RePORT INDIA

2023 ANNUAL CONFERENCE

HOSTED BY

International Centre for Genetic Engineering & Biotechnology

New Delhi

February 8 – 10, 2023

Participating Institutions

- Bhagwan Mahavir Medical Research Center (BMMRC)
- Byramjee Jeejeebhoy Government Medical College (BJGMC)
- Byramjee Jeejeebhoy Government Medical College (BJGMC)-Johns Hopkins University (JHU) Clinical Research Site (BJGMC-JHU CRS)
- Boston University/Boston Medical Center (BU/BMC)
- Christian Medical College, Vellore (CMC)
- Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER)
- Johns Hopkins University (JHU)
- Prof. M. Viswanathan Diabetes Research Centre (MVDRC)
- National Institute for Research In Tuberculosis (NIRT)
- National Institute for Research In Tuberculosis (NIRT) – International Centers for Excellence in Research (ICER)
- North Eastern Indira Gandhi Regional Institute of Health & Medical Sciences (NEIGRIHMS)
- P.D. Hinduja National Hospital and Medical Research Centre (Hinduja)
- Postgraduate Institute of Medical Education and Research (PGI), Chandigarh
- Rutgers University
- University of California—San Francisco (UCSF)
- University of Massachusetts (UMass)
- University of Texas Health Science Center at Tyler (UTT)

Specialized Labs & Collaborators

- All Indian Institute of Medical Sciences (AIIMS), New Delhi, India
- Cornell University, New York, USA
- Emory University, Georgia, USA
- Fundação Oswaldo Cruz (FIOCRUZ), Bahia, Brazil
- Indian Institute of Science (IISc), Bengaluru, India
- Indian Institute of Technology Bombay (IIT-B) – Proteomics Core, Mumbai, India
- Medgenome, Bengaluru, India
- National Center for Functional Glycomics, Massachusetts, USA
- Office of Cyber Infrastructure and Computational Biology (NIAID), Maryland, USA
- South African TB Vaccine Initiative (SATVI), Cape Town, South Africa
- theraCUES Innovation Pvt Ltd, Bengaluru, India
- Translational Health Science and Technology Institute (THSTI), Faridabad, India

Sponsors

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AT LONG LAST
We meet again

RePORT India 2020 Annual Meeting in Mumbai

RePORT INDIA

Overview

CMC-Vellore

MVDRC

BMMRC

Background

RePORT (Regional Prospective Observational Research for Tuberculosis) India is a bilateral, multi-organizational, collaborative research effort established in 2013 under the Indo-US Vaccine Action Program (VAP). RePORT India is now the largest of six regional consortia—China, Brazil, Indonesia, Philippines, and South Africa are also undertaking multi-organizational tuberculosis (TB) research efforts. Each RePORT consortium is designed to support local, in-country, TB-specific data and specimen biorepositories and associated research. Taken together, the anticipated results include greater global clinical research capacity in high-burden settings and increased local access to quality data and specimens for members of each consortia and their domestic and international collaborators. Leveraging the data, specimens, infrastructure, and scientific partnerships established by RePORT India in Phase 1, the consortium has now launched Phase II.

Mission

RePORT India is charged with:

1. Advancing regional TB science in India, towards fulfilling the TB strategic goals of the country;
2. Strengthening TB research capacity and infrastructure; and
3. Fostering research collaboration within India and with other countries focused on research that can lead to clinically important biomarkers, vaccines, drugs, and diagnostics.

Phase I – Parent Protocols

Phase I (2013–18) commenced with six Clinical Research Sites (CRSs) in Western and Southern India that were partnered with five U.S. academic institutions. P.D. Hinduja National Hospital and Medical Research Centre was subsequently added as the seventh Indian site. Initially, each site had its own "Parent Protocol" with distinct research topics. Clinical, behavioral, radiological and biological samples were collected from the enrollees, including sputum, blood, urine etc. The specimens were stored at the ICMR-NIRT biobank for scientific analysis. TB patients and their household contacts were followed for a period of two years.

Cohort A: Participants who have active TB disease. Studies involving this cohort of patients focused on TB diagnosis and treatment outcomes.

- 2455 patients enrolled with TB inside the lungs (including 133 with drug-resistant TB)
- 588 patients enrolled with TB outside the lungs
- 207 children enrolled with TB

Cohort B: Participants who are household contacts (HHCs) of an active case of TB. Studies involving this cohort of participants focused on risk of infection and progression to TB disease after exposure.

