

TB PAN-NET: Pan-European network for study and clinical management of drug resistant tuberculosis.



Duration: 01/01/2009 - 31/12/2013 (60 months)

Instrument: Collaborative Project (Large-scale integrating project) FP7-HEALTH-2007-B

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Project summary

This project will establish an integrated and synergistic network to address the challenge of multi-drug resistant tuberculosis (MDR-TB) facing the EU. The objective will be attained through the establishment of a European consortium of expert partners with extensive experience in the conduct of basic and clinical research relating to MDR-TB, TB control and epidemiology.

This Consortium will achieve this by:

- Conducting an extensive and focused programme of basic/clinical research to improve the diagnosis and management of MDR-TB
- Develop a broad training curriculum leading to the creation of a new generation of scientists and clinicians expert in the management of drug resistant TB
- Create field sites across the EU with the capacity for evaluating new diagnostic systems and novel drug therapies on behalf of European industry and government
- Establish a unified and robust quality assurance mechanism for the accurate and rapid diagnosis of drug resistance and develop appropriate safety standard for European health care workers
- Improving our understanding of the transmission of MDR-TB at the molecular level and host-related risk factors for its development,
- The Consortium will disseminate its findings and analyses widely to the benefit of specialists, general health care staff, EU governments, NGOs and health policy makers.

This will provide researchers and clinicians with appropriate knowledge and improved tools to fight MDR-TB, and assist European industry in the development of new diagnostics and treatments. Consortium outputs will assist governments in the development and implementation of appropriate health and social policies to limit and control the spread of MDR-TB within the member states of the EU. Internationally, these objectives will assist countries bordering the EU and international agencies such as the WHO and ECDC in reducing the impact of drug resistance.

Overall, our proposal combines Europe's outstanding experts in the field of drug resistant tuberculosis. Many of the partners have a history of successful development of state-of-the-art diagnostic tools, conduction of clinical trials, productive collaboration in previous EU-and other agencies funded projects, and we are assisted by a professional management company. The project is designed to foster both the highest possible degree of mutual interactions and a great flexibility in the interactions with other partners, as required for high quality science with a strong socio-economic impact.

Aims of the project

The project aims to coordinate activities to limit the spread of MDR strains by supporting high quality epidemiological and molecular analysis as well as training on MDR-TB. Basic and clinical research on MDR-TB aimed to understand the development of drug-resistances and the characterization of virulence features will provide further insight for likely novel diagnostic/risk factors in MDR-TB. The project adopts a multidisciplinary approach, integrating different clinical and scientific professionals including molecular biologists, mycobacteriologists, infectious diseases specialists, pneumologists, epidemiologists and international public health experts in TB control programmes, through a partnership between universities, public and private research centres, scientific societies and institutions in Eastern and Western Europe.

The major critical issues involved in the spreading of MDR-TB, i.e. early detection of DR cases through rapid identification and DST and effective treatment will be addressed, in particular through the development of effective, standardised training on TB management, improved tools for MDR/XDR epidemiology (e.g. automation and standardization of molecular typing) and the standardization of microbiology methodology needed for the correct management of drug-resistant TB cases.

The integration between basic research on the characterisation of molecular mechanisms of DR and the effective contribution to the mutation to the therapy outcome, will permit the introduction of novel and more effective diagnostic tools and will provide likely new targets for drug development. The partnership between international experts in clinical mycobacteriology and one of the most active European SME in the field, will generate the scientific know-out and tools needed for the necessary improvement in the overall management of MDR and XDR-TB cases. A transcriptional regulatory (TR) network of *M. tuberculosis* will be generated to address the contribution of different genetic background and/or different sensitivity pattern, in the same genetic background, to stress in terms of survival and transcriptional response and the “cost” in terms of bacterial fitness of acquisition of MDR phenotype.

