible, because although the proteins on the outside of the virus are constantly changing, the ones on the inside are remarkably conserved, even if the virus was previously found in birds or pigs, and an immune response that was generated in response to one influenza virus can be effective in attacking a different one. However this cross-reactive immune response is not mediated by antibodies, but by T cells that are able to recognize and destroy the first cells that become infected by the virus, and prevent it from spreading further, thereby stopping the infection in its tracks.



Anna Tanczos/Wellcome Images

Using viral vaccine vectors that were originally tested at the Jenner Institute in the development of malaria vaccines, we have now completed the first safety, immunogenicity and efficacy studies of the new vaccine in volunteers. The vaccine was safe; T cell responses to the conserved influenza proteins increased in vaccinated volunteers but not control subjects, and the small efficacy study in which volunteers were exposed to influenza virus dripped into their nose resulted in fewer vaccinated volunteers developing influenza than the non-vaccinated volunteers. We saw that the T cells recognizing influenza in the vaccinated volunteers were better equipped to kill virus infected cells, as well as being present in greater numbers. More clinical studies are planned, but the initial findings support the view that it may be possible to produce a vaccine that protects people against any influenza virus, allowing production and vaccination to go ahead rapidly. This type of vaccine could prove to be extremely important in our future defence against influenza.



Profiling: Jenner Investigators

Adrian Hill


Rob Judges

Adrian Hill trained at Trinity College Dublin and Oxford, and is now Professor of Human Genetics and Director of the Jenner Institute at Oxford University. He leads research programmes in genetic susceptibility to tropical infectious diseases and in vaccine design and development.

His group identified heterologous prime-boost immunisation using non-replicating vectors as an exceptionally potent approach for inducing protective T cell responses in mouse model of malaria and undertook the first clinical trials of this vaccination strategy. In 2005 he was appointed Director of the Jenner Institute, a new initiative aimed at accelerating public sector vaccine development for a variety of human and livestock infectious diseases. The Institute aims to fill the gap between pre-clinical vaccine design and large-scale field efficacy trials, particularly for infections that pose great disease burdens in developing countries. Over fifty clinical trials have been undertaken in recent years by Jenner Investigators who are developing new vaccines against malaria, HIV, tuberculosis, meningitis, pandemic influenza and hepatitis.

He currently also chairs the Centre for Clinical Vaccinology and Tropical Medicine and the Clinical Biomanufacturing Facility in Oxford. He has published over 350 research papers. He is a Fellow of the UK Academy of Medical Sciences and the Royal College of Physicians and a NIHR Senior Investigator.

Key Publications

Khor, C. C., F. O. Vannberg, S. J. Chapman, H. Guo, S. H. Wong, A. J. Walley, D. Vukcevic, A. Rautanen, T. C. Mills, K. C. Chang, K. M. Kam, A. C. Crampin, B. Ngwira, C. C. Leung, C. M. Tam, C. Y. Chan, J. J. Sung, W. W. Yew, K. Y. Toh, S. K. Tay, D. Kwiatkowski, C. Lienhardt, T. T. Hien, N. P. Day, N. Peshu, K. Marsh, K. Maitland, J. A. Scott, T. N. Williams, J. A. Berkley, S. Floyd, N. L. Tang, P. E. Fine, D. L. Goh, and A. V. Hill. 2010. CISH and susceptibility to infectious diseases. *N Engl J Med* 362:2092-2101.

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Sarah Gilbert


Rob Judges

I obtained my BSc Biological Sciences in 1983 from the University of East Anglia and my PhD in Biochemistry in 1986 from the University of Hull. After appointments as a Research Scientist at the Brewing Research Foundation, Leicester University and Delta Biotechnology Ltd, I joined the Hill Group at Oxford University as a Senior Molecular Biologist in 1994. I was appointed a Reader in Vaccinology in 2004 and a Jenner Investigator in 2006.

I have filed 6 patents, 1997 – 2007, published 100 research papers, have been a visiting lecturer at Imperial College and am currently a visiting lecturer at the LSHTM, participant in the Oxford University examining process and have senior management responsibilities within the Jenner Institute.

