

# Outsmarting HIV

**Professor Tomáš Hanke** discusses his challenging research developing a vaccine for HIV-1, and the novel approaches that could hold potential applications for treating a range of infectious diseases

## What led you to research vaccine immunology?

I enjoy the challenge of designing new genes and inserting them into bacteria and viruses, so the development of subunit genetic vaccines is the perfect area of research for me. The organisms' defense against microbial infections is fascinating and involves extremely complex communications between specialised cells and proteins of the immune system. Exploring these mechanisms keeps revealing new information about the workings of the immune system, the microbes' life cycles and their mutual interactions and adaptation. Like other systems in nature, a healthy organism is in a state of dynamic equilibrium and any disturbance – such as infection – evokes an action to restore it. HIV-1 infection of humans is a relatively recent event and neither host nor virus have had time to adapt to each other. Consequently, the disturbance is still huge: without the help of antiretroviral treatment, the majority of infected people would succumb to infection. Although we have learnt a great deal about HIV-1 and the immune system in recent years, much more must be understood about both before we can rationally design an effective vaccine.

## Can you discuss the preclinical models that are used to test the immunogenicity of particular vaccine formulae?

Models for preclinical studies are chosen depending on whether one wishes to test vaccine safety, immunogenicity or protective efficacy. Immunogenicity refers to the ability of an immunogen (typically a protein or polysaccharide) to provoke an immune response in the body by eliciting cell-mediated responses, antibodies or both. Antibodies are either neutralising (preventing the infection of cells) or non-neutralising (exerting their function together with other arms of the immune defences) and protection can either be against the infection or the development of the disease. Different preclinical models preferentially suit different questions. Ultimately, the choice of model can depend on its stage of development,

repertoire of germline genes, availability of reagents and/or pathogenic challenges. Humans, of course, remain the most relevant model; however, in contrast to a growing number of other diseases, there is currently no safe human challenge to assess HIV-1 vaccine efficacy.

## Can you provide an insight into the difficulties encountered in your research on HIV/AIDS vaccinations and how they have been overcome?

Apart from the challenge of raising adequate funding, there are huge scientific obstacles to overcome, including the variability of HIV-1, and the difficulties associated with finding the optimal T and B cell immunogens and their most efficient delivery method. There are also significant ethical challenges because we are able to protect volunteers from infection by administering antiretroviral drugs or encouraging condom use, yet in order to prove the vaccine's protection, volunteers in the placebo arm must become infected. Finally, vaccine development is very slow and any shortcuts, if they are possible at all, must be proven safe and ethical.

## Many other major diseases such as TB and malaria are also lacking effective vaccination programmes. To what extent have your studies contributed towards efforts to tackle these diseases?

When it comes to fighting infections, there are common principles and strategies that should be taken into account. The incredible variability of microorganisms is one challenge, whereby an effective vaccine must have the ability to protect against multiple strains of the same species. The same principle applies to all microbes: it makes sense to tackle variability by refocusing immune responses through vaccination on conserved protein regions common to many variants. Likewise, similar delivery vectors are being used for different diseases and their semi-empirical combinations into heterologous prime-boost regimens – mainly avoiding build-up of antivector antibodies – apply universally.



Additionally, vaccine development depends on basic research into the molecular basis of infections and immune responses, and upon advances in state-of-the-art research tools such as proteomics, structural biology, systems biology, microarray analysis, increasing resolution of tandem mass spectrometry, complete genomic sequencing and bioinformatics. Vaccination programmes against different human and animal infections, therefore, synergise.

## What advances in vaccination immunology do you hope to see further into the 21<sup>st</sup> Century?

Every scientist in the immunology field would love to see new technologies that provide threefold benefits. Firstly, more precise, relevant and integrated measurements of immune responses; secondly, more reliable, earlier and thus more cost-efficient predictability of vaccine efficacy; and finally, more emphasis on small, iterative clinical trials that address the various aspects of vaccine optimisation in the most relevant species, followed by a systematic testing of the efficacy of the most promising strategies. In terms of HIV-1 infection, it is highly desirable that strategies are developed that control virus infection early and eliminate latent HIV-1 reservoirs in infected people.

