Annual Report 2011

TBVI

TuBerculosis Vaccine Initiative

TBVI – Runderweg 6 - 8219 PK Lelystad - The Netherlands – www.tbvi.eu

ANNUAL REPORT 2011

TuBerculosis Vaccine Initiative (TBVI) facilitates the development of safer, more effective vaccines to protect future generations against tuberculosis.

TBVI

TuBerculosis Vaccine Initiative

Five-year-old Priscilla Jimenez Flores plays with her neighbour in the Ate district of eastern Lima. Priscilla is recovering from multidrug-resistant TB. According to the World Health Organization at least half a million babies and children become ill with TB each year and as many as 70 000 die from the disease.

Contents

New partnerships, grown commitment and intensified collaboration

The enormous burden of TB, including the increasing rates of drug resistance, remains a huge concern for the whole world. New vaccines are an essential tool with which to prevent and control the disease and will have a vast impact in eventually stopping this threat. In order to deliver these new, more effective vaccines, commitment, collaboration and partnerships are absolutely key. Looking back at 2011, I am happy to see all of these have grown and intensified, together with steady progress in TB vaccine research and development.

With twelve vaccine candidates in clinical trials worldwide and several new ones rapidly advancing towards clinical evaluation, the hope of having a licensed vaccine by the end of this decade is becoming more and more realistic (see page 14). Looking at the global portfolio of TB vaccine candidates, I am proud of the work that has come out of TBVI's research network.

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This progress is being made possible through our funding base which we have managed to broaden and sustain. A new grant from EDCTP has allowed us to engage with African partners again within the TBTEA project (see page 26). TBVI is also involved in the recently launched ADITEC project, a collaborative research programme that aims to accelerate the development of pioneering immunisation technologies, funded by the European Union (see page 32). Throughout the year, we continued our work on innovative funding mechanisms that will enable the speedy development of new vaccines. One of the political highlights in that process was a resolution which was widely supported in the European Parliament in early 2011. The resolution called for European dedication to TB vaccine research and development, and reserved a key role for TBVI; a role that we will be honoured to fulfil.

In these times of financial and economic challenges, funding remains a worry, especially with regard to upcoming large and expensive clinical trials. Not finding the necessary financial and logistic resources would mean no vaccines reaching the market. Still, a positive side-effect of this challenge is that it forces all parties to seek collaboration. We have to join forces to reach our goals and I am happy to see that the work that has been carried out in the past year has really brought us closer to true global partnership.

The relationship with with TB vaccine developer Aeras, our strategic partner overseas in TB vaccine development, grew stronger on a strategic as well as an operational level. Together, Aeras and TBVI took the lead in launching a collaborative strategic document that presents the way forward in TB vaccine research (see page 20). The groundwork for "TB Vaccines: a Strategic Blueprint for the Next Decade" was carried out in 2010 in Tallinn and the document was launched and presented in March 2012. I look forward to seeing this strategy unfold in the near future. In that light, I am also very pleased with the preparations for the Third Global Forum on TB Vaccines that will be held in Cape Town, South Africa in March 2013. Moreover, this vision for the next decade will resonate in a renewed strategy that we will adopt in 2012.

Packed with meetings, symposiums, conferences and a heap of scientific work, 2011 was a good year. As a team, we look forward to stepping up the search for new TB vaccines in 2012 and beyond.

The case for new vaccines

New, more effective tuberculosis vaccines are urgently needed, yet without an increase of funding, research and development projects are at risk. TBVI therefore listed a range of arguments and built a business case, to show how TB vaccine development could be a viable and necessary investment for governments, industries and other players.

Annually, close to nine million people fall ill with tuberculosis. Worldwide nearly one and a half million people die from this devastating disease every year, leaving nearly 10 million children orphaned. Tuberculosis is also one of the main causes of death in people living with HIV. New vaccines could help eliminate TB and save those lives.

The financial and economic impact of tuberculosis is considerable. TB forms a significant financial burden to developing countries as well as to the rest of the world. Not only are treatment and hospitalisation expensive, TB patients lose productivity, which in many countries means that these patients also lose income and therefore purchasing power. On a personal level, the disease primarily affects people in their most economically productive years, causing financial hardship among families and communities. On a global level, the World Bank has calculated the worldwide cost of TB to be 0.52 percent of the world's GNI, which amounts to several hundred billion euros. In Europe alone, TB-related costs are calculated to be approximately 2.1 billion euros, according to the European Lung Foundation. The rise of drug-resistant strains of the bacterium is causing a steep rise in costs.

"Developing new TB vaccines fits very well in innovation programmes such as the Innovation Union"

Developing new tuberculosis vaccines is complicated, time-consuming and costly, but is without doubt worth the investment. Substantial cost reduction will be achieved through disease prevention, and calculations of the market demand for vaccines show a strong business case for investment. European governments have committed to spending 3% of their GNI on innovation. Developing new tuberculosis vaccines fits very well in innovation programmes such as the 'Innovation Union', one of the flagship initiatives of the Europe 2020 strategy that strives for a smart, sustainable and inclusive economy.

