ABSTRACTS

Coordinators

Carlos Martín, MD, PhD.
Is Professor of Microbiology at the Faculty of Medicine at University of Zaragoza and member of the Steering Committee of Tuberculosis Vaccine Initiative (TBVI) with more than 25 years of experience in mycobacterial genetics. He and his team aim to develop novel tuberculosis vaccines and vaccination strategies to improve protection against pulmonary TB. He currently works in collaborative tuberculosis research projects together with research groups of Europe and Latin America inside of EurolacTB.

Dr. Martin came to the University of Zaragoza from Pasteur Institute in Paris, where he worked as permanent researcher. He has published more than one hundred international publication in tuberculosis cited more than 5.500 times in the last years. Dr. Martins's research has been continuously funded by National and European Union Research Programs since 1992 in tuberculosis research and belong to CIBERES, research network on respiratory diseases of the Spanish Ministry of Health, Instituto de Salud Carlos III.

Jelle Thole
Is TBVI's Executive Director. He graduated in medical biology in 1984, PhD in Medicine in 1988 and has more than 25 years of experience in molecular and immunological research on mycobacteria (> 70 peer reviewed publications).

Since 2004, he acted as coordinator of TBVAC, a consortium of 33 European and African universities and research institutes that worked together to develop and clinically test new vaccines against tuberculosis (supported by the EC Sixth Frame work). The success of this project has been the basis for the establishment of TBVI.

Jelle: "The task of setting up and organising TBVI with a highly enthusiastic and committed group of people here in Lelystad, and with the more than 50 of the best research organisations TB is a fantastic experience. I am really looking forward to continue to work with all these people in our own unique way and help to eliminate tuberculosis by developing new vaccines".

Jelle's related activities: Chair of Vaccine Program Advisory Group (VPAG) advising DEFRA on a vaccine program against bovine TB in the UK. Member of Stop TB Partnership Working Group on new TB vaccine. Member of the Editorial Board of the Journal Tuberculosis. Board member of the vaccinology division of the Royal Dutch Society for Microbiology.

Session I

PERSPECTIVES FOR NEW TB VACCINES

Douglas Young holds a joint appointment as Head of the Division of Mycobacterial Research at the MRC National Institute for Medical Research, and **Fleming Professor of Medical Microbiology at Imperial College London.** He has more than 30 years of experience in research on the molecular basis of mycobacterial pathogenesis. As chair of the New Vaccines Working Group he coordinated the vaccination component of the Global Plan to Stop TB, and he is currently a member of the TBVI Governance Board. Recent projects include coordination of a TB drug discovery consortium as part of the Grand Challenges in Global Health programme sponsored by the Bill & Melinda Gates Foundation, and a Wellcome Trust-funded programme to study bovine tuberculosis in Ethiopia. Current laboratory interests include application of sequence-based transcriptomics as part of the EU-funded SysteMTb consortium, and analysis of the influence of *M. tuberculosis* strain diversity on innate immune recognition.

Pathogen: Mycobacterium tuberculosis: Evolution of Functional Diversity

Douglas Young
MRC National Institute for Medical Research, London UK.

The ability of vaccination programmes to protect the unvaccinated by reducing transmission at a population level is central to the dramatic success of vaccines in disease control. Current tuberculosis vaccine strategies aspire towards this goal by preventing disease at the individual level. *M. bovis* causes disease in humans but rarely results in further transmission. *M. tuberculosis* is isolated from cattle lesions in rural Ethiopia, but opportunities for epidemic disease in intensively-farmed urban dairy herds are exploited by *M. bovis*. What's the difference? both bacteria are perfectly capable of causing pathology in mice and guinea pigs. Can we view sustainable transmission as a layer of biological fine-tuning that sits on top of the basic ability to generate pathology? If so, could we target this with novel vaccine strategies, taking advantage of clinical trials that have a primary endpoint of reducing transmission parameters at a population level rather than the number of individual cases? In the absence of experimental models to study transmission, perhaps we can begin to map biological determinants of transmission by analysing the emergence of *M. tuberculosis* from microbial progenitors and subsequent diversification to optimise transmission in different host populations.

Stefan H. E. Kaufmann is founding director of the Max Planck Institute for Infection Biology in Berlin where he heads the Department of Immunology. He is professor for microbiology and immunology at the Charité, Humboldt and Free University, Berlin, honorary professor of the Universidad Peruana Cayetano Heredia, Lima, Peru and guest professor at the Tongji University, School of Medicine, Shanghai, China. He holds a Doctor Honoris Causa from Université de la Mediterranée, Aix-Marseille II.

Prof. Kaufmann is former president and honorary member of the German Society for Immunology, former president of the European Federation of Immunological Societies (EFIS) and past president of the International Union of Immunological Societies (IUIS). He studied biology at the Johannes Gutenberg University of Mainz, 1977 PhD (highest degree, summa cum laude). He was professor for medical microbiology and immunology (1987-1991) and full professor for immunology at the University of Ulm (1991-1998). His scientific interests are: immunity to bacterial pathogens with emphasis on tuberculosis and rational vaccine design. Prof. Kaufmann initiated the Day of Immunology to raise public awareness in immunology. He received numerous scientific awards. He is coordinator of several international and interdisciplinary projects. He is Alternate Board Member of the Global Alliance for Vaccines and Immunisation (GAVI Alliance) and member of the Strategic Advisory Committee of the European and Developing Countries Clinical Trials Partnership (EDCTP). Prof. Kaufmann has more than 700 publications mostly in high-ranking journals with an h-Index of 86. He is editor or member of editorial boards of more than 20 international scientific journals, member of various professional societies and academies.

Time to think about the next generation of tuberculosis vaccines

Stefan H. E. Kaufmann
Max Planck Institute for Infection Biology. Berlin. Germany.

With numerous candidates undergoing clinical assessment, the tuberculosis (TB) vaccine pipeline prospers. All current candidates aim at preventing active TB. Some vaccines are administered preexposure, other postexposure, with *Mycobacterium tuberculosis* (Mtb). However, none of these vaccines aim at preventing or eliminating infection. The time is now ripe for new strategies to reach this goal. Novel rational strategies can build on: (i) recent insights into immunology and pathology of TB; (ii) data generated in clinical trials with current TB vaccine candidates; (iii) insights into mechanisms responsible for sterile eradication of naturally acquired Mtb; (iv) elucidation of mechanisms underlying prevention of Mtb infection over long periods of contact with TB patients. Finally, insights into the different life stages of the pathogen ranging from metabolic/replicative activity to almost complete shutdown of these functions during dormancy can help in this endeavor. These research directions need to be complemented by novel and innovative vaccine trial design and licensing procedures.