- 3766 HHCs of coughing adult patients with TB inside the lungs enrolled

Phase I – Parent Protocol Achievements

- 106 scientific publications to advance TB science and public health
- 64 new projects utilizing the collected and stored samples for new biomarkers
- 245 presentations to showcase the work done in the RePORT Consortium
- New child TB diagnosis and treatment response gene-signatures unique for India
- New Transcriptomic, Lipidomic and Metabolomic signatures as blood biomarkers
- New vaccine trials to prevent TB relapse, Clinical biomarkers of TB death and relapse
- Key public health finding that informed the country's National TB Elimination Program guideline policies and more public health findings in the list with potential to guide further.

Phase I – Common Protocol

Based on the tremendous productivity of RePORT India's Phase I identifying new blood-based, sputum-based and urine-based biomarkers that can diagnose TB, or predict TB patients treatment success or failure or death, and for assessing new vaccines to prevent getting TB again (relapse) for those starting TB treatment, the governments of India and the US bilaterally funded the extension of Phase I in to a "Common Protocol" in 2017. The Common Protocol allowed for standardized data elements and harmonized procedures for enrollment across all sites to 1) identify newer, more accurate biomarkers and 2) confirm the utility of previously discovered biomarkers by validating them on samples stored in the ICMR-NIRT sample bank. The Common Protocol enrolled and followed TB patients and their HHCs for a period of two years.

Cohort A: Participants who have active TB disease.

- 724 adult patients enrolled with TB inside the lungs

Cohort B: Participants who are household contacts (HHCs) of an active case of TB.

- 898 household contacts of coughing adult patients with TB inside the lungs enrolled

Phase II – Common Protocol

Both Indo-US governments have further supported the scientific research goals of RePORT India by expanding the number of sites represented across the country, especially by involving scientists and participants from the Northern and North-eastern parts of the country. In addition to the existing group of TB patients and their household contacts across nine Indian sites in the RePORT India Phase II Common Protocol, the consortium plans to support the enrollment of 1500 adult and child patients who are suspected of having TB inside of outside their lungs, 588 adult patients with TB inside the lungs, and 794 household contacts of adult patients with TB inside the lungs. On the following pages, the Phase II CRSs and their study focus areas are outlined.

BMMRC & UTT

- **Topic of Study:** Immunologic Markers of Persons at Highest Risk of Progression of Latent TB Infection to TB
- **India PI:** Dr. Vijaya Valluri, Bhagawan Mahavir Medical Research Centre (BMMRC), Hyderabad, India
- **U.S. PI:** Dr. Krishna Vankayalapati, University of Texas Health Science Center, Tyler (UTHCT), TX, USA
- **Participating Patient Cohort:** Cohort B

BJGMC, NIRT, & JHU

- **Topic of Study:** Host and Microbial Factors Associated with Poor Treatment Response and Progression to Active TB (C-TRIUMPH)
- **India PIs:** Drs. Sanjay Gaikwad, Aarti Kinikar and Shashikala Sangle, Byramjee Jeejeebhoy Government Medical College (BJGMC), Pune, India; Dr. Vidya Mave, BJGMC-JHU CRS, Pune, India; Drs. Padma Chandrasekaran and Bhavani PK, National Institute for Research in TB (NIRT), Chennai, India
- **U.S. PI:** Dr. Amita Gupta, Johns Hopkins University, Baltimore, MD, USA
- **Participating Patient Cohorts:** Cohort A (Adult Pulmonary TB, Pediatric TB, and Extrapulmonary TB) and Cohort B

CMC Vellore & U of Wash/U of Cambridge

- **Topic of Study:** Host Determinants in the Eicosanoid Pathway that Modulate the Inflammatory Response, Disease Outcome, and Treatment Responsiveness in TB
- **India PI:** Drs. DJ Christopher and Balamugesh Thangakunam, Christian Medical College (CMC), Vellore, India
- **U.S. PI:** Dr. Lalitha Ramakrishnan, University of Washington/University of Cambridge, UK
- **Participating Patient Cohort:** Cohort A (Adult Pulmonary TB and TB Meningitis)