Supporting TB vaccine development is not only a case for governments. TBVI seeks socially responsible companies and responsible business leaders to engage in supporting vaccine R&D programmes. Companies can support TBVI with financial resources and in-kind contributions such as expertise services or products and through opening their business and political networks.

TBVI also teams up with socially engaged foundations. Organisations such as the Bill & Melinda Gates Foundation and the Calouste Gulbenkian Foundation have proven to be indispensable in their strategic and financial support of TBVI's advocacy and fundraising work and scientific projects. TBVI's Council of Trustees brings together representatives of those institutions, other foundations and industries that support the work and this way fuel cross-sector collaboration.

"Organisations such as the Gates Foundation and the Gulbenkian Foundation have proven to be indispensable in their strategic and financial support of TBVI's advocacy and fundraising work and scientific projects"

Investment in new vaccines against tuberculosis works both ways; not only will it help put an end to the great suffering of families, employees and customers, but it will also reduce cost of treatment and care, improve productivity, and boost economies.

With promising vaccine candidates advancing through the consecutive stages of vaccine development and trials, funding is becoming more and more of an issue. Pre-clinical and early stage clinical trials as well as large Phase IIb and III trials that will involve thousands of volunteers spread over different regions, requires solid long-term commitment from donors and investors.

If financing for these trials does not come together, no vaccines will reach the market. That would be an unimaginable scenario.

TB: a threat to all countries, high burden and low burden, rich and poor

Dr Lucica Ditiu, Exectutive Secretary of Stop TB Partnership

Honest dismay about the havoc that tuberculosis still wreaks, and a sincere drive to ban the disease once and for all, is what Dr Zsuzsanna Jakab, Regional Director of the WHO European Region and Dr Lucica Ditiu, Executive Secretary of the Stop TB Partnership, have in common. Both women are well aware of the impact of TB and determined to put an end to it.

"It is unacceptable that so many people are dying from TB. People affected by this disease deserve to have more of a voice and be seen, but most of them belong to poor and vulnerable groups." Dr Lucica Ditiu was appointed Executive Secretary of the Stop TB Partnership in January 2011. Having devoted her career to improving the lives of people affected by TB, she has made it her goal to make people think and talk about TB as much as possible. "I have always been dissatisfied with how little attention is given to TB. The TB community does great work, but somehow we have not been able to turn up the volume sufficiently on our message. The HIV community has so much energy and has succeeded in drawing the world's attention to the need for vaccines and new drugs. I always have felt we can raise the profile of TB to this level too. Now is the time to make more noise."

"The only available vaccine for TB was discovered in the 1920s and offers only limited protection"

Dr Jakab looks at tuberculosis from a mainly European perspective. As a WHO Regional Director, she oversees a region consisting of 53 countries situated between the Atlantic and the Pacific Oceans. Tuberculosis is a serious problem in this region; so serious that in 2011 the WHO regional office rang the alarm on TB rates. Dr Jakab: "TB knows no borders, which makes it a serious threat to all countries, high burden and low burden, rich and poor. We need to mobilise all resources - human, technical and financial - to build strong partnership and solidarity. I want to see TB eliminated during my children's lifetime, and as the WHO Regional Director for Europe, I will ensure that we continue to make TB control a high priority in Europe and elsewhere."

Dr Ditiu says there is a clear need for people to express their outrage. "The number of people dying of TB is almost equal to the number of people dying of HIV/AIDS. We need to push. The only available vaccine for TB, was discovered in the 1920s and offers only limited protection. In most places we use the microscope – the same diagnostic tool that has been in use for nearly 100 years. And we use drugs that are 50 years old," she says.

Another challenge we need to confront urgently, Dr Ditiu says, is that millions of people are not being provided with TB diagnosis and treatment. "There are so many people whose TB is never found. We are talking about roughly 3.5 million undetected cases every year worldwide. These are the people who are most vulnerable, and we need to develop innovative ways to reach them and get them high-quality treatment. Drug resistance is tragic too; the number of cases is outrageous. Again, we need to push case detection rates so we can push treatment."

Although the incidence of TB has slowly declined in the European Region as a whole, the discrepancy between east and west is worrisome. Drug resistance rates are alarming and, the European Region also has the fastest-growing HIV epidemic in the world. Dr Jakab: “During recent years, the case detection rate in the European Region has been increased to 74% in 2010, the highest case detection rate worldwide. However, we have the poorest treatment outcomes in the world with less than 70% of new patients successfully treated. This is mainly due to drug-resistant TB, but also due to late diagnosis, poor treatment practices, lack of patient-centered approaches and lack of community support.” Dr Ditiu adds: “TB touches all Europeans. We have to be aware that it is here, on our own doorstep.”