# A vital vaccine

Scientists at the **Jenner Institute** at the **University of Oxford** are conducting research into preventive and therapeutic strategies for HIV-1, aiming to induce protective T cell and neutralising antibody responses

**HIV IS AMONG** the world's leading infectious killers. Although highly active antiretroviral therapy (HAART) has been beneficial since its introduction in 1996, it does not eliminate the virus and does nothing to prevent its spread by people unaware of being infected. Historically, vaccines have been the most effective means of preventing or eradicating infectious diseases, but the past 30 years of research have highlighted the immense difficulty of developing an HIV-1 vaccine. Yet, with 2.3 million people becoming infected each year, a safe, affordable and effective HIV-1 vaccine is urgently needed.

Professor Tomáš Hanke is Head of the Jenner Institute's HIV-1 Vaccine Development Group at the University of Oxford, UK, which is carrying out cutting-edge research into HIV-1 vaccine development. In collaboration with other experts in the field, Hanke's group explores novel approaches and emerging technologies to induce protective T cell and neutralising antibody responses. Hanke oversees the 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.

## FACING THE CHALLENGES

Designing an effective vaccine against HIV-1 is far from straightforward. The HIV virus is highly mutable and thus highly variable, meaning it evolves to evade the adaptive arm 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 responses, but easily change under their selective pressure," Hanke explains. "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 advent of increasing computing power has led Dr Bette Korber's team at the Los Alamos National Laboratory, USA, to develop mosaic proteins. As artificial proteins assembled from all HIV-1 sequence variants in the database, these molecules are computed over every HIV-1 protein to maximise the perfect match by vaccines of the potential killer T cell epitopes present in all circulating HIV-1 isolates.

Hanke and his colleagues have studied the potential impact of vaccine-induced T cells targeting the most functionally conserved regions of the HIV-1 proteome. This approach should generate effectors that pinpoint and kill the virus-infected cells soon enough after transmission to slow HIV-1 replication and prevent damage to the immune system. In general, focusing both T cells and antibodies on functionally conserved regions is very attractive and possibly the most effective method for tackling the variability of pathogens.

## CLINICAL TRIALS

Successful vaccine development requires systematic and iterative clinical trials using humans – but the challenge is to do this safely yet rapidly. To date, Hanke has pioneered clinical tests of HIV-1 vaccines that focus T cell responses on the most conserved regions of the HIV-1 proteome: "The first generation of the conserved T cell immunogen, delivered by a combination of plasmid DNA, simian (chimpanzee) adenovirus ChAdV and modified vaccinia Ankara (MVA) in trial HIV-CORE 002, demonstrated safety and highly promising



Electroporation of the DNA vaccine into muscle enhances induction of immune responses.



Modified vaccinia Ankara vaccine was administered to 20-week old babies in Africa.

## INTELLIGENCE

### HIV PREVENTIVE AND THERAPEUTIC VACCINES, AND PREVENTING TRANSMISSION IN BREASTFEEDING

#### OBJECTIVES

To develop an effective HIV-1 vaccine by inducing protective HIV-1-specific T cell responses and combining them with vaccines inducing protective antibodies.

#### KEY COLLABORATORS

**Professor Sir Andrew McMichael**; **Dr Lucy Dorrell**, University of Oxford, UK • **Professor Walter Jaoko**, University of Nairobi, Kenya • **Dr Bette Korber**, Los Alamos National Laboratory, USA • **International AIDS Vaccine Initiative** • **Dr Katie Flanagan**, Medical Research Council Laboratories, The Gambia • **Professor Grace John-Stewart**, University of Washington, USA • **Professor Marie Reilly**, Karolinska Institute, Sweden • **Dr Joan Joseph**, Hospital Clinic Barcelona, Spain

#### FUNDING

Medical Research Council (MRC), UK • European and Developing Countries Clinical Trials Partnership (EDCTP) • Bill & Melinda Gates Foundation • International AIDS Vaccine Initiative • United States Agency for International Development (USAID)

#### CONTACT

**Professor Tomáš Hanke**  
Professor of Vaccine Immunology

The Jenner Institute  
University of Oxford  
ORCRB Roosevelt Drive  
Oxford, OX3 7DQ  
UK

T +44 1865 617 630  
E tomas.hanke@ndm.ox.ac.uk

[www.ndm.ox.ac.uk/principal-investigators/researcher/tomas-hanke](http://www.ndm.ox.ac.uk/principal-investigators/researcher/tomas-hanke)