I lead the Jenner Institute's influenza vaccine programme and have completed the first efficacy study of an influenza vaccine designed to work through cellular immunity, in which vaccine efficacy and a protective T cell phenotype was demonstrated. In a phase I study, this vaccine, MVA-NP+M1, was shown to have a good safety profile and to boost pre-existing T cell responses to conserved influenza antigens. This study is now being extended to examine boosting of immune responses as the immune system ages, and I am seeking a commercial partner for further vaccine development, as well as funding for future clinical trials (US BARDA, Wellcome Trust). I am currently developing a simian adenovirus-vectored influenza vaccine with funding from the Medical Research Council, and pre-clinical vaccine development is funded by the James Martin 21st Century School.

As pre-clinical programme manager for the Wellcome Trust Strategic Award to the Jenner Institute I lead three core facilities to provide recombinant viral vectors, adjuvants and immunomonitoring expertise to Jenner Investigators. I am expert in all aspects of viral vectored vaccine development from design, through construction, quality control, pre-clinical testing, GMP manufacturing, regulatory and ethical applications to Phase I and II clinical trials.

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Venugopal Nair

IAH

I obtained my Bachelors Degree in Veterinary & Animal Sciences from the Kerala Agricultural University, Trichur, India in 1976. After obtaining my PhD in Veterinary Medicine from the Tamil Nadu Agricultural University, Chennai, India in 1987, I started my research career as a post-doctoral scientist at the Indian Institute of Science, Bangalore. I joined Dr. Ernie Gould's group at the Institute of Virology & Environmental Microbiology, Oxford, as postdoctoral research fellow in 1989, where I carried out extensive research on the molecular biology of arthropod-borne flaviviruses until 1994.

I then moved to the Institute for Animal Health (IAH) in 1994 to join the work on avian oncogenic viruses, and became the Head of the Viral Oncogenesis group following Dr. Payne's retirement. I have since been leading the research on the pathogenesis of avian oncogenic viruses such as Marek's Disease (MD), and am the designated expert of the OIE (Office International des Epizooties) Reference Centre on MD. I have also been a Visiting Professor at Imperial College London since 2005. I am currently the Head of the Avian Infectious Disease (AID) Programme at IAH.

My research focuses on MD, which is one of the highly contagious and economically important neoplastic diseases of poultry. These diseases are estimated to cause economic losses up to £ 1billion worldwide. Despite the widespread and successful use of vaccines for the last 40 years, MD virus shows a continuous evolution of virulence. One of the aims of my research is to investigate the molecular mechanisms of the continued increase in virulence. In collaboration, with Prof. Andrew Read, University of Edinburgh, I am examining the role of vaccines in driving MDV virulence.

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Paul Klenerman

Rob Judges

I completed my medical training in Cambridge and Oxford in 1988 and then came back to Oxford in 1991, to specialize in infectious diseases. I did my DPhil with Rodney Phillips and Andrew McMichael (Oxford), on T cell responses to HIV, especially looking at the influence of escape mutants. My postdoctoral work was done with Rolf Zinkernagel and Hans Hengartner in Zurich, looking at virus persistence in the LCMV model. I returned to Oxford in 1999 and have been analysing immune responses to hepatitis C virus (HCV). My laboratory is also engaged with projects that use new tools to analyse immune responses to cytomegalovirus (CMV), parvoviruses and HIV. My work has been funded largely through the Wellcome Trust since 1992, most recently with a senior fellowship.

The current principal area of my research is focused on T cell responses to persistent viruses, especially HCV. This virus infects nearly 200 million people globally and is a major cause of liver disease, including liver cancer. About a quarter of those initially infected clear the virus spontaneously, although the majority become persistently infected. The aim of much of the research is to try and understand the key differences between host responses which lead to a successful outcome (clearance), as opposed to an unsuccessful outcome (persistence). Harnessing the successful T cell responses for protection and therapy forms the basis of the current vaccine trials.