“Drug resistance rates are alarming and, the European Region also has the fastest-growing HIV epidemic in the world”

In response to this situation, WHO has established a Special Project to Prevent and Combat MDR and XDR-TB in the European Region. In collaboration with technical agencies, Member States, civil society organization and communities, a Consolidated Action Plan has been developed. The plan paves the way for strengthening the quality of implementation of essential tools such as rapid molecular detection, notification of all TB cases and adequate treatment with patient-centred models of care. The plan focuses on preventing the emergence and spread of drug-resistant TB by addressing the social determinants and health system weaknesses.

Development of new tools also plays an important role in the plan. Dr Jakab: “It is clear that TB elimination is not possible using the current tools, which are extremely old, some of them about 100 years. We need to find new and better tools to fight TB that can rapidly and effectively control this disease. More resources are needed to promote research and development and convert scientific discoveries into new and better drugs, diagnostics and vaccines.” Dr Ditiu agrees: “It is difficult to maintain this on the agenda, but we must. Without new diagnostics and drugs, our progress in achieving zero TB deaths will be stalled. Without new vaccines, we will not be able to eliminate TB. I can only urge donors to be open-minded and to invest.”

Dr Zsuzsanna Jakab, Director of the World Health Organization’s Regional Office for Europe

Progress in research

In the past ten years, an unprecedented fifteen TB vaccine candidates have entered clinical trials. In 2011, twelve candidates were actively being evaluated in clinic. Seven of these are or have been part of the TBVI portfolio and more candidates are to follow. The EU-funded research network NEWTBVAC has entered its second year and many projects within it have produced valuable data. What progress has been made within the TBVI network? Here is an overview.

Several vaccine candidates from TBVI's portfolio deserve to be mentioned. MTBVAC01, developed by Dr Carlos Martin and his team at the University of Zaragoza in Spain, is the first vaccine that is based on attenuated Mycobacterium Tuberculosis. The vaccine is expected to enter the clinic in the second half of 2012. H56, a candidate from the Statens Serum Institute in Denmark and the first candidate that also targets latent TB, has entered a Phase I study. Together with Aeras, TBVI supports HBHA, a protein-based candidate from Institute Pasteur in Lille, France. A production line is being developed and decisions about, for example, the choice of adjuvants will have to be made.

In 2011, promising data was collected, indicating a number of hopeful second generation vaccines that are more effective, and safer for certain target groups, than BCG. TBVI's director, Dr Jelle Thole: "BCG zmp1, from the University of Zurich, for example, proved to be significantly better in some preclinical studies. The development of candidate vaccines based on new viral delivery systems and new antigens has made good progress, with promising candidates being evaluated in preclinical studies. Looking at the coming year, I'm excited that preclinical studies will be carried out, in which different prime-boost combinations will be evaluated in a head-to-head fashion; these studies aim to provide information on what booster would be best suited to what primer."

The past year brought two new projects. A new network, coordinated by the German Max Planck Institute for Infection Biology together with TBVI, brings together African and European research organisations. Dr Thole: "This is important, not only for the exchange of clinical and research experience, but also to prepare for the clinical evaluation of TB vaccine candidates." TBVI has also become involved in ADITEC, a programme that focuses on new immunisation technologies. The INYVAX project, a project for the optimisation of the development of vaccines against Poverty-Related Diseases, coordinated by EVI and in which TBVI was a partner, was finalised with a symposium in Switzerland. The project delivered an overview of European companies and organisations that are active in the development of vaccines against poverty-related diseases. Vaccine researchers and developers can use the database to find knowledge, technology or, for example, adjuvants. INYVAX also initiated a lab in which vaccines can be formulated patent-free. This lab has since generated a wide variety of vaccine formulations that are being developed across the globe and supported by a range of other sources. The Brighton Collaboration, a partner in INYVAX, has harmonised and updated protocols for assessing safety in clinical trials.

A great highlight in 2011 for everyone involved in the TB vaccine field has been the design of so-called Gating Criteria. "Aeras and TBVI agreed on a common set of criteria for the selection of new vaccine candidates as these move along the vaccine pipeline," says Jelle Thole. "This is an important step. Both our organisations have already applied them successfully and we're looking forward to seeing these criteria widely used." The Gating Criteria are part of a strategic document that was published in early 2012 (see page 20), setting the agenda for the next decade of TB vaccine research.

PDT & CDT: supporting the development of ideas into products

A good scientific idea does not turn into a useful product automatically. Sometimes, complicated steps have to be taken to bridge the gap. To prevent scientists from having to reinvent the wheel, TBVI offers advice, reviews and support from two teams of world leading experts.

