INTEGRATED STRATEGIES FOR RESEARCH AND CONTROL OF TUBERCULOSIS IN BRAZIL: NEW DRUGS AND VACCINES, DIAGNOSTIC TESTS AND CLINICAL-OPERATIONAL EVALUATION
Over the time in epidemic countries, like in Brazil, no emphasis was given to integrated efforts in the fields of prevention, chemoprophylaxis, diagnostic and treatment, operational research, and human resources qualification to fight TB.

Thus, it became a consensus for the Brazilian TB Researchers, that to combat TB in the new Millenium, especially in urban areas, are necessary new strategies.

To achieve the strategic goal to reduce TB transmission, morbidity and mortality, it will require scaling up of current efforts to implement interventions of proven effectiveness, and research to determine how to implement these interventions and monitor their impact, and to develop improved and new interventions, including specific TB control tools (e.g. a more effective vaccine and drugs, better diagnostic tests and preventive and therapeutic approaches).

Thus, the new strategic framework recently proposed by the Brazilian TB researchers was the implementation of the Brazilian TB Research Network (REDE-TB), whose mission is to capacitate the country for the innovation and development of new technologies necessary to the control and treatment of TB, and the training of high quality human resources in this area, through an integrated multi-disciplinary and multi-institutional strategy.
The constituents of REDE-TB have already proven capacity, by using advanced resources, to develop in an isolated manner:

- Basic researchers on *M. tuberculosis* biology and TB immunopathology
- Development of new vaccines to prevent and treat TB
- Development of new diagnostic tests and their validation
- Development of new drugs using random screening or rational design against defined molecular targets
- Multicentric clinical trials of new anti-TB therapies
- Epidemiologic studies using post-genomic techniques
- Interaction with the productive sector and the regulatory bodies
- Establishment of clinical-operational research and monitoring TB control
- Capacitation of high quality human resources in the area of Science & Technology applied to TB and other infectious diseases
TUBERCULOSIS’ RESEARCH AND COMBAT

BASIC RESEARCH

HUMAN RESOURCES

IMMUNOPATHOLOGY

VACCINE

DIAGNOSTIC

DRUGS

CLINICAL STUDIES

EPIDEMIOLOGICAL

OPERATIONAL

PRODUCTION

REDE-TB
TUBERCULOSIS’ RESEARCH AND COMBAT

Ministério da Ciência e Tecnologia - Ministério da Saúde
UFMG-Fac. de Medicina
UFGO- Universidade Federal de Goiás
SES-Goiás
Sec. Municipal de Saúde do Rio de Janeiro
SMS-RJ-Hospital Raphael de Paula Souza
SES- Rio de Janeiro
UENF-Universidade Estadual do Norte Fluminense
UFRJ-Instituto de Biofísica Carlos Chagas Filho
UFRJ-Inst. de Puericultura e Ped. Martagão Gesteira
UFRJ-Núcleo de Saúde Coletiva
UGF-Fac. de Medicina da UFM, Gama Filho
HUCFF- Hospital UFM, Clementino Fraga Filho
UFRJ-Inst. de Química
UFRJ-Instituto de Microbiologia
UFRJ- Faculdade de Farmácia
UFRJ-Instituto de Doenças do Tórax
FIOCRÚZ- Instituto Fundação Oswaldo Cruz - RJ
FIIOCZ- Hospital Evandro Chagas - RJ
FIIOCZ-Inst. Nac. de Controle de Qualidade em Saúde
FIIOCZ- Escola Nacional de Saúde Pública
FIIOCZ- Instituto de Tecnologia de Fármacos

UFSC-Universidade Federal de Santa Catarina

SMS-Sec. Munic. e Saúde de Macaúbas
INPA-Instit. Nac. de Pesq. da Amazônia

UFES-Dep. de Medicina Socia/Nucleo de Doenças Infecciosas
SESA-ES-Lacen da Sec. de Estado da Saúde do Espírito Santo - ES
SMS-Vitória - ES

USP-Fac. de Medicina de Rib. Preto
USP-Fac. de Ciências Farmacêuticas de Rib. Preto
USP-Instituto de Ciências Biomédicas
UNESP- Fac. de Medicina Veterinária de Araçatuba
UNIFESP-Dep. de Micro, Imunologia e Parasitol.
USP-Fac. de Medicina
UNICAMP-Instituto de Química
UNICAMP- Fac. de Engenharia Química
UNESP-Inst. de Biociências - Botucatu
IBU-Instituto Butantan
SMS-Ribeirão Preto
SES-IAL-Instituto Adolfo Lutz
SES- SP-Centro de Ref. Trat. de AIDS