Further reading

Kaufmann, S.H.E.: Tuberculosis vaccines: Time to think about the next generation.
Sem. Immunol. 25: 172–181 (2013)
Kaufmann, S.H.E., C. Lange, M. Rao, K.N. Balaji, M. Lotze, M. Schito, A.I. Zumla, M. Maeurer: Progress in tuberculosis vaccine development and host-direct therapies –a state of the art review
Lancet Resp Med, in press (2014)

Per Brandtzaeg obtained his postgraduate training in microbiology, immunology and pathology at the Medical Center, Univ. of Alabama at Birmingham, AL, and received his PhD in immunology at the Univ. of Oslo (1971). He is the former Head of the *Faculty Division, Rikshospitalet University Hospital, and the founder of the Laboratory for Immunohistochemistry* and Immunopathology (LIIPAT), Institute and Department of Pathology, which is devoted to research on mucosal immunity. He is also the founder (2001) of a thematic research network called the *Center for Vaccinology and Immunotherapy* (CEVI) at the University of Oslo, with a focus on basic mechanisms of importance for active and passive immunization. In 2007, CEVI obtained status as a Center of Excellence funded by the Research Council of Norway. Professor Brandtzaeg's main research interest is in the immunobiology and immunopathology of mucous membranes. He obtained the top score of leading European scientists in the field of mucosal immunology in a worldwide peer judgement carried out by the US National Academy of Sciences *Immunology Benchmarking Panel* in 1998, and has been one of Norway's most cited researchers over the last two decades. He has received several major national and international science awards, and is Commander of the Royal Norwegian Order of St. Olav.

Mucosal host-pathogen interaction in the lung with special reference to Mycobacterium tuberculosis

Per Brandtzaeg

Laboratory for Immunohistochemistry and Immunopathology (LIIPAT), Department of Pathology, Oslo University Hospital Rikshospitalet, and Centre for Immune Regulation (CIR), University of Oslo, Oslo, Norway.

Several mucosal vaccine candidates for tuberculosis have been evaluated in animal models and their formulations, including adjuvants as well as the delivery systems, have been found to be crucially important. Mucosal immune effector mechanisms can principally be divided into secretory IgA (SIgA) antibodies operating in the human bronchial tree down to bronchioles approx. 1 mm in diameter, and intraepithelial and luminal T cells. Both these layers of protection against *Mycobacterium tuberculosis* (M.tb) have been shown to operate in animal models, and intranasal vaccination has been found to provide better defence than parenteral vaccination. Induction of mucosal immunity takes place in mucosa-associated lymphoid tissue (MALT). Although such structures (BALT, bronchus-associated lymphoid tissue) are virtually absent from healthy human lungs in adulthood, they frequently occur in infancy. This probably reflects a response to the establishing lung microbiome before locally produced SIgA can keep microbial components away from the respiratory epithelium. It would be attractive to have a vaccine that could inhibit *a* at its portal of entrance – that is, the nasal and bronchial epithelium. Regional mucosal immunization should therefore have advantage over other routes of vaccine administration. It is known that immune induction in MALT of this region, particularly nasopharynx-associated lymphoid tissue (NALT), provides effector/memory B and T cells expressing homing molecules compatible with extravasation at local effector sites – such as the airway mucosa – and

at systemic effector sites – such as lymph nodes and lung interstitium. An interesting and safer alternative to intranasal vaccine delivery is sublingual immunization, and this route induces immune effector cells with the same homing properties as intranasal vaccination. Local appearance of reactive SIgA antibodies has been demonstrated by this approach both in mice and humans. Moreover, passive immunization with SIgA obtained from human breast milk has documented that innate-like, cross-reactive SIgA is capable of inhibiting M.tb invasion in a mouse model.

Willem Hanekom trained in paediatrics in Cape Town, in paediatric infectious diseases at Northwestern University in Chicago, and completed a postdoc in immunology at Rockefeller University in New York City.

Willem is director of the South African Tuberculosis Vaccine Initiative (SATVI) at the University of Cape Town, where he is Professor at the Institute of Infectious Diseases and Molecular Medicine and in the School of Child and Adolescent Health. He is currently on sabbatical at the Bill and Melinda Gates Foundation, as Deputy Director in Global Health, leading the TB vaccine programme.

SATVI focuses on TB vaccine research. The group is involved in clinical testing of new, better TB vaccines in humans and is addressing many clinical and immunological questions that hamper TB vaccine development. Among these, large cutting edge studies aim to identify biomarkers of risk of TB disease, or protection against TB disease.

Willem has authored >100 publications, and has been successful in generating competitive research funding from the NIH, EDCTP and many other agencies. He is actively involved in training postgraduate students, and has won various research and teaching awards.

Willem is past president of both the South African Immunological Society and the Federation of African Immunological Societies. He is a regular reviewer for international funding agencies, and an editor/reviewer for many scientific journals. He serves on multiple World Health Organization-affiliated and other international advisory committees in TB vaccine development and translational immunology.

Rethinking the Gates Foundation's TB Vaccine Strategy
Willem Hanekom
Bill and Melinda Gates Foundation.

The evolving TB vaccine strategy at the BMGF focuses on interruption of *M. tuberculosis* transmission, as modeling studies suggest this would have the greatest impact on the epidemic. The focus is therefore on preventing lung disease in adolescents and adults, and on prevention of infection in these populations.

On the discovery side, optimized animal models and uncommon/unnatural immunity are receiving major emphasis. Antibody approaches to prevent infection, and CD1-mediated T cell immune induction, are currently tested in human to guinea pig transmission models. Our strategy also involves rapid

support of multiple preclinical advances thatmight signal useful clinical intervention.

New aims of clinical trials include early upselection of vaccines/vaccine concepts, and examination ofimmunbiology at every opportunity possible. We are planning early phase experimental studies to test various vaccine concepts, to be completed in parallel with non-human primate studies, which could inform further development in an iterative process as M. tuberculosischallenge would be possible. Later phase efficacy trials focus on targeted enrollment, or endpoints such as prevention of infection, for testing concepts within designs that allow smaller sample sizes.

We are also considering mechanisms for stimulating greater innovation and collaboration within the global TB vaccine world, by learning from the best models in the HIV vaccine world. Initiatives forglobal TB vaccine portfolio management, and for optimal community engagement on a global level, are also supported.

Session II

PRIME VACCINES IN CLINICAL TRIALS

François Spertini, MD, is currently Associate Professor of Medicine at the Faculty of Biology and Medicine of the University of Lausanne and chief-physician at the Centre HospitalierUniversitaireVaudois in Lausanne. He is Board Certified in Internal Medicine and in Allergology and Clinical Immunology.

Dr Spertini studied medicine at the University of Lausanne. He developed strong background in immunology during successive fellowships at the University of Geneva and at Harvard Medical School, Boston, before establishing his group in Lausanne in 1992. He focuses on immune response to tuberculosis and malaria, as well as on the downregulation of the allergic response. He has led several early phase clinical trials on novel vaccine candidates in the field of tuberculosis and malaria. He was President of the Swiss Society of Allergology and Immunology (2001-2003) and is involved in several scientific associations.

Early phase clinical trials: from subunit to live tuberculosis vaccines. Clinical Trial of attenuated MTBVAC

François Spertini
CHUV. Lausanne. Switzerland.

Two classical approachesof TB vaccine development will be described, subunit vaccine and live vaccine, with focus on respective interests but also caveats of each strategy. Present vaccine BCG is based on attenuated strain of *Mycobacterium* bovis isolated from cows. MTBVAC, developed by the University of Zaragoza, is a live vaccine based on attenuated *M. tuberculosis* isolated from humans; a strongly weakened version of the bacterium that causes TB and the first candidate of this kind ever tested in humans. Made harmless

in the laboratory, the vaccine stimulates the human immune system to recognise, and eventually prevent, TB disease.