Hinduja & JHU

- **Topic of Study:** MDR-TB Treatment Outcomes, Adverse Effects, Mtb Genotyping, and Pharmacokinetic Testing
- **India PIs:** Drs. Zarir F. Udwadia, Tester F. Ashavaid, and Camilla Rodrigues; P.D. Hinduja National Hospital and Medical Research Centre, Mumbai, India
- **U.S. PIs:** Drs. Amita Gupta and Jeffrey Tornheim, Johns Hopkins University (JHU), Baltimore, MD, USA
- **Participating Patient Cohorts:** Cohort A (Adult/Adolescent MDR-TB) and Cohort B

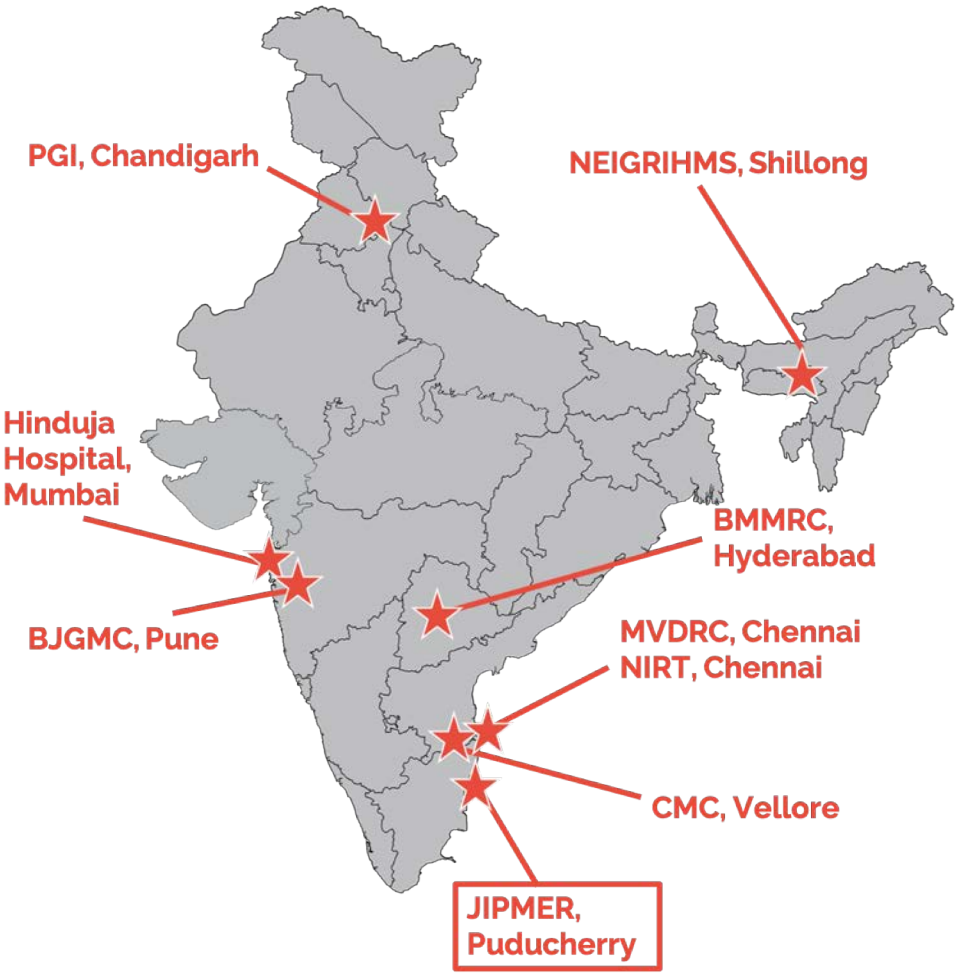
JIPMER, BU/BMC, & Rutgers

- **Topic of Study:** Biomarkers for Risk of TB and for TB Treatment Failure and Relapse
- **India PIs:** Drs. Gautam Roy and Sonali Sarkar, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India
- **U.S. PIs:** Drs. Jerrold Ellner and Padmini Salgame, Rutgers University, Newark, NJ, USA; Dr. Robert Horsburgh, Boston University (BU), Boston, MA, USA; Dr. Natasha Hochberg, Boston Medical College (BMC), Boston, MA, USA
- **Participating Patient Cohorts:** Cohort A (Adult Pulmonary TB and Pediatric TB) and Cohort B