UFRGS-Dep. de Biologia Molecular e Biotecnologia
UFRGS-Dep. de Medicina Interna

FIOCRUZ- Instituto Fundação Oswaldo Cruz - RJ
FIIOCZ- Hospital Evandro Chagas - RJ
FIIOCZ-Inst. Nac. de Controle de Qualidade em Saúde
FIIOCZ- Escola Nacional de Saúde Pública
FIIOCZ- Instituto de Tecnologia de Fármacos

UFSC-Universidade Federal de Santa Catarina

FIOCRUZ-Centro de Pesquisas Aggeu Magalhães
SMS-Recife

UFES-Dep. de Medicina Socia/Nucleo de Doenças Infecciosas
SESA-ES-Lacen da Sec. de Estado da Saúde do Espírito Santo - ES
SMS-Vitória - ES

UFSC- Universidade Federal de Santa Catarina

SSMA-Fundação Estadual de Pesquisa e Saúde
SES- Rio Grande do Sul
UFRGS-Dep. de Biologia Molecular e Biotecnologia
UFRGS-Dep. de Medicina Interna

INPA-Inst. Nac. de Pesq. da Amazônia

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SMS-Recife
MISSION

Integration of investigators, working in network, to capacitate the country for the development of new technologies necessary to the control and treatment of TB, and the training of high quality human resources in this area, through an integrated multi-disciplinary and transinstitutional strategy.
TUBERCULOSIS’ RESEARCH AND COMBAT

General coordinator
Celio Lopes Silva

Vice-Coordinator
Diógenes Santiago Santos

Basic research: Sylvia cardoso leão

Humam resources: José Roberto Lapa e Silva

New vaccines: celio Lopes Silva

New drugs: Diógenes Santiago Santos

Diagnostic: Afrânio Kritski

Epidemiology and Operational: Antonio Ruffino Netto

Clinical trials: Reynaldo Dietze

Immunopathology: José Roberto Lapa e Silva

Interaction between public and private companies: David Tabak

47 INSTITUTIONS – 170 RESEARCHERS
To study in detail the host-parasite relationship

Gene expression in M. tuberculosis as well as in the human host cells infected with M. tuberculosis evaluated by microarrays

Protein expression in M. tuberculosis and M. avium strains with different virulence profiles evaluated by bi-dimensional gels

Interaction of M. tuberculosis with human and animal cells – apoptosis and cell signaling

Analysis of the response of cells in culture to M. tuberculosis infection after exposure to DNA vaccines

Analysis of gene expression in mice immunized with DNA vaccines using microarrays

Comparison of immunogenicity and protection of different TB vaccines
IMMUNOPATHOLOGY

• To study the host-parasite relationship, granuloma formation, bacterial dissemination, latency, reactivation of infection, innate and acquired immunity, and co-infections (HIV, parasites)

• Identification of microbiological and immunological markers of cure and relapse, which could be used as surrogate markers to predict success or failure of new anti-M. tuberculosis therapies

• Establishment of immunological parameters that correlate the findings in vaccinated animals with those in humans during and after vaccination or drug treatment
Vaccines

- Development of new vaccines to prevent and treat TB
- Development of new systems of controlled antigen release or gene-based vaccines
- Characterization of immune response mechanisms of cell activation during prophylaxis and/or gene therapy
- Establishment of immunological parameters that correlate the findings in vaccinated animals with those in humans during and after vaccination or drug treatment
- Pre-clinical tests and side-effects of the new vaccines
- Prophylactic and therapeutic efficacy of new vaccines
- Scaling up and preparation of pilot lot
- Phase I, II, and III clinical trials in humans
DIAGNOSTIC

• Establishment of sites capable of conducting clinical trials and validation of new diagnostic tests to detect *M. tuberculosis*

• Development and standardization of new immunological, colorimetric or molecular methods to detect *M. tuberculosis* in patients with TB

• Clinical and laboratory validation of new methods to detect drug resistant and drug susceptible strains of *M. tuberculosis*

• Clinical laboratory validation and cost-effectiveness evaluation of new immunological or molecular methods to diagnose *M. tuberculosis* infection
Several drugs are been assayed

Interactions with the target are due to coincidence rather than design

Artificial compounds

Natural products

Aleatory screening

200 PRODUCTS

4000 PRODUCTS

MIC
MACROPHAGES
MICE, GUINEA PIG

28 ACTIVE PRODUCTS
Lead compound
DRUG DISCOVERY
Rational design

- Specific Target in *M. tuberculosis*
  - Lipids
  - Carbohydrates
  - Proteins
  - Receptors

- Crucial factor in medicinal chemistry

- Unknown target explore the structure of the compounds with activity

Computational chemistry:
Molecular Mechanic (MM), Neural net, PCA,
QSAR/QSAR-3D

HIGHTHOUGHPUT SCREENING
HUMAN RESOURCES

• Improvement of human resources through the implementation of training and updating courses on science and technology for TB and other infectious diseases