January 2013 started a Phase I study in Lausanne. Thirty-six healthy volunteers participated in order to ensure the safety and immunogenicity of the vaccine candidate MTBVAC. The participants were divided into three groups depending on the dose which has been administered (1,000 or 10,000 or 100,000 units of MTBVAC). In the first two cohorts, seven months after the monitoring period considered necessary to confirm possible side effects or disease infection, the vaccine has been shown to be safe. The last dose of the latter group was administered on 6 November and so far no safety issues occurred. Possible side effects or disease generally occurs in the first days after vaccination, so this first positive signal is very promising.

Leander Grode(1970) joined VPM in May, 2003. As Manager he was responsible for all of VPM´s projects until June, 2005. Since April, 2008 he has been responsible for Business Development. He studied biology in Giessen and Frankfurt/Main with focus on cell biology and zoology. As an exchange student, he visited the University of California San Francisco in the Department of Biochemistry and Biophysics in the lab of Prof. John Watson. He graduated in 1997 with a degree in biology at the Max Planck Institute of Biophysics in Frankfurt/Main in the Department of Molecular Membrane Biology under Prof. Hartmut Michel. In the year 2000 he graduated as a PhD at the Max Planck Institute of Infection Biology in the Department of Immunology under Prof. Stefan H.E. Kaufmann. The focus of his thesis was vaccine development against tuberculosis based on live carriers, such as samonella or mycobacterium bovis BCG. Between 2001 and 2003 Leander Grode was the coordinator of the vaccine development group at the MPI in the Department of Immunology.

Clinical Trials of recombinant BCG VPM1002

Leander Grode
Vakzine Projekt Management (VPM). Hannover. Germany.

VPM1002 is a live vaccine against tuberculosis (TB). As BCG is not sufficiently effective to stop the spread of TB, two modifications have been implemented in VPM1002 to improve its immunogenicity. Two Phase I studies and one Phase II in humans using multiparameter flow cytometry characterized the quality of the T cell response following immunization with our VPM1002 tuberculosis vaccine candidate or BCG. We completed a Phase II clinical trial in neonates in South Africa and first safety and immunogenicity data are available. All clinical Phases were open-label, randomized, controlled studies which evaluated safety and immunogenicity of VPM1002 in comparison with BCG. Safety and tolerability results from all clinical trials showed no serious adverse reactions after VPM1002 vaccination. VPM1002 induces multifunctional T cell subsets which are thought to play a important role in protection against tuberculosis.

Session III

EVOLUTION OF MYCOBACTERIUM TUBERCULOSIS AND BCG VACCINES

Roland Brosch is an Associate Professor at the Institut Pasteur in Paris, France. He received his doctoral training at the Universities of Graz and Salzburg in Austria, and continued his post-doctoral studies at the University of Wisconsin, USA, and at the Institut Pasteur in France. He was involved in pioneering genomics-, evolution- and virulence studies on *Mycobacterium tuberculosis*, the causative agent of tuberculosis and the attenuated BCG vaccine. He became director of the Research Unit for Integrated Mycobacterial Pathogenomics at the Institut Pasteur in 2008 and focuses his current work on mycobacterial genome evolution and its impact on host-pathogen interaction, antigen secretion and vaccine efficacy.

Origin and evolution of the Mycobacterium tuberculosis complex and impact on BCG vaccines

Roland Brosch
Institut Pasteur. Paris. France.

Global spread and limited genetic variation are hallmarks of M. tuberculosis, the agent of human tuberculosis. In contrast, *Mycobacterium canettii* and related tubercle bacilli that also cause human tuberculosis and exhibit unusual smooth colony morphology are restricted to East Africa. We sequenced and analyzed the whole genomes of several representative *M. canettii* strains and show that *M. canettii* isolates are highly recombinogenic and evolutionarily early branching, with larger genome sizes, higher rates of genetic variation, and distinct CRISPR-Cas systems and prophages relative to *M. tuberculosis* and other members of the *M. tuberculosis* complex such as the attenuated live vaccine *Mycobacterium bovis* BCG. We conclude that *M. tuberculosis* emerged from an ancestral *M. canettii*-like pool of mycobacteria by gain of persistence and virulence mechanisms.

Apart from genomic regions that differed, we also found regions that were highly conserved among the different strains. One of these regions was the genomic locus encoding the ESX-1/type VII secretion system. This system, which is absent from the attenuated BCG and *Mycobacterium microti* vaccine strains, has been recently shown to be involved in the rupture of the phagolysosomal membrane in THP1 cells. The presence of ESX-1 or its absence from certain mycobacterial strains or strain-lineages thus strongly influences the virulence potential and the immunological properties of a given strain. This knowledge is of importance for the search of potential virulence factors of *M. tuberculosis* and for the construction of better recombinant vaccines and diagnostic tools. By comparison of various BCG strains additional differences can be found that might have an impact on the vaccine efficacy.

Iñaki Comas is a Ramón y Cajal Researcher (Spanish Young Group Leader fellowship) and have started a new Tuberculosis research programme as part of a public health institute (FISABIO-Public Health) in Valencia, Spain. Dr. Comas received his PhD from the University of Valencia in 2008 on evolutionary genomics of bacteria. Thereafter, he spent more than three years at the National Institute for Medical Research, (London, UK) as Career Development Fellow under the supervision of Dr. Sébastien Gagneux. After that he came back to Spain as a Marie Curie researcher.

Dr. Comas applies genomic sequencing to study genetic diversity of the *Mycobacterium tuberculosis* complex at different levels. He has made contributions to understand how the MTBC variation is shaped by different selective forces like the immune system, antibiotics use or changing human demography. He is currently working on expanding these topics. He is also focusing on the use of genomic characterization for epidemiological purposes to guide public health interventions and to understand better the co-evolution of the host and the pathogen.

Understanding TB genomic diversity: from millennia to minutes
Iñaki Comas
Centre for Public Health Research. Valencia. Spain.

A detailed description of the tempo and mode of accumulation of variation in tuberculosis at the genomic level is paramount to understand the relationship between the host and the pathogen. A proof of that is the lack of antigenic diversity in known human T-cell epitopes of *Mycobacterium tuberculosis* complex. To expand our knowledge on the host-pathogen interaction we and other are studying the genomic diversity of the bacteria at different evolutionary scales. At the global level MTBC strains have accumulated more than thirty thousand genetic changes. While most of these changes are neutral other have a predicted impact at the phenotypic level and maybe relevant for the development of diagnostics, treatments and vaccines. Much less diversity is observed during host-to-host transmission or during infection in a single host but understanding their nature and the evolutionary forces behind them is equally important. Some of these changes can have a functional impact that can translate in a change of the fitness of the strain. This is the case of the acquisition of compensatory mutations to rifampicin resistance. Remains to be seen if similar patterns can be linked to other selective forces like human demographic changes or immune selective pressures.

Jesús Gonzalo-Asensio. Research University of Zaragoza PhD in Biochemistry and Molecular and Cellular Biology. Predoctoral stays in Pasteur Institute (Paris) and McGill University (Montreal). Post-doctoral stay in National Center for Biotechnology (Madrid). Expertise in molecular biology of intracellular bacterial pathogens: *Mycobacterium tuberculosis*, *Salmonella typhimurium*, *Listeria monocytogenes*. Most relevant scientific findings are: i) decipher the PhoP-PhoRmechanistics and ii) identification of the PhoPregulon in *Mycobacterium tuberculosis*. Both findings have substantially contribute to understand

the role of PhoP in *Mycobacterium tuberculosis* virulence and consequently to comprehend the attenuation basis of the MTBVAC vaccine candidate.