"Being a good researcher is not a guarantee for delivering a good, useful product. Translating research is so complicated that no one can do it alone," explains Dr Luc Hessel, chair of the Clinical Development Team (CDT) of TBVI. His team, together with the Product Development Team (PDT) led by Dr Georges Thiry, helps researchers to take the steps in between discovery and clinical evaluation.

"The teams are there to ensure TBVI meets two targets from its objectives; to ensure vaccines are being helped through early and pre-clinical trials, and to increase clinical trials capacity," explains Dr Hessel. "We don't take the lead, we advise the researchers. Science is not enough; there are technical, strategic and financial aspects that we also have to look at." The two teams include prominent experts with specific knowledge in crucial areas such as regulatory issues, pre-clinical development, vaccine safety and clinical trial design.

"We academics know about models and responses, but we needed help with product-specific issues"

"We provide technical support to researchers," explains Dr Georges Thiry, chairman of the PDT. The teams started many years ago as an ad hoc consultancy organised by Paul Henri Lambert, who was chair of TBVI's Steering Committee at the time. The different specialists worked together so well that they started forming a team. "From then on, we formalised our work more and more and eventually realised that we actually needed two teams. One, the PDT, which looks at the product, at what is in the vial, and the other, the CDT, which has specific expertise on how to clinically evaluate that product."

Dr Camille Locht of Institut Pasteur Lille in France received support from the Product Development Team for his TB vaccine candidate HBHA. "Our vaccine candidate is in the development stage and there are issues that we as academics do not know about. We know about models and responses, but we needed help with product-specific issues such as criteria for purity, compatibility with adjuvants and toxicology data, to name just a few."

The way TBVI offers expert advice about product and clinical development is rather unique. Without taking over, the teams help researchers to solve issues and advance their projects. Luc Hessel: "Researchers are often shocked at how many issues play a part in the 'real life' of product development and clinical evaluation. There are so many questions that need to be addressed during the process. 'I didn't realise' is a much-heard comment, and it proves that we speak different languages. There is a language of research, strategy, finance and regulatory issues; that is why we need constant translation." Researchers can approach TBVI's Development Teams, but the teams sometimes also approach the scientists. Dr Thiry: "TBVI has really created some good portfolio

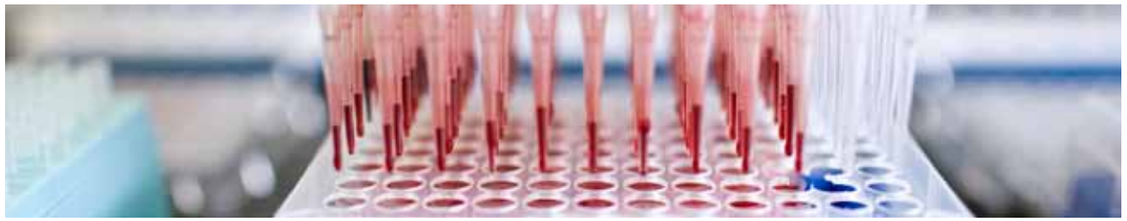
management. Therefore we now know which vaccine candidate is in which stage and may require our input."

Dr Locht sees great advantage in having access to these kinds of teams. "You really feel support for your project. The members of the team not only have specific expertise, but also great dedication and a very positive helpful attitude." The scientists find the support given by the Development Teams essential. Too many projects in the academic world disappear because of lack of translation. Camille Locht: "I see interesting projects with good ideas and good data, but they come to a halt because the investigators do not have the knowledge to go beyond the academics and develop an actual product. That is a waste of time and resources."

"Looking at these candidates, I just appreciate how they all progress. They all move nicely, and I know how much effort that takes"

In 2011, TBVI's PDT and CDT conducted reviews of several TB vaccine candidates. Dr Georges Thiry: "Having worked in this field, I look at these candidates the way I look at a horse race. I just appreciate how they all progress, they all move nicely, and I know how much effort that takes."

Another activity that the PDT and CDT undertook in 2011 that both chairs are proud of is the development of 'Gating Criteria'. Dr Hessel: "For me, this work was really one of the highlights of 2011. These criteria describe what will allow a vaccine candidate to move to the next phase and they were developed together with Aeras." The project, and the collaboration with Aeras, TBVI's strategic partner specialised in TB vaccine development through later clinical development stages, is also important to Dr Thiry. "I see our relationship maturing, and I enjoy it, working on these criteria, working on our mutual portfolios. It is important to join forces in this way." The Gating Criteria are part of a larger document published in March 2012 that sets out a strategy for the development of new TB vaccines for the next decade.



Tuberculosis vaccines: a strategic blueprint for the next decade

As tuberculosis continues to be a serious global health problem, there is no doubt that new, more effective vaccines are urgently needed. Researching and developing the right TB vaccines, however, is a large and complicated task; no single organisation or country can do it alone. In 2011, international organisations and scientists worked together to create a strategic Blueprint for the development of new TB vaccines.

