MESA: Redes internacionales de investigación en TB

Moderadores: **Anna Vilella.** *Hospital Clínic. Barcelona.*
Eva Cuchí. *Catlab. Parc Logístic de Salut. Viladecavalls.*

TBnet

José Domínguez
Institut d'Investigació Germans Trias i Pujol

Correspondencia:
José Domínguez
E-mail: jadomb@gmail.com

The Tuberculosis Network European Trials Group (TBnet) (www.tbnet.eu) was formed in 2006 to promote clinical research in TB, support TB education, and allow for the sharing and development of ideas and research protocols. TBnet is a European consortium consisting of health care professionals and scientists, aimed at promoting quality of care for TB patients by addressing health-inequalities, providing expert guidance in areas where clinical evidence is missing, defining research priorities, conducting multicenter clinical studies, and training early career European clinicians and scientists. TBnet has two daughter organisations: ptbnet for addressing the same activities in children and NTM-NET for diseases caused by nontuberculous mycobacteria.

TBnet is an organisation with almost 700 members from across the world, the majority practising in the European Union. With 54 peer-reviewed publications to date, TBnet has become the largest European research organisation in TB. In 2008 was created the first Clinical Research Collaboration (CRC) with the European Respiratory Society. The latest CRC addresses the clinical aspects of MDR-TB.

Education has always been a high priority for TBNET. The TBNET Academy is a forum for young clinicians and researchers to exchange ideas and learn from each other under expert guidance and mentorship. Participants were grouped into five sections (clinical TB, immunology, microbiology, molecular biology and epidemiology with public health) to present jointly the state of the art in their field. Teaching is also given on writing research protocols and papers, along with how to give an effective presentation. TBnet Academies have been held in Austria, Moldova, Ukraine, Armenia and Russia, so that local participants may interact with others from across Europe.

In the last years TBnet has generated important data for managing latent TB infection (LTBI) and also multidrug-resistant TB (MDR-TB) patients. Contact tracing in TB is a necessary part of TB control. The TBNET study[1] showed that nowadays, active TB develops in 16 (3.2%) out of 494 with LTBI who did not receive preventive treatment but in just three (0.6%) out of 481 who received preventive treatment and five (0.16%) out of 3141 with a negative IGRA (consistent with background infection rates for communities with TB). A negative IGRA was of most value in stopping further investigations and reassuring contacts that they would not develop active TB from their family contact. From this study and similarly large European studies, which have shown much the same results, we can now estimate the potential yield of active TB from contact tracing (0.5%) and the value of preventive treatment in a low incidence area (number needed to treat 30.4). The risk of TB was greater (3.3 per 100 person-years) in those with HIV co-infection and a positive IGRA, but only if the virus could be detected in their blood and they lived in high or medium TB incidence countries[2].

MDR-TB is a significant problem, especially in Eastern European countries. Genetic tests for resistance are already widely used; microbiologists and practising TB physicians have assessed the clinical implications of these tests, as in the TBNET consensus statement by Domínguez *et al.*[3]. On the other hand, WHO has definitions of TB outcome with particular reference to MDR-TB. However, when using the latter definition for a cohort

of patients with MDR-TB, TBNET contributors Günther *et al.*[4] noted that extensively drugresistant (XDR)-TB appeared to have a better outcome than MDR-TB. This seemed intuitively incorrect. TBnet has described new outcome definitions in an attempt to reflected clinical realities[5].

The clinical management of TB is evolving. TBnet remains committed to evaluating expert views and scientific advances, particularly as to how they affect and might improve the clinical management of TB.

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ESCMID Study Group for Mycobacterial Infections (ESGMYC)

Miguel Santín

Hospital Universitari de Bellvitge. L'Hospitalet de Llobregat. Barcelona.

Correspondencia:
Miguel Santin
E-mail: msantin@bellvitgehospital.cat

La tuberculosis (TB) es la primera causa de muerte infecciosa en el mundo junto con el VIH, constituyendo un problema de salud pública de gran magnitud a nivel global. A falta de una vacuna eficaz, la lucha contra la pobreza y la mejora de las condiciones de vida en países subdesarrollados, así como el abordaje del diagnóstico y tratamiento del gran reservorio de la infección que representa la infección TB latente, constituyen los pilares principales del control de la pandemia.

En los países desarrollados, como España, asistimos a un descenso progresivo de las tasas de incidencia y prevalencia tras la eclosión de la co-infección con el VIH en la década de los 80 hasta mediados de los 90. Esta disminución también ha traído consigo una pérdida de habilidad clínica para el diagnóstico y manejo por parte de profesionales menos experimentados, lo cual trae como consecuencia retraso diagnóstico en unos casos y tratamientos sub-óptimos en otros. Por otra parte, la investigación traslacional se ve dificultada, incluso en los grupos con más recursos y tradición.