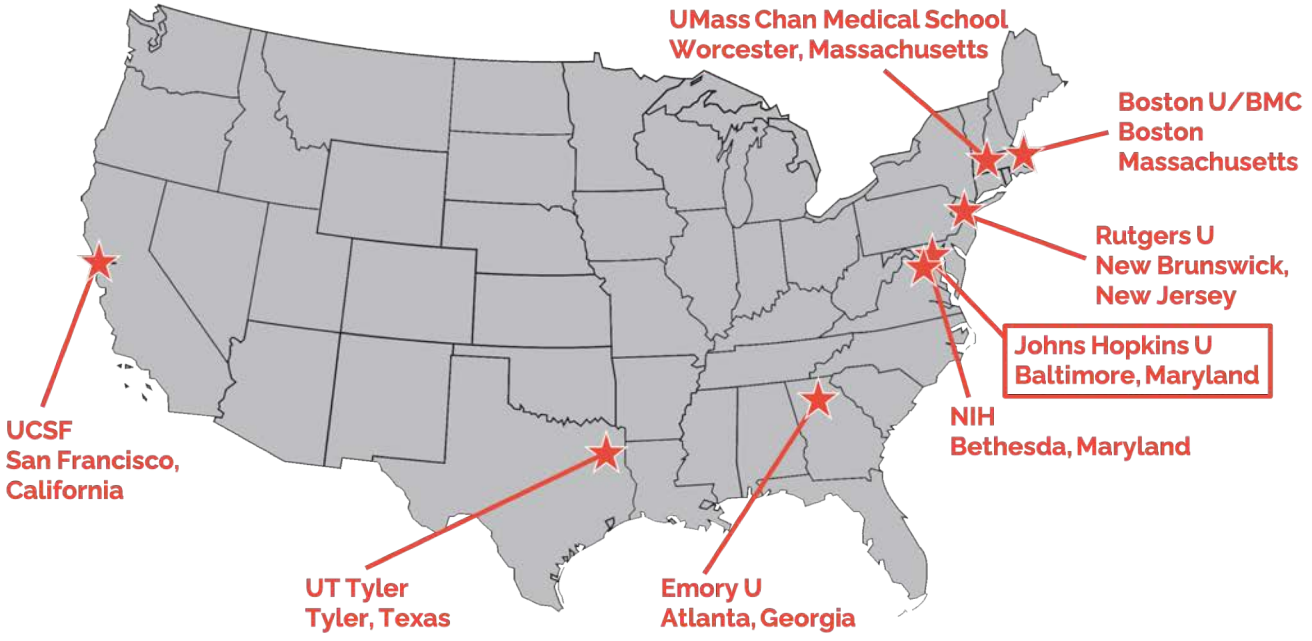
MVDRC, NIRT-ICER, & UMass

- **Topic of Study:** Effects of Diabetes and Prediabetes on TB Severity
- **India PIs:** Dr. Vijay Viswanathan, MV Diabetes Research Centre (MVDRC), Chennai, India; Dr. Subash Babu, National Institute for Research In Tuberculosis (NIRT) – International Centers for Excellence in Research (ICER), Chennai, India
- **U.S. PI:** Dr. Hardy Kornfeld, University of Massachusetts (UMass) Medical School, Boston, USA
- **Participating Patient Cohort:** Cohort A (Adult Pulmonary TB)

RePORT India Phase II



Under a Phase II Common Protocol, we are pursuing five specific scientific aims including the following cohorts: Diagnostic (New TB suspects), Cohort A (Active TB disease), and Cohort B (HHCs). Samples collected under this protocol will be curated, stored, and managed at the RePORT India Central Biorepository at NIRT where Phase I Common Protocol samples are currently stored. A data management center is being established at JIPMER in Puducherry and PPD will continue to provide technical support. The Phase II Common Protocol Co-Chairs are: Drs. Kamakshi Prudhula Devalraju (BMMRC) and Robert Bollinger (JHU). The consortium has now been expanded to include two new CRSs in Northern India.



Phase II Scientific Aims

AIM 1. DIAGNOSTICS

Evaluate Novel Diagnostics & Biomarkers of Diverse States of Mtb Infection

Participating Patient Cohort: Diagnostic (New TB suspects)
Leads: Dr. Sonali Sarkar (JIPMER) and Dr. Jerry Ellner (Rutgers)

Participating Patient Cohort: Cohort B (XDR HHCs)
Leads: Dr. Tester Ashavaid (Hinduja) and Dr. Jeff Tornheim (JHU)

AIM 2. MARKERS OF TREATMENT RESPONSE

Participating Patient Cohort: Cohort A (Active TB disease)

2.A: Identify TB Treatment Response Biomarkers
Leads: Dr. Vijay Viswanathan (MVDRC) and Dr. Hardy Kornfeld (UMass)