"The Blueprint is a sort of working plan, an overall global plan, a consensus agreement about the sensible way forward in TB vaccine research", says British scientist Dr Barry Walker, member of TBVI's Product Development Team and one of the contributors to the Blueprint. "TB vaccine researchers from all over the world were more or less following their own plan. I would not say they were working in isolation, but resources are scarce, so it is sensible to focus research and maximise resources."

Tuberculosis Vaccines: "A Strategic Blueprint for the Next Decade", as the strategy is called officially, outlines the major scientific challenges and priorities in TB vaccine research. It describes the critical activities and crucial questions that need to be addressed in order to develop TB vaccines as soon and as efficiently as possible. Published in the academic journal 'Tuberculosis' in March 2012, the document presents five key priorities vital to the successful development of these life-saving tools.

TBVI's director Jelle Thole, who co-edited the Blueprint together with Michael Brennan of Aeras, is proud of the collaborative effort. "This document represents the best thinking in the field," he said. "It makes clear that the next 10 years will be vital in moving forward in the global search for a dramatically improved vaccine against tuberculosis."

The Blueprint focuses on a wide audience, explains Dr Walker: "Scientists can use it as a guide to the bigger picture. Governments, WHO and funders can use it for their strategic processes. The document will find broad support; I have no doubt about that."

Several leading experts have given their support to the strategy already. The document was welcomed by Dr Christine Sizemore and Dr Anthony Fauci of the US National Institutes of Health in an article in the journal Tuberculosis, saying that: "The new Blueprint provides a roadmap for close collaboration among all stakeholders and for scientists to address practical and relevant fundamental and translational questions, and for funders to maximise resources in the current economic climate." EDCTP director Charles Mgone welcomes the Blueprint too. "It provides a sound framework to jointly face challenges in the research, development and deployment of effective TB vaccines. The fact that it addresses issues along the entire value chain from innovation and discovery to clinical trials and community mobilisation is highly commendable."

Five key priorities

- Creativity in research and discovery
- Correlates of immunity and biomarkers for TB vaccines
- Clinical trials: harmonization & cooperation
- Rational selection of TB vaccine candidates
- The critical need for advocacy, community acceptance and funding

Gating criteria: a rational selection of vaccine candidates

One important aspect discussed in the Blueprint is the Gating Criteria. This is a set of criteria, a tool that can help determine which candidates are suitable to progress to subsequent phases.

“These are well-defined, robust criteria,” says Dr Barry Walker, a member of TBVI’s Product Development Team and one of the inventors of the gating criteria. “Not only do they help us determine whether the candidate is effective and safe or not, we also apply very practical criteria. Can we produce it? Can we deliver it? Can it be freeze dried? But also: Are there any issues with the intellectual property? Do we have to rely on someone else’s technology to produce or develop it? We look at legal, practical and financial issues as well as more scientific things.”

Both TB vaccine developer Aeras and TBVI are already using the gating criteria to evaluate and review projects within our own portfolios. Dr Walker: “If a scientist knocks on our door to ask for support, we now use these criteria. If there are gaps, we tell the researcher how to improve, and if the gaps are filled, the project can move on. This way, candidates are being moved from gateway to gateway and whenever a candidate moves from one phase to another, a new set of criteria comes in that is focused on what is important at that point.” The two organisations hope that the gating criteria will eventually be used globally.

Dr. Luc Hessel of TBVI’s Clinical Development Team is confident the criteria will be used widely. “We have already used the model and it works. Now the challenge for 2012 is to get it accepted and recognised as a reference tool. The gating criteria are a great achievement. A year ago we had nothing, now we have a model that, with some adaption, could even be used for other diseases too.”

“A year ago we had nothing, now we have a model that, with some adaption, could even be used for other diseases too”

Scientists have actively pursued new TB vaccines for over a decade now. So why were these gating criteria not developed years ago? “Before, we had a limited number of candidates”, says Dr Barry Walker. “There was a practical pressure to take things forward and we simply had no reason or justification not to support candidates. The field was just too small. Now we have reached a point at which we might have several candidates that are good, effective and safe. We have to look for the best and eliminate any lesser candidates. It is a luxury but also a responsibility to downsize the portfolio and keep the very best.”

Investing in new TB vaccines:
a responsibility for Europe

Member of European Parliament Charles Goerens

Two political heavyweights were added to TBVI's Council of Trustees in 2011, Member of European Parliament (MEP) Charles Goerens, and Dr Bernard Petit, who is taking up the position of chairman. Both come with extensive political insight.