Los profesionales implicados en el tratamiento de pacientes con TB, pero también de micobacterias ambientales, cada vez más aglutinan esfuerzos organizándose en grupos y redes que facilitan la formación e investigación en este campo. En este sentido, la Sociedad Europea de Enfermedades Infecciosas y Microbiología Clínica (ESCMID –acrónimo en inglés de *European Society of Clinical Microbiology and Infectious Diseases*) dispone de un grupo multidisciplinar de estudio de infecciones de micobacterias el Grupo de Estudio de Micobacterias del ESCMID (ESGMYC). El grupo, que se constituyó hace ya 8 años, tiene como misión principal la de formar en todos los aspectos de las infecciones por micobacterias. Sus objetivos principales incluyen el mejorar el diagnóstico, el tratamiento y la prevención de las infecciones micobacterianas, incluyendo TB, lepra y micobacterias ambientales. Mantiene una relación estrecha con otros grupos de estudio del ESCMID y con sociedades internacionales de lucha contra la TB.

En esta presentación se hará una revisión de las actividades formativas y de investigación llevadas a cabo en estos años, así como proyectos de futuro.

Update on new vaccines against tuberculosis. The role of the EU consortiums

Pere-Joan Cardona

Experimental Tuberculosis Unit (UTE). Fundació Institut Germans Trias i Pujol (IGTP). Universitat Autònoma de Barcelona (UAB). Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERES). Madrid.

Correspondencia:
Pere-Joan Cardona
E-mail: pj.cardona@gmail.com

This review pretends to be an update on the new TB vaccines that are currently in clinical trials where the different EU consortiums have had a role in its development

Whole cell vaccines

There are two live vaccine candidates in the global pipeline intended to replace BCG while being safer, namely VPM1002 and MTBVAC. VPM1002 is a recombinant *Mycobacterium bovis* rBCG DureC::Hly+ whose safety and immunogenicity have been demonstrated in three clinical trials (CT). This candidate is currently in phase II/III in the clinical development pathway to check its efficacy in preventing the recurrence of TB (https://clinicaltrials.gov NCT#03152903). MTBVAC was generated from an Mtb strain and carries two independent attenuating mutations in the transcription factor phoP and the lipid biosynthesis gene fadD26, respectively. After showing its efficacy in experimental animal models and two phase I clinical trials in adults and children, it is now being evaluated in a phase Ib/IIa study (NCT#02933281).

RUTI, DAR-901, *M. vaccae* and *M. indicus pranii* (MIP) are the four inactivated whole- cell vaccine candidates currently in the pipeline. The RUTI vaccine was primarily designed as a therapeutic vaccine, although it was subsequently found to be effective as a prophylactic in animal models. After a successful phase IIa trial in South Africa, it is now being tested as co-adjuvant treatment in MDR-TB patients (Phase IIa, NCT#02711735). DAR-901 is a whole-cell vaccine manufactured in compliance with Good Manufacturing Practice from SRL172, which is derived from inactivated *M. obuense* (initially thought to be *M. vaccae*), and which was used in a successful phase III trial to show the efficacy and safety for the prevention of disseminated TB in HIV-positive patients (DARDAR study, NCT#00052195) (30). DAR-901 is now being tested in a phase II clinical trial as a booster to BCG for preventing infection with TB (NCT#02712424). Another vaccine made from inactivated M. vaccae is being tested in a Prevention of Disease (PoD) phase III clinical trial in China in 10,000 Mtb-infected adults (NCT#01979900) and as an adjunct to standard chemotherapy in the form of an oral pill (V7) in a phase III clinical trial in the Ukraine involving MDR-TB patients (NCT#01977768). The MIP vaccine, which is used against leprosy and has already been tested as adjunct therapy in three TB clinical trials, will be soon evaluated together with VMP1002 in a phase III PoD trial in 19,000 household contacts of people with TB in India.

Adjuvanted subunit vaccines

There are currently 11 vaccine candidates in the global pipeline that fit into this category: six of these include a protein plus an adjuvant (M72/AS01E, H4:IC31, H56:IC31, ID93/GLA-SE, GamTBvac and AEC/BCO2) and five are viral-vectored (MVA85A (aerosol), Ad5Ag85A, ChAdOx1.85ª+MVA85A, MVA85A-IMX313 and TB/FLU-04L).

H4:IC31 and H56:IC31, both of which are in phase IIa, are the most advanced in terms of clinical development. Both are fusion proteins with the adjuvant IC31, which is a T-cell stimulator. H56:IC31 is based on ESAT-6, Ag85B and Rv2660c Mtb antigens, and is now being evaluated in two phase II clinical trials, one concerning the prevention of infection in healthy adolescents (NCT#03265977) and another assessing its safety and immunogenicity when administered to MDR-TB patients in combination with standard chemotherapy and a COX-2 inhibitor (NCT# 02503839). H4:IC31 is based on Ag85B and TB10.4 Mtb antigens and its ability to prevent Mtb infection has recently been evaluated in a phase II clinical trial in South Africa, which showed it to be safe and immunogenic. Although, in terms of the main efficacy endpoint, it didn't prevent Quantiferon (QTF) conversion, it nevertheless reduced the rate of sustained QTF conversion, thus suggesting some level of protection.

