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Searching for novel TB vaccine paradigms

Douglas Young

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Encouraging progress has been made in taking lead TB vaccine candidates forward into clinical trials, and initial indications of efficacy are anticipated within the next few years. In parallel with this effort, it is important that we continue development of the next generation of candidates. First generation candidates are based on the paradigm that amplifying the naturally-induced repertoire of IFNγ-expressing CD4 and CD8 T cells will result in enhanced protection. Several alternative paradigms can be proposed as a basis for next generation candidates. Rather than focusing on dominant responses induced by natural infection and BCG vaccination, candidates that elicit sub-dominant or novel responses could be explored. The absolute number of primed T cells may be less important than the kinetics of their recruitment to the site of infection; this could be influenced by vaccine formulation or route of inoculation. Immune effector function operates in a window between activation and restoration of homeostasis; manipulation of regulatory circuits could enhance protection by extending this window. Manipulation of innate immunity – in terms of both anti-mycobacterial activity and signalling to the adaptive response – could be explored. Potential strategies for antibody-mediated manipulation of immune responses will be discussed.

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Animal models for TB vaccines

Ann Rawkins nee Williams

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A more effective vaccine that improves upon the current BCG would dramatically reduce the global burden of TB disease in humans. The progression of new vaccines to clinical trials requires evaluation in well-characterised pre-clinical animal models to ensure that only the safest and most effective vaccines reach the clinic. Animal models played a critical role in the search for improved vaccines supporting vaccine developers in the major European efforts, in Framework Programmes 5, 6 and currently in the FP7 project NEWTBVAC. The majority of the vaccines were evaluated in well-established, guinea pig experimental aerosol challenge models of human TB infection and included all of the commonly used antigens and delivery systems including different routes of administration. In addition, evaluations were performed in mice and in non-human primate models of TB, the latter allowing the definition of biomarkers of disease and vaccine-induced immunity. The most promising vaccines to emerge from these evaluations included prime-boost regimes involving BCG prime and novel sub-unit boost, orally delivered BCG, BCG over-expressing novel antigens and attenuated *M. tuberculosis*. Orally delivered BCG in a suitable delivery system has been shown to be highly protective against *M. tuberculosis* challenge and such convenient administration offers many advantages to control TB in humans. Overall, the animal models have provided important data to inform the selection of novel vaccines for progression towards phase 1 clinical trials.

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Pere Joan Cardona

UTE. Fundació Institut Germans Trias i Pujol, Badalona.

The dynamic hypothesis of latent tuberculosis infection (LTBI) is the only one that can explain its actual treatment with isoniazid (INH) for 6 to 9 months. And what is most important: it also justifies the development of therapeutic vaccines. This hypothesis is far from the traditional view that justifies LTBI by the capacity of *M. tuberculosis* to remain dormant inside an old lesion for the whole life of the host.

Taking into account this rational a new therapy against LTBI has been designed based on the benefits given by short-term chemotherapy (INH for one month), that reduces 90% of the replicating bacilli and the positive feed back of the immune response towards them; together with limiting the local immunosuppression and inflammatory response. Two shots of a therapeutic vaccine made with fragmented *M. tuberculosis* cells (vaccine RUTI® manufactured by Archivel Farma, Badalona) are given after stopping the INH administration to avoid immediate regrowth and to help the surveillance against non-replicating bacilli.

After demonstrating its utility in experimental models of infection in mice, guinea pigs, goats and minipigs, RUTI® started its clinical development with a Phase I clinical trial revealing a good safety and immunogenicity profile. A Phase II has already started in 3 sites in South Africa to demonstrate its tolerability and the induction of specific immune response in people HIVnegative and HIVpositive with LTBI. Data obtained will decide which dose will be used for the proof of concept trial (Phase III) that will be started next year to compare the efficacy of 6 months INH treatment with the RUTI-based one.