The development of a panel of *M. tuberculosis* strains monoresistant to selected second-line drugs is a major step in the strategy in that it will establish a clear reference for all

EU laboratories to guarantee the accuracy of clinical laboratory analysis of MDR-TB and XDR-TB cases, enhancing European surveillance and individual clinical management.

Clinically the programme will train new clinicians and microbiologists in state-of-the-art clinical management and diagnosis. Through the creation of the TBnet work package, an integrated clinical network encompassing nearly 150 independent clinical researchers from 18 different countries will be created.

Epidemiological and clinical studies will be supported by an innovative and easy to use instrument for local and global TB surveillance: a European integrated clinical and molecular web database will be built that, by combining automated strain identification with clinical and geographic information, will represent a completely new tool for a sensitive early warning system for TB outbreak detection and for the control of the emerging problem of drug resistant TB spread.

Finally a series of integrated field sites in EU states with the highest rates of MDR-TB will be created, working to common protocols and ethical, governance and financial standards. The sites have sufficient patients to produce longitudinal MDR-TB cohorts which will enhance our understanding of the clinical risk factors for DR, HIV co-infection rates and provide a vital resource for the analysis of new diagnostic systems and clinical trials of new drugs for the EU and internationally.

Work Packages

The project is built around eight different work packages. Each work package is coordinated by a WP Leader. The WP Team includes all partners included in the WP. The WP Leader assists and monitors all work package-related activities.

- WP1: Molecular epidemiology of drug-resistant strains in selected metropolitan settings in Western and Eastern Europe.
- WP2: Characterization of novel mutations involved in drug-resistant phenotype and virulence markers.
- WP3: Development and standardization of EQA for drug-resistant TB and expansion of capability for culture-based and molecular-based techniques for drug-resistant TB .
- WP4: Development of integrated sites for clinical and diagnostic trials of new drug applications, new diagnostics, and development of markers for treatment success, and identify clinical and social factors, including HIV as markers of resistance.
- WP5: Training on TB clinical management, control and research.
- WP6: TBNET: Clinical research on TB drug-resistance in Europe.
- WP7: Dissemination and information sharing.
- WP8: Management.

Expected results

Our integrated research programme will have a significant impact within the EU on the following areas: (1) understanding of the risk factors (including HIV co-infection) for MDR-TB and poly-drug resistance, the nature of the transmission routes at the molecular level and the mutations associated with the development of XDR-TB; this will complement existing surveillance initiatives within the EU conducted by ECDC; (2) rapid diagnosis of drug-resistant TB and of infectivity of MDR patients already under therapy; (3) an integrated network of MDR-TB sites will be established across the EU supported by a common training curriculum for laboratory and clinical staff, with common ethical, study protocol and governance arrangements and harmonised financial

management. These sites will form cohorts of MDR-TB patients and be able to provide an EU-wide capacity for diagnostic and clinical trials of new drugs. These will be complemented by a wider network of individual expert clinicians in TBNET; (4) EU-centred training documents and training curricula will be developed complementing existing international efforts of the WHO and comparable bodies. A cadre of experienced laboratory and clinical staff will be created within the EU capable of addressing all the clinical and laboratory aspects of drug resistant TB; (5) These networks will be underpinned by high quality national reference laboratories across the EU; the quality of the laboratory output will be guaranteed by the training curricula above and by a system of EQA for drug susceptibility across the EU.

Basic research will provide the identification of novel mutations involved in drug-resistant phenotype (in particular, for second-line and recently introduced drugs used in MDR- and XDR-TB treatment). This aims to improve molecular diagnostic tools and will provide genome-scale metabolic modelling to further advance understanding of key aspects of the metabolism of tubercle bacilli during infection.

The TB PAN-NET proposal dedicates a specific work package on promotion of information sharing. The objective is to act as an intermediary to disseminate, explain and exploit findings to various stakeholders such as public authorities, economic operators and industry. This will be obtained by developing a web-based database of findings, by the production and dissemination of technical dossiers of findings in various formats to explain results to different stakeholders, and by the organization and the presentation of data at appropriate conferences and to stakeholders by members of the study team.