How to domesticate Mycobacterium tuberculosis and attenuate the pathogen?

Jesús Gonzalo
University of Zaragoza. Spain.

At the end of XIX century, Louis Pasteur discovered that weakened forms of a microbe could be used as an immunization against more virulent forms of the microbe. Since then, scientists have pursued in vitro attenuation of diverse microorganisms. Today, our cumulative knowledge of the tubercle bacillus has greatly contributed to understand the virulence pathways of this pathogen and consequently, to design novel attenuation strategies.

We will review the state-of-the-art of attenuated *Mycobacterium tuberculosis* strains with particular focus on MTBVAC, a BCG replacement strategy based on rational attenuation of *M. tuberculosis* by inactivating *phoP and fadD26* virulence genes. Unlike BCG, MTBVAC retains the whole antigen repertoire of *M. tuberculosis* –including RD1– recently demonstrated to be an epitope-rich region. Further, proteomic studies demonstrate that inactivation of *phoP* in MTBVAC results in increased secretion of some well-known antigens. These results suggest a robust antigenicity of MTBVAC which otherwise might result in better immunity when compared with BCG. This hypothesis is corroborated in the mouse model: MTBVAC is able to elicit long-lasting immunity compared to BCG and importantly, this response is expanded at the site of infection after *M. tuberculosis* challenge. We also get insight in the attenuation phenotype of MTBVAC. This strain induces lower apoptosis and cell-to-cell spread than virulent mycobacteria, a phenotype unambiguously related with impaired ESAT-6 secretion in MTBVAC.

Overall, our work integrates molecular, cellular and immunology approaches to comprehend the attenuation basis of MTBVAC, this knowledge otherwise helps to better understand the pathogenesis of the tubercle bacillus.

Session IV

VACCINES FOR ADOLESCENTS AND ADULTS IN CLINICAL TRIALS

Lewis Schrager is a graduate of the Johns Hopkins University, Baltimore, MD and the Vanderbilt School of Medicine, Nashville, TN. He trained in internal medicine at the University Hospital/Bellevue Medical Center, New York City, from 1981-1984 and received his training in infectious diseases at the Harvard School of Medicine Combined Infectious Disease Program, Boston, MA, and at the Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY. He has served as chief of the Epidemiology Branch, National Institute of Allergy and Infectious Diseases, NIH and as a chief of clinical review in the Office of Vaccine Research and Review, Center for Biologics Evaluation and

Research, U.S. Food and Drug Administration. Dr. Schrager joined Aeras in September 2013 as Vice President, Scientific Affairs.

Clinical development of TB vaccines for adolescents and adults: importance and rationale

Lewis Schrager
Vice President of Scientific Affairs at Aeras. USA.

The WHO has set a goal of reducing global *Mycobacterium tuberculosis* (Mtb) transmission to one new case of tuberculosis (TB) per one million persons by 2050[1]. Reaching this goal will require interruption of Mtb transmission by combining TB control modalities, including effective treatment of active TB cases, with the development of vaccines that prevent both TB disease among persons already infected andde *novoMtb* infection[2]. Because infants and young children rarely contribute to disease transmission[3], adolescents and adults with active TB disease are high priority targets for TB vaccines geared to prevent TB disease and new Mtb infection.

[1]World Health Organization (WHO), Stop TB Partnership 2010: The Global Plan to Stop TB 2011-2015: Transforming the Fight Towards Elimination of Tuberculosis. Geneva:WHO.

[2]Dye, C, Glaziou P, Floyd K, Raviglione M. Prospects for Tuberculosis Elimination.Annu Rev Public Health 2013;34:271-86.

[3]Marais BJ and Schaaf, HS. Childhood Tuberculosis: An Emerging and Previously Neglected Problem. Infectr Dis Clin N Am 2010;24:727-49.

Helen McShane obtained an intercalated BSc in 1988, and then a degree in medicine in 1991; both from the University of London. After junior hospital posts during which she obtained MRCP in 1994, she worked as a registrar in Infectious Diseases and HIV/GU medicine for 3 years. She was awarded an MRC Clinical training Fellowship to undertake a PhD with Adrian Hill in Oxford in 1997, and was awarded a PhD in 2001, also from the University of London. In 2001 she was awarded a Wellcome Clinician Scientist Fellowship to establish a translational programme of vaccine research evaluating new TB vaccines in the clinic. This fellowship also allowed her to complete her clinical training and she was awarded a CCST in HIV and GU Medicine in 2003. In 2005, she was awarded a Wellcome Senior Clinical Research Fellowship, which she took up in 2006; this Wellcome Senior Fellowship was renewed in 2010. She was appointed Professor of Vaccinology at the University of Oxford in 2010. She collaborates extensively with TB research groups in Africa including the South African TB Vaccine Initiative at the University of Cape Town, Chu Le Dantec in Senegal and The MRC Laboratories in Uganda and The Gambia. Her research team continues with the programme of translational Vaccinology in TB vaccine development, and is involved in developing new assays for monitoring vaccination induced cellular immune responses, developing a BCG challenge model in humans and the aerosol delivery of vaccines.

MVA85A: Update on recent trials and correlates

Helen McShane
The Jenner Institute, University of Oxford. UK.

Recombinant viral vectors expressing antigens from *Mycobacterium tuberculosis* (M.tb) are a potent way to boost BCG-induced cellular immunity. MVA85A is a recombinant Modified Vaccinia virus Ankara expressing the immunodominant mycobacterial antigen 85A; and ChAdOx1.85A is a recombinant simian adenoviral vector expressing the same antigen. Priming with BCG and boosting with ChAdOx1.85A and MVA85A is significantly more protective against aerosol *M.tb* challenge than BCG alone in mice. This promising regime is currently being evaluated in guinea pigs, non-human primates and in a phase I clinical trial. Furthermore this promising ChAdOx1 –MVA regime is being evaluated with several novel antigens.

MVA85A alone is currently being evaluated in a homologous boosting regime using aerosol and systemic routes of delivery in a phase I clinical trial. Ongoing work using correlate samples from the infant efficacy trial may identify correlates of risk of TB disease which help guide subsequent vaccine development.

Despite progress in the field of TB vaccine development, there are significant challenges. The lack of an immunological correlate of protection, together with uncertain predictive value of preclinical animal models means it is difficult to select which vaccines should progress to field efficacy testing. In other fields of vaccine development, human challenge models can facilitate vaccine development. Whilst we cannot challenge humans with virulent *Mycobacterium tuberculosis*, we are developing a human BCG challenge model to evaluate *in-vivo* mycobacterial suppression. We are also developing an *in-vitro* mycobacterial growth inhibition assay to further facilitate vaccine development.

Else Marie Agger, M.Sc., Ph.D., was appointed Director of the Department of Infectious Disease Immunology, Statens Serum Institut in Denmark in 2011. Prior to this, she has been heading two different research groups focusing on tuberculosis (TB) vaccine research and adjuvant development, respectively. She holds a Ph.D. degree within immunology from the University of Copenhagen.