ID93/GLA-SE is based on Rv2608, Rv3619, and Rv3620 Mtb antigens with the GLA-SE adjuvant. After a successful phase I

Table 1. Vaccine candidates in clinical development.

Whole cell vaccines		Subunit vaccines	
Inactivated	**Alive**	**Adjuvanted-proteins**	**Viral vectored**
M. vaccae DAR-901 (*M. obuense*) RUTI MIP (*M. indicus pranii*)	VPM1002 MTBVAC	M72/AS01E H4:IC31 H56:IC31 ID93/GLA-SE GamTBvac AEC/BCO2	MVA85A (aerosol) Ad5Ag85A ChAdOx1.85ª+MVA85A MVA85A-IMX313 TB/FLU-04L

trial, a phase IIa trial to evaluate the safety and immunogenicity of ID93+GLA-SE was carried out (NCT02465216). In this clinical trial, the vaccine was administered to adult pulmonary TB patients following successful completion of TB treatment with confirmed bacteriological cure.

GamTBvac is a recombinant subunit vaccine consisting of two mycobacterial fusion proteins with an adjuvant that has just completed a phase I clinical trial in BCG-vaccinated adults (NCT#03255278).

The last adjuvanted subunit vaccine to enter clinical development is AEC/BCO2, the safety of which is currently being evaluated in a phase I clinical trial (NCT#03026972).

Viral-vectored subunit vaccines

MVA85A, ChAdOx1.85ª+MVA85A and MVA85A-IMX313 are all based on the modified Vaccinia Ankara virus expressing antigen 85A (MVA85A). MVA85A alone in infants previously vaccinated with BCG and administrated intradermally showed no increased efficacy when compared to BCG vaccination in a phase IIb clinical trial even though it had been found to be highly immunogenic in previous studies. As the reasons for this could be manifold, efforts to improve the immunogenicity of MVA85A are ongoing. New phase I trials are now evaluating administration via aerosol inhalation in LTBI-infected adults (NCT#02532036). In another strategy, MVA85A has been combined with IMX313, a protein with adjuvant effect designed to boost immunity primed by BCG that was found to be well-tolerated and immunogenic in a phase I clinical trial. Finally, MVA85A has also been evaluated in combination with a replication-deficient chimpanzee adenovirus expressing Ag85A (ChAdOx1.85A), both in experimental animal models and in a phase I clinical trial (NCT#01829490). Another approach involving Mtb antigen 85A involves Ad5Ag85A, a recombinant replication deficient human adenoviral (Ad5) TB vaccine containing the immunodominant antigen Ag85A that is intended to be delivered by aerosol. A phase I clinical trial is being conducted in BCG-vaccinated individuals (NCT# NCT02337270).

M72/AS01E is a subunit vaccine candidate based on two Mtb antigens (32A and 29A) with the AS01E adjuvant, which has recently been evaluated in the first phase IIb trial after the MVA85A trial. Although the vaccine triggered persistent humoral and T-cell-mediated responses, recruitment was terminated prematurely due to a high incidence of important local adverse reactions in M72/AS01E-vaccinated individuals, a result which obviously raises safety concerns. The candidate is now being evaluated in a phase IIb PoD CT in infected individuals (NCT#01755598).

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TB Trials Consortium Research: Present and Future

Timothy R. Sterling
Vanderbilt Tuberculosis Center. EEUU.

Correspondencia:
Timothy R. Sterling
E-mail: timothy.sterling@vumc.org

The Tuberculosis Trials Consortium is funded by the U.S. Centers for Disease Control and Prevention to conduct programmatically relevant research. The Consortium includes sites in the United States, Peru, Vietnam, South Africa, Uganda, Kenya, and Hong Kong. Current research priorities include:

Top tier

- Shorten treatment duration for drug-susceptible TB.
- Shorten treatment duration for latent *M. tuberculosis* infection.

Rationale: shorter treatment and improved tolerability → higher completion rates → higher cure rates → lower disease burden

Improved treatment of TB disease and LTBI: ↓ the pool of drug-resistant TB.

Include in the above studies:

- HIV-positive persons.
- Children.
- Pharmacokinetic, biomarker, diagnostics sub-studies.

Assess safety in pregnant women when possible.

Perform as possible and at specific sites.

- MDR-TB

The overall approach has been to perform:

- Phase 2 TB treatment studies to inform phase 3 treatment shortening studies.
  - Improvements in treatment of TB disease is important for the U.S., but particularly globally.
- Phase 3 studies of treatment of latent *M. tuberculosis* infection.
  - Of greatest importance for TB elimination in the U.S., but now also of increasing importance globally.
- Important to be engaged in both areas, but with a mix of primary and secondary focus so that there is always ongoing activity of the Consortium.

The TB Trials Consortium's important qualities for addressing challenges in TB treatment and prevention:

- A scientific agenda that addresses both global and U.S. research priorities.
- A unique and geographically diverse array of clinical trial sites.
- Highly engaged, experienced U.S. and international site coordinators and staff.
- A highly collaborative network, with a blend of junior and experienced senior investigators.
- Integration of the Community Research Advisory Group—aligning the Consortium with patient-centered approaches

Recent publications of note

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