Potential applications

Establishment of a European integrated and inter-dependent network for basic science and clinical research.

Development of a European clinical and molecular web database for a sensitive early warning system for TB outbreak detection.

Development of new rapid diagnostic systems for the detection of MDR-TB and XDR-TB in cultures and primary diagnostic specimens.

Establishment of an integrated network of MDR-TB sites.

Development of common training curriculum for laboratory and clinical staff, with common ethical, study protocol and governance arrangements and harmonised financial management.

Implementation of a system of EQA for drug susceptibility for first and second line anti-TB drugs across the EU.

Project website: <http://www.tbpannet.org/>

Key words: Drug resistance (DR); Multi Drug-Resistant Tuberculosis (MDR-TB), Extensively Drug-Resistant Tuberculosis (XDR-TB), Molecular Diagnosis, Markers of Resistance.

Project Partners:

1. USR – Università Vita-Salute San Raffaele, Milan, Italy (TB PAN-NET Coordinator)
2. HPA MRU – Queen Mary and Westfield College, University of London, London, United Kingdom
3. FZB – Forschungszentrum Borstel, Leibniz-Zentrum für Medizin und Biowissenschaften, Borstel, Germany
4. FSM – Fondazione Salvatore Maugeri, IRCCS, Tradate, Italy
5. HSG – Azienda Ospedaliera S. Gerardo di Monza, Monza, Italy
6. ERS – European Respiratory Society, Lausanne, Switzerland
7. FIND – Foundation for Innovative New Diagnostics, Cointrin/Geneva, Switzerland
8. SMI – Swedish Institute for Infectious Diseases Control (Smittskyddsinstitutet), Solna, Sweden
9. SSI – Statens Serum Institut, Copenhagen, Denmark
10. CNIPH – Croatian National Institute of Public Health (Hrvatski Zavod Za Javno Zdravstvo), Zagreb, Croatia
11. UNISI – Università degli Studi di Siena, Siena, Italy
12. Hain GmbH – Hain Lifescience GmbH, Nehren, Germany
13. SATLD – State Agency of Tuberculosis and Lung Disease, Riga, Latvia
14. Montessori – Guido Montessori Company, Rome, Italy
15. TUH – Tartu University Hospital (Sihtasutus Tartu Uelikooli Kliinikum), Tartu, Estonia
16. NRL Lithuania – National Tuberculosis and Infectious Diseases University Hospital, Vilnius, Lithuania
17. IBT – Institute of Biotechnology (Biotechnologijos Institutas), Vilnius, Lithuania
18. NIPH – Norwegian Institute of Public Health (Nasjonalt Folkehelseinstitutt), Oslo, Norway
19. NRL Slovenia – University Clinic of Respiratory and Allergic Diseases Golnik (Bolnisnica Golnik Klinicni Oddelek Za Pljucne Bolezni In Alergijo), Golnik, Slovenia
20. ITM – Prins Leopold Instituut Voor Tropische Geneeskunde /Institute of Tropical Medicine Prince Leopold, Antwerpen, Belgium
21. SPF Brasov – Pneumophtisiology Hospital Brasov (Spitalul de Pneumoftiziologie Brasov), Brasov, Romania
22. I-M.NASTA – “Marius Nasta” Institute of Pneumology (Institutul De Pneumoftiziologie "Marius Nasta"), Bucharest, Romania
23. IPL – Institut Pasteur de Lille, Lille, France
24. THL – National Institute for Health and Welfare (Terveyden ja hyvinvoinnin laitos), Turku, Finland
25. IPH – Scientific Institute of Public Health, Institut Pasteur, Brussels, Belgium
26. NRL Poland – National Tuberculosis and Lung Disease Research Institute (Instytut Gruźlicy I Chorob Pluc), Warsaw, Poland
27. UMDNJ – University Medicine and Dentistry of New Jersey, Newark, New Jersey, United States of America