The role of T cells in chronic infection, i.e. in determining long term clinical outcome, also needs to be addressed. Certainly T cells can contribute to tissue damage as well as eliminating virus-infected cells. A major clinical and immunological question is the impact of HIV (globally about 1 in 10 HIV carriers is also HCV infected). This both limits the T cell response in chronic infection and increases the rate of disease progression.

Most recently, my Group has been focusing on the specific functions of liver-homing T cells, many of which express the marker CD161. Understanding how the various novel functions of CD161-expressing cells play a role in protection and pathogenesis of HCV and other chronic infections remains an important goal for the future.

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PedVacc trials of a candidate HIV vaccine against mother-to-child transmission through breast-feeding have started

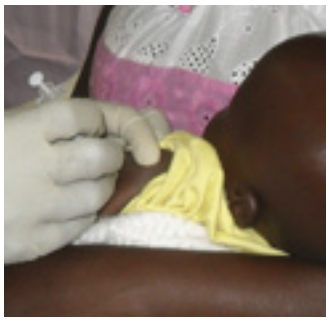
Tom Hanke, Weatherall Institute of Molecular Medicine, University of Oxford

The Medical Research Council (MRC UK), together with researchers from Kenya, The Gambia, United States of America, Sweden, and Spain, has opened enrolment in two infant HIV-1 vaccine trials in Kenya and the Gambia, known collectively as PedVacc. These trials examine the safety of a novel HIV-1 vaccine, MVA.HIVA, in infants.

The ultimate aim of this vaccine strategy in infants is to prevent mother-to-child transmission of HIV after birth. Over 60% of the global HIV-infected population lives in Africa and about half of the infected adults are women of childbearing age. Approximately half of mother-to-child transmission is due to breast-feeding, but formula feeding is not an option for many HIV-1 infected mothers. One of the best hopes for protecting newborns and infants in developing countries against mother-to-child transmission of HIV is through a safe, effective, accessible prophylactic vaccine, which would both reduce the adult burden of infection and/or protect neonates against acquiring HIV from their infected mothers during pregnancy or while breastfeeding.

The vaccine is called MVA.HIVA and was developed at the University of Oxford, UK. The vaccine carrier is a weakened virus previously used as a smallpox vaccine, modified vaccinia virus Ankara (MVA). Small pieces of HIV proteins have been added to this MVA carrier, but the vaccine does not contain the whole HIV virus. The MVA.HIVA vaccine cannot cause HIV infection or AIDS.

MVA.HIVA has been previously tested in 13 trials in 375 adult subjects from UK and Africa. There have been no serious reactions related to this vaccine. It is safe and well tolerated. Furthermore, the carrier MVA was administered to more than 120,000 vaccinees as part of the smallpox eradication programme, with no reported reactions, despite the deliberate vaccination of high-risk groups. More recently, a similar MVA-based vaccine for tuberculosis has been shown to be safe in infants in The Gambia.



First Vaccinations of babies enrolled in the Trial in Sukuta, The Gambia

The PedVacc studies are sponsored by MRC UK and funded by the European and Developing Countries Clinical Trials Partnership (EDCTP). Both trials will entail a single injection into the muscle of infants aged 20 weeks. The trials are taking place in The Gambia and Kenya and will recruit in total 120 healthy, HIV-negative infants born to healthy, either HIV-positive or HIV-negative mothers. Any HIV-positive women in this study will be provided with antiretroviral drugs and extensive feeding counselling during pregnancy and while breastfeeding to reduce the risk of HIV transmission to their infants. Half of the infants in the study will be randomised to receive the MVA.HIVA study vaccine in addition to their regular childhood immunisations. The other half will serve as the comparison group and will only receive their regular immunisations, but not the study vaccine.

Importantly, parents must give consent for their child to participate in the study. The study has been reviewed and approved by local and international ethics and regulatory bodies.

MVA-85A clinical trial update

Helen McShane, Reader in Vaccinology and Wellcome Clinical Senior Fellow

Tuberculosis (TB) is a major global health concern. One third of the world's population are latently infected, each with a 10% lifetime risk of developing active TB disease. In 2008, there were 9.4 million new cases and almost 2 million deaths from TB, the burden of which was in the developing world. With drug-resistant strains of M.tb increasing in prevalence, an effective and affordable vaccine is an urgent global public health priority.