Else Marie Agger has extensive experience within adjuvant research, TB vaccine research and preclinical development of vaccines in particularly within TB field. In addition, Else Marie has previously been involved in antigen discovery primarily with a focus on developing novel diagnostic testes within TB. She has been involved in the coordination of vaccine delivery optimisation within the EU-funded TBVAC and NEWTBVAC consortia and also has previous experience as work-package leader within an EU-funded project focusing on adjuvantation of influenza vaccines. Else Marie Agger is the co-inventor of several adjuvant patents and has published more than 75 papers within TB, vaccines and adjuvant research.

Pre– and Post– exposure recombinant fusion vaccines

Else Marie Agger
Statens Serum Institut. Copenhagen. Denmark.

In only fifteen years we have witnessed remarkable progress with thirteen new tuberculosis vaccines currently in various stages of clinical development and a plethora of other candidates in preclinical development. The vaccine candidates are designed either as whole-organism live mycobacterial vaccines to replace BCG or as subunit vaccines to boost BCG-induced immunity. However, almost all experimental vaccines including the ones currently in clinical trials have been designed and tested as preventive vaccines for administration prior to infection. A staggering 2,000,000,000 individuals are already infected with *M.tb*. Although the majority are non-contagious, a-symptomatic carriers of disease, they represent a huge reservoir for disease reactivation. Thus, preventing latently infected individuals from reactivating disease should be a key priority.

In addition to preventive vaccines, we have at Statens Serum Institut (SS) also worked with post-exposure vaccines for use in humans which already are *M.tb.*-infected. Both strategies are based on polyproteins co-administered with an effective Th1-inducing adjuvant. The SSI TB vaccine program includes the H56 vaccine which was able to induce a strong T cell response when delivered to mice harbouring a low-dose infection and led to efficient control of the reactivation, demonstrating for the first time that a post-exposure vaccine is indeed a feasible strategy for preventing reactivation of latent disease. H56 entered Phase I clinical testing in South Africa in 2012 as the first first-in-man vaccine to be tested in South Africa and was given to healthy quantiferon-negative as well as quantiferon-positive individuals. Herein, I will provide an overview of the use of recombinant fusion vaccines for pre- and post-exposure use.

Session V

CLINICAL SITES AND EVALUATION OF TB VACCINES

Pedro Luis Alonso is currently Director of ISGlobal, Director of the Barcelona Centre for International Health Research (CRESIB), Head of the International Health and Tropical Medicine Unit of the Hospital Clínic of Barcelona, Professor of the University of Barcelona and President of the Governing Board of the Manhiça Foundation / Manhiça Health Research Centre, CISM (Mozambique).

Pedro Alonso started his career in international health 25 years ago as a young physician working in West Africa. Since then his work has focused on the key determinants of morbidity and mortality in the two most vulnerable population groups in Africa: young children and pregnant women. He is increasingly active in building and strengthening human and institutional capacity in developing countries and Europe and in campaigning for support for other global health initiatives.

Some of Dr Alonso's most relevant work has been carried out in the field of

malaria and has led to the development and testing of new tools for the prevention and treatment of Plasmodium falciparum. He conducted the first trials to show the impact of insecticide-treated nets in the reduction of all-cause mortality (Lancet 1991) as well as phase 2b trials of the first malaria vaccine candidate (RTS,S) in Africa (Lancet 1994) and the first proof-of-concept trials of RTS,S in African children and infants (Lancet 2004 and 2007). He is also lead author on papers showing the safety and efficacy of iron supplementation in young infants in malaria-endemic areas (Lancet 1997) and presenting the first proof of concept of intermittent preventive treatment in infants as a potential malaria control tool (Lancet 2001). He has published more than 300 papers in international peer-reviewed journals.

Between 2005 and 2007, together with Professor Fred Binka, he led the steering committee that designed and implemented the European Union EDCTP (European and Developing Countries Clinical Trials Partnership) initiative. He has served on several national and international committees. Currently, he is a board member of the Medicines for Malaria Venture, Co-Chair of the Steering Committee of the Decade of Vaccines Collaboration an initiative promoted by the World Health Organization (WHO), UNICEF, the National Institute of Allergy and Infectious Diseases and the Bill & Melinda Gates Foundation, and Chair of the Steering Committee of the Malaria Eradication Scientific Alliance, MESA. He is also a member of the WHO Malaria Policy Advisory Committee.

Challenges in the clinical development of new global health products: the role of african research centers

Pedro Alonso
Barcelona Institute for Global Health (ISGlobal). Spain.

Only 10% of the funding goes to what causes 90% of the burden of the disease in the world. That is what it is known as the Gap 10/90. This Gap reflects one of the challenges that developing countries face in terms of development of new global health products.

We could think of different mechanisms to overcome or improve this gap, such as Public-Private Partnerships, innovative R+D policies or changes in the funding strategies of international donors. Nonetheless, African Research Centres are increasingly becoming crucial actors in the global health research arena, ensuring sustainable research to find new tools to fight the diseases of poverty. The creation of nodes of excellence among African institutions is playing a pivotal role in this process.

There are few,but outstanding examples of African research institutions that have consolidated their research activities to the highest standards and have greatly contributed to the development of new global health products of prevention, diagnosis and treatment. Continuous capacity strenghtening actions and increasing support from local and national political stakeholders are critical issues to ensure quality research from the countries enduring the highest burden of disease.

Luc Hessel. Chairman of Clinical Development Team. TBVI, graduated in medicine from the University of Bordeaux in 1973, followed by 13 years of clinical and academic activities in Internal Medicine and Public Health at the University of Limoges, France. Dr. Hessel joined Sanofi Pasteur in 1986 to work in clinical research and development of new vaccines and other biopharmaceuticals. In 1992 he was promoted to direct the Medical Department and in 1997 to set up the Medical Department of Sanofi Pasteur MSD, the European Joint Venture between Sanofi-Pasteur and Merck & Co. Until April 2010 he was Executive Director, Policy Affairs Europe at Sanofi Pasteur MSD. He has been an active member of several international scientific committees and advisory boards at the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) and the European Vaccine Manufacturers Association (EVM), has co-authored over 90 articles in renowned journals, contributed several chapters to books on vaccines and is invited regularly to speak at and to chair conferences in the field of vaccinology. As an independent expert, Dr. Hessel is providing advice on the development of new vaccines and the implementation of vaccination policies to public health organisations, NGOs and vaccine companies. Among these activities, he is currently chairing the clinical development team of the TuBerculosis Vaccine Initiative, TBVI (www.tbvi.eu), and coordinating the activities of the Initiative against Diarrheal and Enteric diseases in Asia and Africa, IDEA (www.idea-initiative.info).

Challenges in the clinical development of new tuberculosis vaccines

Luc Hessel
Clinical Development Team, TBVI. Holland.

Over the past decade, major investments and progress have been made to develop vaccines against tuberculosis that would improve the efficacy of BCG either as priming, boosters or immunotherapeutics. To date, a dozen of candidate vaccines are undergoing clinical testing, some already in advanced phase 2b.

Clinical testing is a stepwise approach consisting of a logical and chronological series of clinical trials aimed at answering pre-defined questions to demonstrate the safety and efficacy of the vaccine. They are usually classified in several phases. Phase 1 is the first administration in man providing preliminary safety (and immunogenicity) data in small numbers of subjects (primarily healthy adults). The objectives of Phase 2 studies are to document what is needed before testing the actual efficacy of the vaccine, including the assessment of the safety & immunogenicity of the vaccine in the intended target population(s), defining the optimal dosage, administration route and schedules, and concomitant administration with other vaccines. Getting early evidence of efficacy, also called "clinical proof of concept", represents a critical intermediate step to progress in clinical development before moving to the major financial investment needed for formal efficacy demonstration. This can be obtained in a phase 2b trial, conducted in the same environment and conditions of a phase 3, but in a smaller population, in order to detect a positive trend in protection, without necessarily meeting the compelling statistical efficacy demonstration. Phase 3 is the formal demonstration of protection

against pre-defined clinical outcome(s), i.e. the "pivotal" study to licensure, usually consisting of large-scale, randomized, controlled, double blind trials.