2.B: Investigate Host-Related Mechanisms of Treatment Failure
Leads: Dr. Vidya Mave (BJGMC-JHU CRS) and Dr. Natasha Hochberg (BMC)

2.C: Investigate Pathogen-related Mechanisms & Predictors of Recurrence
Lead: Dr. David Alland (Rutgers)

AIM 3. LUNG INJURY & IMPAIRMENT

Identify Markers of Lung Injury Associated with Unfavorable TB Treatment Outcomes

Participating Patient Cohort: Cohort A (Active TB disease)

Leads: Dr. DJ Christopher (CMC Vellore), Dr. Ashutosh Aggarwal (PGI Chandigarh), and Dr. Akshay Gupte (JHU)

AIM 4. RESISTANCE TO INFECTION

Mechanisms of Protection against TB in Exposed Persons

Participating Patient Cohort: Cohort B (Phase I HHCs)

4.A: Examine Host Antimicrobial Pathways in Inducing their infection resistant (IR) Phenotype in HHC

4.B: Test if IR & Plasma Differ in Modulating Macrophage-Mediated Restriction of Mtb Growth & Evaluate AB Repertoires of Plasma from the IR and infection susceptible (IS) Cohorts

Leads: Dr. Padmini Salgame (Rutgers), Dr. Subash Babu (NIRT-ICER), and Dr. Kamakshi Prudhula Devalraju (BMMRC)

AIM 5. PROGRESSION TO DISEASE

Identify Immunologic Markers of Persons at Highest Risk of Progress of Latent TB Infection to TB

5.A: Stored Samples: Validation of PREDICT29 in Progressors & Nonprogressors from RePORT Sites
Participating Patient Cohort: Cohort B (Phase I HHCs)
Leads: Dr. Padmini Salgame (Rutgers) and Dr. Luke Elizabeth Hanna (NIRT)

5.B: Immune & Hormone Studies in Freshly Collected Samples
Participating Patient Cohort: Cohort B (Phase II HHCs)
Leads: Dr. Vijaya Valluri (BMMRC) and Dr. Ramakrishna Vankayalapati (UTT)

In addition to these five aims, we will assess cross-cutting epidemiologic and COVID-19 related aims.

Administration

RePORT India has established a collaborative governance structure composed of: 1) an Executive Committee led by two Chairs and two Co-chairs from India and the U.S.; 2) an Indo-U.S. Coordinating Hub; 3) three Scientific Working Groups (Basic Science, Clinical Epidemiology, Behavioral Science); 4) five Operational Working Groups (Common Protocol Leadership, Study Coordination, Publications Committee, Laboratory Management, and Data Management); and 5) a Data Coordinating Hub (JIPMER).The EC's mission is to set research priorities, guide scientific activities, and offer administration and logistics in support of research priorities.

The consortium is currently led by:

- Chairs: Dr. Sonali Sarkar (JIPMER, Clinical Epi) and Dr. Amita Gupta (JHU, Clinical Epi)
- Co-Chairs: Dr. Vijaya Valluri (BMMRC, Basic Science) and Dr. Padmini Salgame (Rutgers, Basic Science)

Funding

The RePORT India Consortium is supported with bilateral funding from the Government of India's (GOI) Department of Biotechnology (DBT) and the U.S. National Institutes of Health's (NIH) National Institute of Allergy and Infectious Diseases (NIAID), Division of AIDS (DAIDS), and Office of AIDS Research (OAR). CRDF Global administers and oversees the funding from the U.S. government.