MVA85A, a new TB vaccine developed by Jenner Investigator Dr Helen McShane, is currently being evaluated in Phase IIb trials in Africa and has already been shown to be safe in Phase I and IIa trials in the UK, South Africa, Senegal and The Gambia. MVA85A boosts immune responses previously primed by vaccination with Bacille Calmette Guerin (BCG), which is routinely given to infants in TB-endemic countries. While BCG confers some protection against severe disease in young children, it is only variably effective against pulmonary (lung) TB in all age groups. The trial will determine whether the ability of MVA85A to stimulate potent immune responses results in improved protection.

This double-blind, placebo-controlled Phase IIb efficacy trial for MVA85A commenced in South Africa in July 2009. During the trial 2,784 BCG-vaccinated infants will receive either the vaccine or a placebo at 4-6 months of age and will be followed for two years to compare TB infection and disease rates in vaccinated versus placebo groups. The Western Cape, where the trial site is located, has the highest incidence of infant TB in the world, so the Jenner Institute joined forces with the South African Tuberculosis Vaccine Initiative (SATVI) to conduct the trial precisely where the vaccine would be most needed. This trial, sponsored by Aeras Global TB Vaccine Foundation and funded by Aeras, the Wellcome Trust, and the Oxford-Emergent Tuberculosis Consortium (OETC), has now passed its enrolment halfway-point (see back cover). The very first baby to be vaccinated, Janenique Pienaar, returned in July 2010 for her one year follow-up appointment.

MVA85A is also about to enter a second Phase IIb efficacy trial involving HIV-infected adults in South Africa and Senegal. These adults are an important target group for a successful TB vaccine as they are 20-40 times more likely to develop active TB than their HIV-uninfected peers. This trial, which is due to start in early 2011, will randomise 1,400 adults to receive either MVA85A or a placebo. Also sponsored by Aeras, this adult trial is funded by the European and Developing Countries Clinical Trials Partnership (EDCTP), Aeras and OETC. With these two trials, MVA85A is the most clinically-advanced candidate TB vaccine, and the results of both efficacy trials are eagerly awaited.

Professor Martin Shirley of the IAH Awarded the CBE

Professor Martin Shirley, retiring Director of the Institute for Animal Health, has been awarded a CBE for Services to Science in the 2010 Queen's Birthday Honours. His research on the protozoan parasite Eimeria, a major cause of poor health and performance in chickens, led him to develop the first attenuated live vaccine to control it. This is now used in over a billion chickens annually to reduce gut disease.

Recently Professor Shirley was elected a Fellow of the Royal Agricultural Society of England, and was made an Honorary Associate of the Royal College of Veterinary Surgeons.

Photo courtesy of RCVS

Professor Martin Shirley (right) is appointed an Honorary Fellow of the Royal College of Veterinary Surgeons.

Update on the IAH Pirbright Laboratory Complex

In July 2009, Treasury approved the £100m funding for the new IAH facility that will house all IAH scientists in a single envelope containment facility that will ensure that the UK remains in position to control, contain and eradicate the threats of established and emerging diseases of animals.

The new laboratory is expected to be completed by the end of 2013 and will boast cutting-edge technologies for many engineering solutions required to deliver a high security laboratory complex.

Prior to the turf-cutting event on 1st September 2010 that marked the start of the construction of the new laboratory complex, Mike Johnson, Senior Responsible Officer for the project, took a party of people to the new IS4L building, Pirbright. This provides laboratories that will enable work on viruses, that require a very high level of bio-containment, between now and completion of the new laboratory complex.

The new IS4L laboratory is nearly complete. This will provide DEFRA Specified Animal Pathogen Order Level 4 (SAPO; the 'S' in IS4L) state-of-the-art biosecurity level laboratory space for research on pathogens such as Foot-and-mouth Disease (FMD) virus, African Swine Fever (ASF) virus, Peste des petits ruminants (PPR) virus. This is part of the IAH Pirbright Development Programme 1 phase, and includes the two new isolation units, also for animal experiments with FMD, ASF, PPR.