Clinical testing of tuberculosis vaccines faces several challenges They can be related to the type of vaccine (live vaccines for primary vaccination or booster in BCG-vaccinated individuals), the expected target population (age, HIV status), safety issues related to live vaccines or adjuvants, immunological and clinical endpoints, and other regulatory hurdles, methodological and logistical issues.

These many pitfalls should not refrain the development of new TB vaccines. They must be identified early enough in the selection and pre-clinical development of candidates, and addressed as part of the design of the clinical development plan of the vaccines. They must also stimulate research on the epidemiology of the disease, diagnostic methods, correlates of protection, mathematical modeling and other innovative methodological approaches in order to deliver safe and effective new TB vaccine as fast as possible.

Mark Hatherill is Associate Professor and Interim Director of the South African Tuberculosis Vaccine Initiative (SATVI), and a Member of the Institute of Infectious Disease & Molecular Medicine (IDM), based at the University of Cape Town. He trained as a specialist paediatrician in South Africa and in paediatric intensive care in the UK and Australia. He received his Doctoral degree, based on the pathophysiology of paediatric septic shock, from UCT.

He has worked in the field of TB vaccine development for 9 years, as investigator on multiple clinical trials of new vaccines and related TB diagnostic studies, drug trials, and epidemiological studies. He leads the SATVI clinical trials team, which has conducted 16 trials of 7 new TB vaccines, involving more than 3,000 infants, children, and adults, at the SATVI research site near Worcester. His primary research interest is the design and implementation of novel TB vaccine clinical trial designs, particularly proof-of-concept efficacy studies.

Matching TB vaccine clinical trial site to study design

Mark Hatherill
SATVI, University of Cape Town. South Africa.

The several novel TB vaccines in clinical trials vary widely in target product profile and stage of clinical development. To meet the development needs of these vaccines, Phase I-IIb trials are being designed for different study populations (eg. TB uninfected and infected persons and HIV uninfected and infected persons) and age groups (newborns, infants, adolescents, and adults). Proof of concept studies will target high risk study populations, such as TB uninfected adolescents, or adults with prior TB disease, to test vaccine efficacy against TB infection or disease endpoints with high rates of accrual. Site-specific factors, including study community, geography, and clinical and laboratory capacity, which present either challenges or opportunities for the conduct of TB vaccine trials, will be discussed in the context of clinical trial phase, target age group, and study population.

Harleen Grewal. Professor of Microbiology and Global Health at the University of Bergen, Norway and Adjunct Professor at the St John's Research Institute, Bangalore, India. Her research has focused on the molecular pathogenesis of diarrhoeal and respiratory pathogens. Since 2002, efforts have concentrated on diverse aspects of tuberculosis -related research. Studies include; cross-sectional studies in Myanmar, India, Nepal, Tanzania and South Africa: on the treatment outcome of TB in patients, elucidation of the extent and molecular nature of drug resistance among prevalent *M. tuberculosis* (Mtb) isolates in population based studies, in-depth (microarray studies) molecular characterization of Mtb isolates, development of novel diagnostic methods for rapid identification and drug susceptibility testing of Mtb, development and evaluation of surrogate markers for disease progression and protective immunity and randomised control trials of micronutrient supplementation in TB patients. A major thrust of the current studies; include the development, in collaboration with partners of a phase 1/II TB vaccine efficacy testing site in South India. Prof. Grewal is the recipient of several international prizes including the Schering-Plough prize and theFalchprize in Medical Research.

TB Trials: Development of a TB clinical trial site in Southern India
Harleen Grewal
Department of Clinical Science, University of Bergen. Norway.

The talk will describe the intricate steps involved in the development of a TB clinical trial site (Palamaner, Andhra Pradesh, India). The site developed initially by the Aeras Global TB Vaccine Foundation, USA and later supported by the Research Council of Norway, has since its inception successfully conducted 3 large prospective cohort studies (adolescent, neonatal and a household cohort study) of TB. The broad aims of these studies and efforts, are to measure the incidence of *Mycobacterium tuberculosis* infection and TB disease in target populations; to evaluate the ability of novel diagnostic tools to identify TB at an early stage; contribute to developing immune-correlates of protection against TB for use as endpoints in TB vaccine efficacy trials; measure the immunogenicity and any toxicity of new TB vaccines; strengthen capacity in and transferring technology relevant to TB vaccine development and to build a field site in South India capable of undertaking large-scale TB vaccine efficacy trials.

These efforts, led by the TB Trials consortium, comprising scientists in Denmark, India, Norway, South Africa and the U. S., have also resulted in the recent completion of a phase 1 trial ofAERAS-402/CrucellAd35 (Ad35 vectored TB vaccine candidate). This represents the first approval of a clinical trial of a new TB vaccine in India.

Alberto García-Basteiro is currently the TB Research Coordinator at the Manhiça Health Research Center (CISM) in Mozambique. In 2010, he joined the Barcelona Centre for International Health Research (CRESIB), main partner institution of CISM with which he shares professional affiliation.

He has participated as investigator in different vaccine trials (influenza and

herpes zoster). His current research interest is the epidemiology of tuberculosis and other poverty related diseases. In Moçambique, he coordinates different studies on the clinical, microbiological and sociological characterization of tuberculosis in a high HIV burden setting.

He received his MD from University of Santiago de Compostela in 2007 and finished his training in Public Health and Preventative Medicine at Hospital Clínic in Barcelona in 2012. He holds a Master Degree in Epidemiology by the London School of Tropical Medicine and Hygiene (LSHTM) and received the Enrique Nájera award for young epidemiologists from the Spanish Association of Epidemiology in 2012. He is a lecturer in Epidemiology at the MSc of Global Health organized by the Barcelona Institute for Global Health (ISGlobal) and the University of Barcelona.

The importance of demographic and morbidity surveillance platforms for vaccine clinical trials: The example of Manhiça, Mozambique

Alberto García-Basteiro

Centro de Investigação em Saúde de Manhiça (CISM). Mozambique.

Mozambique is one of the 22 high burden tuberculosis (TB) countries and one of the few ones whose TB figures have not improved in recent years. According to the latest WHO Global TB Report, it has one of the lowest case detection rates in Africa, with only around 34% of estimated cases being notified. It also has one of the highest TB / HIV co-infection rates in the world. However, routine documentation of population health as well as individual hospital records is scarce and poor. Similarly, available demographic data are incomplete and often inaccurate, precluding the possibility of conducting high quality biomedical research.

Within this context, the Manhiça Health Research Centre (CISM from its acronym in Portuguese) was created in 1996 in a rural area of southern Mozambique to promote and conduct biomedical research in priority health areas. It has three intertwined research platforms that are crucial to conduct its activities: 1) Morbidity surveillance; 2) A demographic surveillance systems (DSS); and 3) A geographic platform with all households geopositioned by GPS. The DSS covers a study area of 500 km^2 and follows on a yearly basis around 94 000 individuals living in approximately 20 000 enumerated households. Morbidity surveillance is routinely conducted among all children less than 15 years old visiting the outpatient consultation and inpatient clinics in the study area. Standardized questionnaires are completed for each child seen at the outpatient and inpatient clinic.