MEP Charles Goerens has seen with his own eyes how tuberculosis is present in Europe. "I was invited to visit programmes in Moldova and so I visited a prison in the capital Chisinau. Awful! So many young people there were infected with the disease, and so many of them were drug resistant. That is when I thought, we must do something." Since then, Mr Goerens has been advocating European action against the disease, resulting, for example, in a motion for a resolution to make TB vaccine development part of the EU's innovation strategy. The resolution that recognised TBVI as a key player in the fight against TB was brought up by a group of MEPs and supported by an overwhelming majority of votes.

"Among politicians there are so many issues that need and deserve attention that we need to put the item on the agenda constantly"

In his former position as Deputy Director General at the European Commission (EC), Dr Bernard Petit had already seen something of the damage that tuberculosis causes, albeit indirectly. After being asked to join TBVI's Council of Trustees, he became increasingly aware of the severity of the problem. "Tuberculosis is a worldwide disease," Dr Petit says. "This is truly a global public health issue and even though many organisations have been working on it, the problem has still not been solved. I think it is very important to find solutions for a disease that kills so many people and costs society so much."

Both new trustees see the need to involve international politics in the fight against TB, and both see the need for wide collaboration. MEP Goerens: "We cannot be indifferent to TB. We can and we have to do something to create political will. I see opportunities if we join forces with the private sector and the public sector." Bernard Petit adds: "If one vaccine is found, it will be good for everyone. This is a global problem and we must find the solution together. That is also why I am very keen on TBVI and Aeras working together."

Is Europe sufficiently aware of the issue of TB? MEP Goerens does not think so. "Despite all efforts to spread information, I do not believe it is known widely enough that TB is such a problem. Among politicians there are so many issues that need and deserve attention that we need to put the item on the agenda constantly."

Both men see a responsibility for Europe to invest in the development of new TB vaccines. Besides the fact that TB is also a European problem, Europe is a global player in vaccine development," says Dr Petit. "This also fits in well with the Europe 2020 strategy for innovation," adds Charles Goerens. "We have to do our utmost to be the best knowledge society in the world. We are committed to developing research and one of the sectors in which we can do that is health. There are enough arguments to warrant allocating money for this in Framework 2020. In developing vaccines, we are doing two things at once, supporting research and helping people. This in turn supports innovation in both the developing world and in Europe."

TBTEA: African and European researchers start new network

African and European research institutions are joining forces to strengthen research and development of tuberculosis vaccines. A new network, coordinated by TBVI together with the German Max Planck Institute for Infection Biology, brings together twelve institutions from both continents. The network aims to improve collaboration, to set up joint activities and to exchange knowledge.

"TBTEA is an excellent networking opportunity," says Dr Andre Loxton of Stellenbosch University in South Africa, one of the participants of the project. "This network will bring scientists a step closer in their attempt to solve the daunting task of the TB epidemic." Dr Benjamin Kagina of the South African Tuberculosis Vaccine Initiative (SATVI) adds that "At international level, the TBTEA network provides an enormous opportunity for collaboration, particularly in clinical trials."

TBTEA, or "Collaboration and integration of tuberculosis vaccine trials in Europe and Africa" in full, has received a 765,000 euro grant from the European and Developing Countries Clinical Trials Partnership (EDCTP). The project focuses largely on improving and developing clinical trial sites where vaccine candidates are being tested. Project leader Prof. Stefan Kaufmann: "TBTEA strengthens existing links and fosters new cooperations between European vaccine developers and African vaccine trial sites." Dr Jelle Thole, director of TBVI, explains: "In order to be able to deliver effective tuberculosis vaccines, it is crucial to establish well-developed clinical trial sites. TBTEA will ensure an exchange of knowledge between North and South and aims to enable evaluation of the various different types of TB vaccines that are now entering the clinical pipeline."

"By bringing together new and existing activities in TB vaccine development, we ensure the efficient use of scarce resources and we prevent scientists from having to reinvent the wheel"

Both European and African partners are enthusiastic, and hopeful that TBTEA will bring benefit to all parties involved. It will contribute to improving sustainable research infrastructures in African countries where TB is a public health threat and it will prevent overlap and unnecessary duplication of work. European partners can learn how to make more efficient use of existing trial sites whereas African partners will benefit from the translation of European knowledge. African postdoctoral researchers will perform experiments in collaboration with European organizations, and workshops and field site visits will be organised. Dr Loxton sees advantages for his university but also feels his institute has something to offer: "This provides an additional resource for our already established collaboration with northern partners to expand and receive additional training. We have a specialised immunology laboratory and are in the process of being accredited. That means we can provide another high-level immunology laboratory for northern partners to perform trials."

The new network puts great emphasis on exchange of knowledge. TBVI project manager Danielle Roordink: "By bringing together new and existing activities in TB vaccine development, we ensure the efficient use of scarce

resources and we prevent scientists from having to reinvent the wheel. Furthermore, junior researchers can benefit from the experience of more senior colleagues and there is space for collaboration with other, already existing networks."