• Education and training of personnel through post-graduate courses (Master’s and PhD’s courses)

• Establishment of new clinical-operational research and monitoring of TB control using the infrastructure of the new governmental family health care program which will allow the development of a stronger integration between clinical care and research
1- Development of operational research in tuberculosis at the basic health services of the SUS (Health System of Health), using support strategies proposed by the World Health Organization (Health System Research), with the support of training workshops and projects with well-defined goals and funding

- (UFAM, UFPE, UFES, UFRJ, USP, UNICAMP, )

2- Tuberculin testing of medical students and other health professionals, in order to evaluate the kinetics of M. tuberculosis

- (UFRJ, U.G.FILHO, U.S. MARQUES, FM TERESOPOLIS,
CLINICAL-EPIDEMIIOLOGICAL-OPERATIONAL STUDIES

• 3-Identification and study of factors related to non-compliance to anti-TB therapy
• (FMRP-USP, EERP-USP, UFRJ,UFES, SES-SP, UNICAMP, UGF-RJ, LCTB, SES-RJ, SMS-RJ, UFPE, UFMG, SMS-P.ALEGRE, SES-RS)

• 4-Evaluation of kinetics of transmition of M.tuberculosis at slums by genotypic information
• (UFRJ, FIO-CRUZ RJ)

• 5- Prevalence of tuberculosis infection/disease in elderly at nursing homes
• (UFRJ, FSP-USP)
CLINICAL-EPIDEMIOLOGICAL-OPERATIONAL STUDIES

- Conduct epidemiological studies based on genotypic data from *M. tuberculosis* strains, especially the transmission of multi-drug resistant strains, which will help the prevention and TB control
  (UFRJ, UFPE, UNICAMP, LACEN P.ALEGRE, FIO-CRUZ PE AND RJ)

- Evaluate the genotypes pattern of Mtb resistant to INH, RIF, SM, BEM, Pza isolates in different areas from Brazil pursuing the identification of more appropriate targets for new diagnostic methods and new clues for immunopathogenesis
  (UFRJ, UFES)
CLINICAL-EPIDEMILOGICAL-OPERATIONAL STUDIES

• 8-Determine the prevalence of *M. tuberculosis* in the studied regions as well as its geo-demographical distribution (age, gender, co-infection with HIV, co-morbidities associated, housing and origin) and correlate them to the genotypic information
  
  • (CRT/AIDS SP, HCFMRP-USP, EPM-UNIFESP, FM USP, SMS-SP, UFPE, FIO-CRUZ PE E RJ, HUCFF, UFRJ, UFES)

• 9-Identify factors (clinical, epidemiological and laboratory) associated with different *M. tuberculosis* genotypes, especially those associated with drug resistance
  
  • (UFRJ, UFES, UFPE, UNICAMP, )
• 10- Mathematical models in tuberculosis disease: decision analysis models, cost-effective, tree-card
• (FMRP-USP, UFRJ)
Objective: Design and conduct clinical trials for new drugs, new formulations of old drugs and diagnostic tests.

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Universidade Federal do Espírito Santo
Brazil
NDI TB Laboratory Capabilities

- ZN/fluorochrome smears
- BACTEC 460 radiometric & std culture; quantitative culture 7H10 agar; BACTEC NAP speciation & susceptibility testing
- DNA fingerprinting (DRE PCR- RFLP)
- specimen processing & storage
- whole blood killing assay
Clinical Laboratory Support

• HUCAM University Hospital Clinical Laboratory clinical chemistry, hematology, serology, EIA, urinalysis, parasitology

• Local commercial laboratories
DATA MANAGEMENT

• NDI connected by fiber optic lines to UFES mainframe; has own resident server & firewall.
• Full Internet access connected to TB health clinics in Vitoria’s metropolitan area.
• Custom Lotus Notes-based database for clinical & microbiological data (TB Notes→).
Clinical Trial Capabilities

• Established patient referral network
• Experienced staff with experience in IND & non-IND clinical trials
• Effective mechanisms for pt retention & long term follow-up
• State-of-the-art mycobacteriology & immunology laboratories
CLINICAL FACILITIES

• 12 bed Clinical Research Ward (CPC) for inpatient studies

• Reception area, exam rooms, sputum induction room & specimen collection & prep areas at CPC for follow-up visits

• X-ray, ultrasound unit in main teaching hospital

• Additional exam rooms & specimen collection areas at NDI
Recruitment of New TB Cases
1500 cases/year

• TB Clinic Post 500 meters from NDI
• Referral network - 6 TB Control Posts in the metropolitan area of Vitória linked by internet
• University Hospital wards & casualty room
• young adults; economically disadvantaged; 1/3 rural; M>F; < 10% HIV+