**TOMÁŠ HANKE** completed his PhD at the University of St Andrews, UK. In 1994, he took up a postdoctoral position in the lab of Professor Sir Andrew J McMichael at the University of Oxford. With the establishment of the MRC Human Immunology Unit in 1998, he started his own group and, five years later, obtained the MRC Career Scientist position. In 2011, his laboratory relocated to the Jenner Institute Laboratories directed by Professor Adrian V S Hill, where he leads the HIV-1 Vaccine Development Programme.

immunogenicity in terms of magnitude, persistence, breadth and functionality of the vaccine-elicited T cell responses," he discloses. These optimistic initial observations are being incorporated into a broader programme that consists of six prophylactic and therapeutic trials of human adults in Europe and Africa, with the results set to emerge over the next one to two years.

Recently, Hanke has collaborated with Korber to develop second-generation conserved region vaccines. Based on the mosaic proteins designed to enhance the T cell epitope match with global HIV variants, these vaccines are currently being prepared for clinical tests. "We aim to assess the T cell induction by the second-generation vaccines in a small bridging trial in Oxford, recruiting healthy, HIV-1-uninfected humans," Hanke explains. "The data from the ongoing programme and the bridging study will help define the future developmental path for the conserved region strategy."

#### PREVENTING BREASTFEEDING TRANSMISSION

According to the UNAIDS 2013 global report, as of 2012 roughly 3.2 million children are estimated to be HIV-positive, 91 per cent of whom live in sub-Saharan Africa. Shockingly, over 700 children are newly infected with HIV every day, with the majority acquiring the virus from their mothers. In 2012 only 57 per cent of HIV-1-infected pregnant women in low- and middle-income countries were estimated to have access to appropriate antiretroviral regimens – raising the risk of mother-to-child transmission. There is, therefore, an urgent need for both effective HIV-1 vaccines that decrease infection rates in mothers, and paediatric vaccines that protect infants against breast milk HIV-1 transmission.

Hanke has participated in two pilot paediatric HIV vaccine trials in Africa. In 2007, he worked to develop a dual vaccine to protect newborns against both TB and HIV-1 infections. The team proposed that the insertion of an HIV-1-derived immunogen into the scheduled BCG vaccine for



The HIV-CORE 004 team at Kenya AIDS Vaccine Initiative-Institute of Clinical Research, Nairobi.

TB, delivered soon after birth, could provoke HIV-1-specific responses, and thus potentially decrease mother-to-child HIV-1 transmission through breastfeeding. In addition, Hanke led randomised clinical trials in 2010 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-one-year age group.

#### VACCINE DEVELOPMENT

Looking to the future, Hanke is planning to continue gathering important data from ongoing clinical studies. Phase IIb of the trial will probably have arms of both separate and combined T and B cell vaccine components as well as a potential background intervention.

As for his long-term aims, Hanke is hopeful that a positive outcome from the phase IIb proof-of-concept trial will pave the way for a large phase III efficacy study in a sample of several tens of thousand high-risk humans: "Only this would deliver a definite efficacy proof for our vaccine hypothesis," he enthuses. "It would also lead to further vaccine development towards licensure, mass production and, last but not least, distribution to the people who need it."

#### Summary of prophylaxis studies

**HIV-CORE 002** (Oxford; Hanke & Dorrell) shows promising immunogenicity and *in vitro* control of HIV replication

**HIV-CORE 003** (London; Pepys & Hanke) tests improvement to DNA delivery by depletion of the main DNA binding protein in human blood

**HIV-CORE 004** (Nairobi; Hanke & Jaoko) assesses immunogenicity in Africa with improved DNA delivery by electroporation

**PEACHI** (Oxford: Dorrell & Barns) co-immunisation against HIV and hepatitis C virus

#### Summary of therapy studies

**HIV-CORE 001** (Oxford; Dorrell & Hanke) tests immunogenicity in HIV-positive people on HAART

**BCN01** (Barcelona; Brander & Mothe) tests immunogenicity in patients early on HAART with acute HIV infection – no damage to immune system

**RIVER** (London; Fidler) assesses immunogenicity in patients early on HAART with reactivation of latent HIV