Dr Yukari Wanabe is delighted that her organisation, the Infectious Disease Institute in Uganda, is able to play a role in vaccine clinical trials. Speeding up tuberculosis vaccine development is important, she explains: "Treatment is currently long, and inadequate to deal with the problem of TB. Prevention is clearly the best way forward for high-burden developing countries in sub-Saharan Africa."

TBTEA has a budget of 765,000 euros and is scheduled to run from September 2011 to July 2013. The following institutions are taking part:
Max Planck Institute for Infection Biology, Germany - TuBerculosis Vaccine Initiative (TBVI), The Netherlands - University of Oxford, UK - Statens Serum Institute, Denmark - University of Zaragoza, Spain - INSERM, Institut Pasteur de Lille, France - South African Tuberculosis Vaccine Initiative (SATVI), University of Cape Town, South Africa - Stellenbosch University, South Africa - The Infectious Diseases Institute (IDI) at Makerere University, Uganda - Armauer Hansen Research Institute (AHRI), Ethiopia - Espoir Pour La Santé (EPLS), Senegal - Hospitalier CHU Le Dantec, Senegal

Clinical trials for TB vaccines

Linking European and African researchers is important for several reasons, one of which is the need to increase clinical trial capacity. Clinical trials are needed to test vaccine candidates for safety and efficacy. Early clinical evaluation involves small groups of volunteers. In the first phase of testing, the safety of the vaccine is ensured and researchers look at immunological reaction and a possible safe dosage-range. If the vaccine candidate meets all criteria to progress to next phases of evaluation, larger groups of volunteers from all kinds of target groups. These trials have to be done in regions with fairly high rates of tuberculosis. Since for TB there are no licensed correlates of protection available that can indicate how effective a vaccine is, the final stage of clinical evaluation will see thousands of participants that will be followed for a longer period of time.

Guiding suitable vaccine candidates through these various phases of clinical development is a challenge that comes with financial, scientific and logistic hurdles. Projects such as TBTEA allow us to make important steps to prepare the way for our most promising projects.

Overview:
TBVI's projects

TBVI financially supports and brings expertise to an integrated network of over 50 universities, institutes and industries to develop more effective, safe vaccines that will be globally accessible and affordable. The consortium works through a list of projects that are being managed, co-managed or otherwise supported by TBVI.

In 2011 TBVI was involved in the following projects:

NEWTBVAC
Around 35 partners are united in NEWTBVAC, a project that involves a wide range of activities focused on discovering and developing TB vaccine candidates and increasing understanding of the disease. The project is funded through the EU Seventh Framework Programme and managed by TBVI and has three objectives: To sustain and innovate the current European pipeline with new vaccine discoveries and advance the most promising candidates to clinical stages; to develop new, second generation vaccines that can boost the current BCG vaccine or replace it and protect people with a latent or 'sleeping' TB infection from developing the infectious disease; to sustain and innovate the discovery, evaluation and testing of new biomarkers.

TBTEA
Bringing together European and African research organisations to improve and strengthen collaboration in TB vaccine research is the aim of the TBTEA network. TBTEA is funded by the European and Developing Countries Clinical Trials Partnership (EDCTP) and coordinated by TBVI and the German Max Planck Institute. The 2-year project has a budget of 765,000 euros and focuses largely on improving and developing clinical trial sites where vaccine candidates are being tested and aims to enable evaluation of the various different types of TB vaccines that are now entering the clinical pipeline. Eleven research partners from Europe and Africa are involved.

INYVAX
TuBerculosis Vaccine Initiative is a partner in INYVAX, a project for the optimisation of the development of vaccines against Poverty Related Diseases (PRD), funded by the European Commission. INYVAX addresses challenges that are faced in the development of PRD vaccines. These include difficulties in accessing know-how and technology platforms in vaccine development, formulation, and delivery; difficulties in harmonizing safety data collection and the insufficient number of trained scientists able to undertake leadership roles in vaccine development. Eight research partners work together through the INYVAX project.

TRANSVAC

TRANSVAC, the European network of vaccine development, was founded by thirteen partners, one of which is TBVI. The network is funded through the EU Seventh Framework Programme and offers a complimentary set of coordinated vaccine research and development facilities, not focused on any particular type of disease. The long-term vision of TRANSVAC is to establish a European Research Infrastructure, providing a spectrum of coordinated vaccine development facilities, managed by each of the participating institutions.

ADITEC

ADITEC, a 5-year project that received 30 million euros via the EU Seventh Framework Programme, aims to accelerate the development of novel and powerful immunisation technologies. TBVI has signed up to manage the project's communications activities. Scientists from 12 countries and 42 research partners collaborate in the ADITEC (Advanced Immunization Technologies) project that focuses among others on tuberculosis and influenza. All possible aspects of vaccination, from basic research, new technologies to clinical trials and public health, are covered.