Among others, these platforms enhance the capacity for subject identification and recruitment, as well as clinical follow up and detection of unnoticed health care visits through passive case detection. Moreover, it allows research on baseline socio-demographic studies and other epidemiological studies on relevant infant and adolescent vaccine trial endpoints which are otherwise hard to obtain. The combination of highly equipped laboratory facilities with demographic, morbidity and geographical platforms facilitates the conduction of GCP compliant clinical trials in a high TB and HIV burden setting.

Session VI

PRECLINICAL DEVELOPMENT OF NEW TB VACCINES

Ann Rawkins nee Williams is a Scientific Leader providing scientific direction to the TB research programme at the Public Health England laboratories at Porton Down, Salisbury, UK. The broad aim of the group is to study the physiology, molecular genetics of *M. tuberculosis* in order to identify and further develop vaccine and/or therapeutic targets and to evaluate these in specialised in vitro and in-vivo models. She has conducted *M. tuberculosis* research for the past 18 years, initially establishing aerosol-challenge in-vivo models leading to an expertise in novel vaccine development and evaluation and in aerobiology and has published widely in the name of Williams. The TB vaccine evaluation team which she established is internationally renowned and collaborates with the majority of TB vaccine developers world-wide including involvement in EU FP7 TRANSVAC and NEWTBVAC projects. Dr Rawkins is a member of the TBVI steering committee.

Preclinical animal models

Ann Rawkins Williams
Public Health England, Porton Down, Salisbury.

There are now more than a dozen new TB vaccines undergoing trials in humans and the first efficacy trial has been completed. Additional candidates are being proposed for clinical testing and, with limited resources, robust and informative criteria are needed to select and prioritise only the most promising vaccines for early and late-stage clinical development. Pre-clinical testing in animal models is an essential component of the decision-making process. Direct comparisons of vaccine candidates head-to-head and the use of pre-agreed selection criteria, are increasingly being used for TB vaccine portfolio management. This requires consensus and acceptance of the animal models and the study designs in order that the selection criteria can be consistently applied by different funding bodies or developers.

Considerable effort is on-going to identify and validate immune correlates of risk and /or protection but in the meantime, in animal models, the efficacy of TB vaccines must be demonstrated by protection against virulent challenge. The PhIIb clinical trial of MVA85A provides an opportunity to compare efficacy in pre-clinical animal models with efficacy in humans and to begin the iterative process to improve pre-clinical screening. In the absence of positive human efficacy data, it is not possible to validate any of the animal models or any of the measures or read-outs of protection, but lessons can be learned. There were several fundamental differences between the MVA85A trial and the animal data on the same vaccine which included the age of the subjects, the strain and dose of *M. tuberculosis* challenge, the measures of vaccine efficacy and, importantly, the magnitude of efficacy which the trial / experiments were powered to observe. It is important to understand these differences to allow improvements to the models such that they are more predictive for future human efficacy trials. Examples of improvements might include the use of lower dose *M. tuberculosis* challenge, including infection by natural transmission and implementation of efficacy read-outs e.g. advanced imaging, which are directly translatable to humans. Improved animal models which take into account the target product

profiles of the vaccine are likely to have increased complexity. It is essential that even the more complex models remain reproducible and robust to allow objective decisions to be made. Different models simulating relevant clinical settings will be discussed in relation to study design and interpretation of data.

Camille Locht holds currently a position as Research Director at the French National Institute of Health and Medical Research (Inserm) and heads the Center for Infection and Immunity of Lille on the campus of the Institut Pasteur de Lille in France. He has obtained his PhD at the Catholic University of Leuven in Belgium in 1984. After a 3-years post-doctoral stay at the National Institute of Allergy and Infectious Disease in the USA, where he started to work on pertussis and cloned the pertussis toxin genes, he joined SmithKline - Beecham (now GSK) to help developing acellular pertussis vaccines. Since 1989 he is the head of a research laboratory at the Institut Pasteur de Lille, where he has been the Scientific Director from 2005 to 2013. His research interest is in molecular pathogenesis of respiratory infections, essentially pertussis and tuberculosis, with the long-term aim to develop new vaccines against both diseases. A very powerful molecular typing system for mycobacteria, invented in his laboratory has already reached the market, and a live attenuated nasal pertussis vaccine developed in his laboratory has now successfully completed phase I clinical trials and is currently in clinical development. He has authored more than 250 international publications, several dozens of patents and has obtained several research awards in France.

Preclinical development of HBHA

Camille Locht
Center for Infection and Immunity of Lille. Institut Pasteur de Lille. France.

The heparin-binding haemagglutinin (HBHA) is a surface-associated protein antigen of *Mycobacterium tuberculosis* and is involved in extra-pulmonary dissemination of the tubercle bacillus. Latently infected subjects mount a strong T-cell response to HBHA, which is much less the case in patients with active disease. The HBHA-specific T cell responses in latently infected subjects is evidenced by IFN-γ secretion by $CD4^+$ and by $CD8^+$ T cells, as well as by bactericidal and perforin-mediated cytotoxic$CD8^+$ T cell responses. These observations suggest that the HBHA-specific T cell responses in latently infected subjects contribute to protection against disease. Several clinical observations have also indicated that low responses to HBHA can lead to progression to active disease, indicating that HBHA may also be a useful antigen for risk stratification of *M. tuberculosis*-infected individuals. In the presence of appropriate adjuvants HBHA also induces significant protection against *M. tuberculosis* infection in mice. This protection requires not only the induction of HBHA-specific IFN-γ, but also of IL-17, as combinations of HBHA with adjuvants that only induce IFN-γ responses do not protect. In addition, HBHA also increases significantly the protective responses induced by BCG, especially when the antigen is administered several months after priming with BCG. Thus, HBHA may be a good antigen to be included in vaccines destined to boost BCG-induced immunity or to strengthen protective immunity in latently infected subjects. It is therefore currently undergoing product and clinical development. However, HBHA is a post-translationally methylated protein, and the proper methylation profile has

so far only been found in *M. tuberculosis* or very closely related mycobacteria such as BCG. Therefore, the antigen is currently purified from a recombinant BCG strain overproducing HBHA. A production process has now been developed in collaboration with Aereas, and the purified product is undergoing preclinical testing in order to prepare clinical trials.

Peter Sander, PhD. Is Professor in Medical Microbiology at the Institute of Medical Microbiology, University of Zurich. He is member of the NewTBVac consortium and co-inventor of BCG *zmp1* vaccine. Dr. Sander is an internationally highly regarded expert in tuberculosis. He has published more than 60 original research articles. Within the last two decades, Dr. Sander made ground breaking contributions to the development of genetic tools for mycobacteria and pioneered lipoprotein research in mycobacteria. He identified lipoprotein biosynthesis as a major virulence factor in the pathogenesis of *Mycobacterium tuberculosis* infection and solved the structure of the membrane anchor of mycobacterial lipoproteins at the molecular level. His research on mycobacterial zinc metalloprotease Zmp1 resulted in a highly promising tuberculosis vaccine candidate. Research of Dr. Sander is funded by Swiss National Science Foundation, European Union (member of several frame work programs), University of Zurich and private foundations.