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Immune responses induced by BCG vaccination in UK and Malawi

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The Bacille Calmette-Guerin (BCG) vaccine is the only currently licensed vaccine against tuberculosis, and has been given to over a billion individuals worldwide, mostly shortly after birth. Some of the new candidate TB vaccines are designed to boost the immunity induced by BCG vaccination, while others are designed to make BCG a safer or more effective vaccine, through genetic modification. However BCG vaccination of adolescents and adults has induced variable protection against pulmonary tuberculosis with evidence of geographic variation. We have compared the immune responses induced by BCG vaccination of infants in Malawi and the UK, and compared these responses to those in unvaccinated UK infants. Production of IFNγ in PPD-stimulated diluted whole blood cultures was present in vaccinated UK infants but not in unvaccinated UK infants, testing at 3 and 12 months post vaccination. Vaccinated Malawian infants showed lower IFNγ responses than vaccinated UK infants. Testing of supernatants using a multiplex assay showed that the Malawian infants had a different cytokine profile than the UK infants, with greater production of some cytokines, including Th2 cytokines. Thus vaccination even of immunologically naïve infants may induce distinct biosignatures in different settings. Further studies are needed to understand such differences, how they may affect the immunity induced by the candidate TB vaccines currently in development, and how they could impact on the protective efficacy of both BCG and any new TB vaccines.

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Clinical evaluation of subunit H1 vaccine

Tom Ottenhoff

Ag85B-ESAT-6 adjuvanted with IC31® promotes strong long-lived *Mycobacterium tuberculosis* specific T cell responses in healthy TB-naïve human volunteers

Tom H. M. Ottenhoff, Jaap T. van Dissel, Sandra M. Arend, Corine Prins, Peter Bang, Pernille Nyholm, Tingskov, Karen Lingnau, Jan Nouta, Ida Rosenkrands, Ingrid Kromann, T. Mark Doherty and Peter Andersen.

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Improved TB vaccines that induce long-term immunity against TB are urgently needed. Protective immunity against *M. tuberculosis* is thought to depend on Th1-type cellular immune responses, which leads to the secretion of IFNγ. Here, we monitored safety and IFNγ responses in healthy TB–naïve humans receiving a novel synthetic TB vaccine, composed of a defined antigen, fusion protein Ag85B-ESAT6 (H1), and IC31®, a new Th1-promoting adjuvant.

The H1 fusion protein was tested in a phase I study in healthy male volunteers, administered at 0 and 2 months as recombinant protein alone or combined with two concentrations of IC31®. Safety was evaluated by physical examination and blood and urine parameters. Immunogenicity was monitored over a 2 ½ year

In conclusion, the TB subunit vaccine Ag85B-ESAT6, given in combination with the novel adjuvant IC31® is safe and well-tolerated in healthy TB - naïve volunteers and induced a strong Th1-type cellular immune response that persisted undiminished for 2½ years after vaccination.

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The improved BCG vaccine: From mouse to man

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The current vaccine against tuberculosis (TB), *M. bovis* BCG protects against severe forms of TB in infants, protective effects in adults are doubtful. Thus, the most prevalent form of the disease today, namely pulmonary TB in adults cannot be controlled by BCG. It has been predicted that TB incidences could be reduced by a new pre-exposure vaccine which prevents TB in adults by up to 50%. Therefore, novel vaccines with improved efficacy and safety profile are urgently required. We have decided to improve BCG by molecular genetic techniques. We have introduced listeriolysin (Hly) from *L. monocytogenes* and deleted the urease-C gene in BCG. This recombinant strain, r-BCG ΔureC:Hly shows superior protection and safety over BCG in preclinical models. It has an excellent toxicity profile and has been graded as P1 organism. The construct has been licensed to Vakzine Projekt Management who sponsor the clinical trials. It was produced at good manufacturing practice (GMP) and introduced into a phase I clinical trial in Germany, which revealed good safety and immunogenicity profile. Hence the vaccine has now started a phase Ib trial in a tuberculosis-endemic area in Sub-Saharan Africa. We analyzed the immune mechanisms underlying superior protection of our r-BCG ΔureC:Hly and found evidence that it induces crosspriming and stimulation of Th17 cells. The most likely immunologic mechanism underlying superior protective immunity is apoptosis of macrophages infected with r-BCG ΔureC:Hly which leads to the formation of apoptotic blebs containing mycobacterial components which serve as antigens and immune stimulators.

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Tuberculosis: A global perspective

Giuliano Gargioni

Stop TB Partnership, World Health Organization

With an estimated burden of 9.4 million new cases and 1.9 million deaths in 2008, tuberculosis remains one of the most challenging global public health emergencies. About 1.4 million people suffer from a HIV-associated TB, responsible for more than half million death every year. The problem is further compounded by the increasing number of MDR-TB cases, close to 450,000 new cases with about 150,000 deaths every year, and by the emergence of extensive drug resistant TB (XDR-TB) over the last few years.