MYCOWALC

The MYCOWALC project is funded by the Portuguese Calouste Gulbenkian Foundation and monitored by TBVI. The project's main objective is to improve understanding of how different LAM species, a type of glycolipids in the cell wall of the bacterium, may affect the induction of protective immune responses and how they protect mycobacteria from these immune responses. MYCOWALC started in July 2010 and is scheduled to finish in July 2013. The project ties together two research organisations.

Financial report

Revenues in euros	2011	2010
EC and Governments	349,308	349,639
Donors	873,553	837,109
Interest	26,623	14,730
Other	5,606	-
Total	**1,255,090**	**1,201,478**

Expenses in euros		
Vaccine Research Programme	1,179,084	1,074,987
Support services	67,277	65,702
Total	**1,246,361**	**1,140,689**

Result	**8,729**	**60,789**

Net assets		
Beginning of Year	17,797	14,738
End of Year	9,231	17,797

The 2011 financial statements have been audited by PriceWaterhouseCoopers accountants NV. In their auditors' report dated 21-03-2012 they expressed an unqualified opinion on these financial statements. The financial report as stated above has been derived from the financial statements 2011. The full report is available upon request.

The following donors have supported TBVI in 2011:

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BIOFABRI

Organisation
(1 March 2012)

TBVI is a non-profit organisation registered under Dutch law, that facilitates the development of new vaccines to protect future generations against tuberculosis. Its highest decision-making body is the Governance Board. A group of European top scientists forms the Steering Committee, which is responsible for scientific and strategic advice and decides on scientific projects. TBVI's donors and stakeholders are represented in the Council of Trustees, which aims to advise about a broad range of strategic issues. Day-to-day business is carried out by the Operational Office based in Lelystad, the Netherlands.

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Stop TB Partnership, Geneva, Switzerland

The Brighton Collaboration, Basel, Switzerland

The Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), Geneva, Switzerland

TB Europe Coalition, Brussels, Belgium

WHO, Geneva, Switzerland

Facts about TB

In 2010, 1.4 million people died of tuberculosis. That is 3,800 deaths a day, or one person dying every 22 seconds. Many millions more struggle with this disease which, apart from causing great human suffering, also hampers the development of countries and slows down economic growth.

BCG, the only currently available vaccine, offers very limited protection against pulmonary TB and is not safe in children infected with HIV. TBVI is committed to facilitating the development of more effective and safer vaccines against tuberculosis.

Around two billion people, or one third of the world's population, are estimated to be infected with the bacterium and are at risk of developing the disease. One in every 10 of those people will become sick with active TB in his or her lifetime. People living with HIV are at a much greater risk.

Although poverty related, and mostly affecting people in developing countries, tuberculosis is prevalent in all continents. The situation is becoming serious in Europe, is alarming in most of Africa and extremely worrisome in parts of Asia.

The disease mainly affects young adults in their most productive years. People in the prime of their lives, who because of the long, burdensome, complicated and possibly even fatal course of the disease, are often no longer able to support themselves and their families (financially or otherwise) or help build up the economy of their country. TB is a leading killer among people living with HIV, which causes a weakened immune system.

There were 8.8 million new TB cases in 2010. Per capita, the global TB incidence rate is falling, but the rate of decline is very slow and the spread of deadly drug-resistant forms of TB is on the rise.

Multidrug-resistant TB (MDR-TB) is a form of tuberculosis that does not respond to the standard treatments using first-line drugs. MDR-TB is present in virtually all countries in the world. There was an estimated prevalence of 650,000 MDR-TB cases in 2010 and although treatment rates went up, only 16% of these patients received appropriate care.

Extensively drug-resistant TB (XDR-TB) occurs when resistance to second-line drugs develops. It is extremely difficult to treat and cases have been confirmed in more than 58 countries.

Worldwide, there are almost 10 million orphan children as a result of TB deaths.

The increased mobility of the world's population, with more people travelling across borders, intensifies the spread of tuberculosis.

The global burden of TB is estimated at hundreds of billions of dollars every year. The annual economic loss is 0.52% of the world's gross national income, according to the World Bank.

Tuberculosis is contagious and spreads through the air. If not treated, each person with active TB can infect on average 10 to 15 people per year.

In the 27 European Union member states, there were 101,566 new cases of tuberculosis in 2009. Treatment in the larger European region costs over €2 billion per year, according to the European Lung Foundation. The region is under specific threat of drug-resistant strains of tuberculosis, which are more expensive and difficult to treat. Researchers are working hard to develop new, safe and more effective TB vaccines. so far, TBVI's portfolio comprises of 39 vaccine candidates, 6 of which are in various phases of clinical evaluation and 3 of which are in the pre-clinical stage.

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