Immunogenicity and protectivity of BCG △zmp1 – a new live vaccine at the horizon

Peter Sander
Institute of Medical Microbiology. University of Zurich. Zurich. Switzerland.

Preclinical results from various immunological and protection experiments suggest that BCG *△zmp1* is a promising and innovative tuberculosis vaccine candidate. Zmp1 encodes a zinc metallopeptidase with structural similarity to human neprilysin (**Ferraris *et al.*, 2011**) and has an optimal enzymatic activity at a slightly acidic pH (**Petrera *et al.*, 2012**). A BCG *△zmp1* mutant is unable to arrest phagosome maturation and elicits an increased pro-inflammatory IL-1β response (**Master *et al.*, 2008**). In-vitro and in-vivo immunological assays reveal that relief of Zmp1-mediated phagosome maturation arrest facilitates antigen presentation and increases immunogenicity of mycobacterial antigens in mice, resulting in an increased immunogenicity of BCG *△zmp1* as compared to BCG (**Johansen *et al.*, 2011**). Corroborating these findings, we recently observed that BCG *△zmp1* also shows enhanced immunogenicity in cattle (**Khatri *et al.*, 2014**). Most importantly, BCG *△zmp1* consistently confers better protection than BCG against an aerosol challenge with virulent *Mycobacterium tuberculosis* in the low dose guinea pig model. Notably, the improved protection is independent of the genetic background of the BCG strain as it is observed with *△zmp1* mutants of BCG Pasteur and BCG Denmark. BCG *△zmp1* shows a satisfying BCG-like safety profile (**Johansen *et al.*, 2011**). Protection experiments in advanced animal models (non-human primates, cattle) are ongoing. A joint product and clinical development team for this promising and innovative vaccine candidate has been built.

Support: European Union (FP7), Tuberculosis Vaccine Initiative (TBVI), AERAS, Swiss National Science Foundation (SNSF), University of Zurich (UZH).

Eugenia Puentes is the Director of R&D and Qualified person of the Spanish biopharmaceutical company Biofabri.

In 1981 she obtained her degree in Pharmacy from the Universidad de Santiago de Compostela (USC), Spain. She did the research work for her PhD thesis in the Immunology group of the Department of Microbiology (USC). She obtained her specialist in Microbiology in 1987 and her PhD in Pharmacy in 1991.

In 1985, she joined to the biological technical department of Cooper-Zeltia. In 1993 was awarded an EC Human and Capital Mobility Programme Fellowship and moved to the UK for 18 months as Research Fellow in the Molecular and Cell Biology Department (University of Aberdeen). In 1994, she moved to Director of R&D and Regulatory Affairs of CZ Veterinaria and in 2009 to her current position. She has extensive experience in the development and production of vaccines. She has participated as principal investigator in several research projects on development of animal health and human vaccines. She is currently working in the industrial development of MTBVAC, a live freeze-dried vaccine against tuberculosis. Biofabri has produced the clinical lot of MTBVAC and has been the sponsor of Phase I clinical trial (NCT02013245).

Industrial production of TB vaccines

Eugenia Puentes
Director Research and Development, BIOFABRI. Spain.

The development of a new tuberculosis vaccine is an urgent need due to the failure of the current vaccine BCG, to protect against the respiratory form of the disease. MTBVAC is a live, rationally attenuated clinical strain of *Mycobacterium tuberculosis*, constructed by two stable deletions, without antibiotic resistance markers, in the virulence genes *phoP* and *fadD26*. MTBVAC is the first live attenuated candidate vaccine developed according with and fulfilling the Geneva consensus requirements for live TB vaccines (Arbues *et al* Vaccine 2013). The experience of taking the vaccine candidate MTBVAC into clinical trials will be presented as an example of industrial tuberculosis vaccine development.

Given the convincing results on safety, immunogenicity and protective efficacy, industrial process development of MTBVAC, as a live freeze-dried vaccine, was initiated. Manufacturing facilities authorizations to work with GMOs and to manufacture the investigational medicinal product were granted. Phase 1 final lot was produced applying the GMP principles and guidelines, and meets essentially the requirements given in the European Pharmacopoeia and WHO recommendations for manufacture and control of the freeze-dried BCG. The consistency approach for quality control of vaccines has been followed. The production is based on a seed lot system. Seed lots have been fully characterised and absence of virulence, genetic stability and antibiotic sensitivity studied. The materials used in all stages derive from animal-free sources. The production process has been optimised and established, production steps standardised and critical stages and QC tests validated. In process and final product precise specifications have been defined. Adequate stability studies to support shelf-life have been performed.

The GMP Phase 1 final lot underwent a battery of non-clinical studies, following regulatory requirements, to support the conduct of human clinical trials. MTBVAC entered Phase I clinical trial in January 2013 (NCT02013245).

Arbues *et al*. "Construction, characterization and preclinical evaluation of MTBVAC, the first live-attenuated *M. tuberculosis*-based vaccine to enter clinical trials. Vaccine. 2013; 31(42): 4867-73.

Barry Walker is Vice President, Preclinical Development at Aeras, based in Rockville, Maryland, USA with offices in Cape Town and Beijing. He is responsible for the management of the portfolio of preclinical and translational tuberculosis vaccine candidates being developed both internally by Aeras and in close collaboration with partners worldwide. He has maintained an active research interest in tuberculosis and the immunology of vaccines against poverty related diseases, including HIV and malaria. Dr. Walker trained in immunology at the University of Western Australia, and completed his PhD in the immunology of renal transplantation. Subsequently he moved to the UK, to the Royal Postgraduate Medical School, where his interest in mycobacterial infection and vaccinology was fostered. After a period at the National Institute for Medical Research at Mill Hill, he moved to a PI and Group Leader position at the National Institute for Biological Standards and Control (NIBSC), where he continued his involvement in tuberculosis, HIV and malaria and also obtained extensive experience in regulatory aspects of vaccine development and the critical parameters for success of preclinical to clinical development. In 2012 he moved to his current position at Aeras, a non-profit product development partnership with the mission to develop safe and effective tuberculosis vaccines and make them available to those who need them most in developing countries.

Stage gating and portfolio management of TB vaccines

Barry Walker

Vice President, Preclinical Development at Aeras. USA.

Stage Gates (SGs) and portfolio management are well established concepts in the pharmaceutical industry, however application within the vaccine development space has been complicated by gaps in our mechanistic understanding of vaccine function, and a lack of correlates of protection and surrogate markers that predict clinical outcome. Having said that, harmonized and agreed-upon SGs are technical criteria that are based on scientific merit and technical feasibility providing a harmonized framework to aid decision making in advancing and investing further in developing vaccine candidates through within the R&D pipeline. The use of SGs creates this framework can provide clarity and consistency to both developers and investors in making vaccine development decisions based on the best available scientific knowledge, utilizing pre-specified within an agreed decision making criteria. Portfolio management uses similar criteria as utilized in Stage Gating, but takes into consideration the overall balance of the entire vaccine portfolio, including the target product profiles and functional/mechanistic similarities between different vaccine candidates being developed. Accordingly, the portfolio management process fosters diversity in the pipeline through identifying gaps in the portfolio and providing the impetus for establishing developing criteria for selecting candidates to fill those gaps.