The international community has set clear targets to reverse the trend of the TB epidemic in the context of the 2015 Millennium Development Goals. Significant results have been obtained in reducing TB prevalence and mortality globally, while incidence is declining more slowly than predicted.

We must acknowledge some achievements of the DOTS and Stop TB Strategy, but also recognize some major challenges ahead. About 36 million patients have been cured over the period 1995-2008 and 6 million deaths have been averted. However, the quality of diagnosis and care is not uniform in all settings; TB/HIV poses great threats in Africa and MDR-TB rates are especially alarming in the former USSR and China; weak health system cannot deliver good care; all health care providers, from the state and the non-state sector, must be involved in addressing this public health issue; communities need to be involved and empowered and, finally, innovative tools (diagnostics, drugs and vaccines) and operational research are necessary.

Finally, we must recognize that if our goal and focus will move from TB "control" to TB "elimination" the traditional area of core TB control activities will not be enough, but will have to be complemented by work in the area of health systems and policies, by the decisive research of new tools and by the commitment of governments to development policies with a positive impact on the social determinants of health.

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Tuberculosis epidemiology in the EU/EEA and the need for new tools to fight TB

Emma Huitric

Tuberculosis program from ECDC (Centro Europeo para la Prevención y Control Enfermedades Infecciosas)

In 2008, 82 611 Tuberculosis (TB) cases were reported in the EU and EEA, showing a decrease of 615 cases compared with 2007 and resulting in an overall notification rate of 16.7 per 100 000. Despite a sustained mean annual decline over the past 5 years (3.3%), the 1.2 % decrease recorded between 2008 and 2007 is the lowest recorded for the past four years. Multi Drug Resistant (MDR) TB increased from 4% to 6% between 2007and 2008 and 90 cases of Extensively Drug Resistant (XDR) Tb were reported. This is the first time XDR TB is reported and these numbers warrant an increased vigilance of resistance to second-line drugs. Although the quality and completeness of treatment outcome monitoring data has improved, these outcome indicators remain sub-optimal; only three countries have achieved the treatment success rate target of 85% or higher, set by the StopTB Partnership. Successful outcome after 24 months' treatment for MDR TB is further extremely low at 30.9%; much below acceptable levels.

To ensure TB control and ultimately reach elimination in the EU and globally, there is an urgent need for new tools for TB; comprising new diagnostics, drugs and vaccines. A key area of work within the ECDC TB programme is to provide EU-Member States with the latest, most up-to-date scientific evidence in the form of guidance, as a support for developing and improving national TB programmes. Furthermore, the ECDC recently formed a European Reference Laboratory Network for TB (ERLN-TB), represented by all MS, which will further play an important role in assuring the optimal introduction of new tools for TB as they become available. During the current talk, an overview of the TB situation in the EU/EEA will be given as well as a description of ongoing work at ECDC within the field of new tools for TB.

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EC towards innovative research for TB

Hannu Laang

Scientific officer European Commission DG Research, Unit F3 Infectious Diseases, Brussels, Belgium

The multi-annual Framework Programmes (FPs) are the main tool of the EU to fund cooperative research in Europe with the goal of boosting European competiveness and solving societal problems. They promote cooperation within Europe across different sectors, but also encourage participation of researchers from countries outside Europe. Health research is a major theme in the Cooperation Programme with a total of € 6.1 billion earmarked for funding during the duration of FP7 (2007-2013). In the specific Health theme, Tuberculosis is one of the diseases that are prioritized.

In supporting Tuberculosis research specific call topics have been published in the Cooperation Health theme. These have been for either small-scale discovery oriented projects looking at e.g., host-pathogen interaction or diagnostics in Tuberculosis, or for large-scale translational projects in the field of Tuberculosis Vaccine development, Tuberculosis Drug development, or management of multi-drug resistant Tuberculosis. The purpose of setting up the large translational projects is to bridge the gaps between discovery and application.

The EC recognizes the importance of Tuberculosis research and is building partnerships with the Member States, disease endemic countries and other stakeholders to integrate European efforts with the global Tuberculosis research agenda. Innovative methods are needed in order to be able to answer to the growing need of research funds for development of better vaccines, drugs and diagnostics. In the last calls of FP7 more emphasis will most likely be put on supporting small- and medium-size enterprises (SMEs) and public-private partnerships. Establishment of the Tuberculosis Vaccine Initiative (TBVI) is an example of innovative funding, with the aim of maintaining and accelerating momentum in generation and testing of new tuberculosis vaccine candidates.