IAH

To mark commencement of the construction of the new laboratory complex, a 'turf-cutting' event was held on a beautiful sunny day at Pirbright on 1st September. This was attended not only by IAH colleagues but also by members of the Trustee Board, the project manager of Shepherds Construction who are building the complex, and many others associated with the project, including contractors.

Afterwards Mike Johnson commented: "Thank you to all who participated in the turf-cutting event yesterday - it marked the start of the new building with staff and contractors forming a one-team approach to delivery of what will be an international class facility".

Royal Society Workshop of Vaccines

New Vaccines for Global Health
15th - 16th November 2010 - The Royal Society, London

The Royal Society, which is celebrating its 350th anniversary in 2010, is holding a discussion meeting 'New Vaccines for Global Health', organised by Professor Brian Greenwood FRS (London School of Hygiene & Tropical Medicine) and Professor Adrian Hill (University of Oxford), at the Society's building at Carlton House Terrace, London on Nov 15th-16th, 2010.

This meeting, which will bring together some of the world's leading experts on vaccination, will discuss new approaches to the development of vaccines, along with progress being made on the development of vaccines against major infectious diseases such as malaria, tuberculosis, HIV and foot-and-mouth disease. It will also consider the development of vaccines against cancer and other non-infectious diseases. Policy issues and the funding of new vaccines will be discussed.

Vaccination has the potential to bring enormous benefits to developing countries where many deaths and much serious illness still occur from infectious diseases that could potentially be prevented. Vaccination could also help to improve food security by improving animal health.

Visit http://royalsociety.org/Event.aspx?ID=2067 for more details and registration

Volunteers for Clincial Trials

Call for Volunteers to Participate in Clinical Trials

The Centre for Clinical Vaccinology and Tropical Medicine (CCVTM) on the Headington campus of the University of Oxford conducts clinical trials on diseases of global importance and impact. If you would like to learn more about the clinical trial process, what it entails and how to volunteer to participate, please contact Laura Dinsmore.

Email: VaccineTrials@well.ox.ac.uk
Tel: +44 (0)1865 857406
Web: www.jenner.ac.uk

Vaccinology Course

Next Dates for The Human And Animal Vaccinology Course at Oxford

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

There are three courses currently in the Vaccinology Programme:

Human and Veterinary Vaccinology

29 November –3 December 2010 (five-day course)

Clinical Vaccine Development

4 –5 April 2011 (two-day course)

Vaccine Biomanufacturing

6 –7 April 2011 (two-day course)

Visit http://cpd.conted.ox.ac.uk/vaccinology/default.asp for more details

Infant TB vaccine study reaches milestone

May 2010, Worcester, South Africa – Celebrations marked a milestone for TB vaccine research when clinical researchers of the South African Tuberculosis Vaccine Initiative (SATVI) vaccinated the 1000th infant in a TB vaccine trial in Worcester, 120 km outside of Cape Town. "Today's vaccination of four and a half months old Janine Dullman is historic for us, as it is the first time that so many infant participants have been vaccinated in a TB vaccine trial since BCG", said Dr Hassan Mahomed, Co-Director at SATVI in charge of the Clinical Research team. The trial, which began in July last year, is running well, with no vaccine-related serious adverse events to date. Babies from Worcester, Robertson, De Doorns, Villiersdorp and Ceres are participating in the study.

Appointment of 3 New Jenner Investigators

At the recent meeting of the Jenner Vaccine Foundation, the following were appointed as Jenner Investigators:

Dr Martin Vordermeier, VLA, works on TB Vaccines for cattle, with a main interest on the discovery of biomarkers of protection and pathology.

Professor Glyn Hewinson, VLA, focuses on developing novel vaccines and diagnostics against tuberculosis in cattle and badgers, and in the application of molecular epidemiology to disease control.

Professor Sarah Rowland-Jones Nuffield Department of Clinical Medicine, University of Oxford, focusing particularly on how immune responses modify the outcome of HIV infection.

THE JENNER VACCINE FOUNDATION
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