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The Bill & Melinda Gates Foundation Strategy to develop new tools for TB

Jan Gheuens, MD, PhD.

Sr. Program Officer, Tuberculosis, Infectious Diseases, Global Health Program, Bill & Melinda Gates Foundation

Today's global TB control, which is based on the DOTS strategy, focuses on the treatment of advanced infectious patients. Our goal is to shift this focus toward the prevention of transmission through prompt diagnosis and treatment in the short term and ultimately vaccination. Transforming global practices from treatment to prevention will require improved diagnostic tests, drugs and vaccines as well as systems redesigned to exploit their advantages.

We are pursuing this goal through a pragmatic, risk-balanced portfolio of investments. We have committed $887M toward TB to date with approximately 74% focused on the development of new vaccines, drugs and diagnostics, largely through investment in product development partnerships (PDPs). This and other's commitments have resulted in credible pipelines of vaccine, drug and diagnostic candidates.

Development of an improved TB vaccine has always been the highest priority of our TB program and, to date, we have committed about 36% of our total budget, mostly through AERAS. In 2009, we also made a grant to the Tuberculosis Vaccine Initiative (TBVI) to enable resource mobilization.

Until we have an effective vaccine, TB diagnostics that can promptly diagnose all TB patients will remain our primary tool for interrupting TB transmission – and are thus our third highest priority.

In its 2009 progress report, the Stop TB Partnership, using data from TAG and G-FINDER, estimated that there was a TB R&D funding gap of $520 million in 2007 and $530 million in 2008, based on total TB R&D costs for drugs, diagnostics and vaccines and operations research to achieve Global Plan targets. Despite an expected increase in total available resources for TB, Stop TB estimates that TB R&D funding through 2011 will still only cover 45% of the need. Looking ahead, funding for TB R&D will continue to be a challenge and will require significant efforts to maintain existing levels.

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European Initiative to develop TB Vaccines for the world

Jelle E.R. Thole

Director of TBVI, Lelystad, Holanda

BCG, the only available vaccine against TB, has little to no efficacy in preventing lung TB, the most common and most infectious form of TB. To eliminate TB, the world needs several types of new vaccines to replace or improve BCG. The development of new vaccines is a complex and long process, but we are making good progress. Up to now our consortium has developed already 6 concrete vaccine candidates. The University of Zaragoza has in this context shown promising results with its highly effective and unique MTBVAC01 vaccine candidate, which will soon enter the clinic.

The Spanish government has shown great commitment by putting TB on the European agenda and signing a resolution to support TBVI's activities. We need support like this to continue the search for new vaccines. Europe has the knowledge and the technology to play a crucial role in the fight against tuberculosis. Only with sustained political and financial support can we make affordable, effective vaccines against tuberculosis a reality.

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Development of a new attenuated vaccine: from preclinical to clinical evaluation

Carlos Martín
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The attenuated live vaccine BCG, is the current vaccine against tuberculosis (TB), has been used for more than 90 years but is ineffective at providing protection against adult pulmonary TB. Based upon the observation that *phoP* is an essential gene for *M. tuberculosis* virulence, we rationally attenuated the tubercle bacillus by inactivating *phoP.* The mutant was strongly attenuated in cellular and animal models. The *phoP* mutant resulted more attenuated than BCG Pasteur in immunocompromised SCID mice and protected guinea pigs and non-human primates against tuberculosis infection. The signal transcriptional factor PhoP has been recently shown to be crucial for intricate virulence networks in *M. tuberculosis*. This observation was used to construct a new generation of live vaccines based on *phoP* inactivation carrying a second additional mutation which affects the synthesis of a new family of lipids associated with *M. tuberculosis* virulence. The final construct MTBVAC01 developed at the University of Zaragoza was constructed by engineering two independent, unmarked, non-reverting deletion mutations in a clinical isolated of *M. tuberculosis* the *phoP* and the *fadD26* genes both being essential for *M. tuberculosis* virulence. MTBVAC01 is the first live attenuated candidate vaccine developed fulfilling the Geneva consensus requirements for live mycobacterial vaccines. The GMP manufacturer and industrial partner is CZ Veterinaria and its subsidiary BIOFABRI with extensive experience in GMP production of live mycobacterial vaccines.

Our plan of investigation is to progress the live attenuated MTBVAC01 vaccine candidate to first-in-human clinical evaluation. The vaccine candidate has demonstrated excellent attenuation, safety and protective efficacy profile conferred by rigorous preclinical studies in relevant animal models.

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