MVDRC

JIPMER

RePORT INDIA

Junior Investigator Abstracts

BJGMC

NIRT

Hinduja

Junior Investigator Abstracts

TITLE	INVESTIGATORS
Plasma immune correlates of risk for the progression of latent tuberculosis infection to active tuberculosis disease among household contacts of tuberculosis patients	**Anuradha Rajamanickam**, Evangeline Ann Daniel, Bindu Dasan, Fayaz Ahamed. S, Kannan Thiruvengadam, Padmapriyadarsini Chandrasekaran, Sathyamurthi Pattabiraman, Brindha Bhanu, Amsaveni Sivaprakasam, Mandar Paradkar, Vandana Kulkarni, Rajesh Karyakarte, Shri Vijay Bala Yogendra Shivakumar, Vidya Mave, Amita Gupta, Luke Elizabeth Hanna, Subash Babu
Elevated baseline cytokine and chemokine profile in recurrent tuberculosis upon tuberculosis antigens specific stimulation	**Arul Nancy P**, Nathella Pavan Kumar, Kadar Moideen, Vijay Viswanathan, Kannan T, Syed Hissar, Shanmugam Sivakumar, Ramalingam Bethunaikan, Hardy Kornfeld, Subash Babu
Decreased IL-1 family cytokine production in patients with nontuberculous mycobacterial lung disease	**Bock-Gie Jung,** Kristin Dean, Carly Wadle, Buka Samten, Deepak Tripathi, Richard J. Wallace, Jr., Barbara A. Brown-Elliott, Torry Tucker, Steven Idell, Julie V. Philley, Ramakrishna Vankayalapati
Potential miRNA biomarkers from QuantiFERON supernatants that can predict progression from Mycobacterium tuberculosis infection to active TB disease in healthy household contacts of TB patients	**Evangeline Ann Daniel**, Padmapriyadarsini C, Sathyamurthi Pattabiraman, Murugesan Selvachithiram, Brindha Bhanu, Amsaveni Sivaprakasam, Manohar Nesakumar, Mandar Paradkar, Vandana Kulkarni, Rajesh Karyakarte, Shri Vijay Bala Yogendra Shivakumar, Vidya Mave, Amita Gupta, Luke Elizabeth Hanna
Development of a four-gene host gene signature for TB diagnosis in individuals with Xpert MTB/RIF Ultra very low and trace results	**Kattya Lopez,** Vaishnavi Kaipilyawar, Xutao Wang, Nisha Modi, Robert Reiss, Christie Eichberg, Lydia Nakiyingi, Chad Centner, Kimberly McCarthy, David Alland, Susan Dorman, W. Evan Johnson, Yingda Xie, Padmini Salgame
Immune cell phenotypes in HIV-infected children	**Kamakshi Prudhula Devalraju**, Venkata Sanjeev Kumar Neela1, Deepak Tripathi, Anvesh Kumar Bogam, Vara Lakshmi Mallidi, Mohammad Soheb Ansari, Ramakrishna Vankayalapati, Vijaya Lakshmi Valluri
Mtb antigen-specific CD4+ memory T cell subsets demonstrate distinct immunometabolic pathways	**Vaishnavi Kaipilyawar,** Samantha Leong, Arianne Lovey, Lorenzzo Stringari, W. Evan Johnson, Reynaldo Dietze, Jerrold J. Ellner, Rodrigo Ribeiro-Rodrigues, Padmini Salgame
Tuberculosis risk signatures and differential gene expression predict individuals who fail treatment	**Arthur VanValkenburg**, Padmini Salgame, W. Evan Johnson, Jerrold J Ellner

Junior Investigator Abstracts

Plasma immune correlates of risk for the progression of latent tuberculosis infection to active tuberculosis disease among household contacts of tuberculosis patients

Submitting Author: Anuradha Rajamanickam

Co-authors: Evangeline Ann Daniel, Bindu Dasan, Fayaz Ahamed. S, Kannan Thiruvengadam, Padmapriyadarsini Chandrasekaran, Sathyamurthi Pattabiraman, Brindha Bhanu, Amsaveni Sivaprakasam, Mandar Paradkar, Vandana Kulkarni, Rajesh Karyakarte, Shri Vijay Bala Yogendra Shivakumar, Vidya Mave, Amita Gupta, Luke Elizabeth Hanna, Subash Babu

Background: Why some persons progress to tuberculosis (TB) disease while others do not after exposure remains poorly defined. Determining plasma biomarkers that potentially predict the progression of Mycobacterium tuberculosis infection to disease could guide interventions that combat tuberculosis spread. Our objective was to determine the plasma immune biomarker profiles at baseline in healthy household contacts of index pulmonary TB (PTB) patients who progress to TB versus those who do not.

Methods: Among a cohort of household contacts of adults with pulmonary TB disease, we compared soluble markers of 15 contacts who progressed to TB disease and 15 non-progressors who did not. Samples were analysed at enrolment, 4 months and 12 months, to allow for the determination of predictive markers of TB disease. We used a Luminex Bead Array to measure 45 parameters including cytokines, chemokines and growth factors in plasma samples and standard statistical methods for comparing concentrations were employed.

Results: We found that the progressor group showed significantly decreased levels of IFN*y*, IL-2, TNFα, IL1α, IL1β, IL-17A and IL-1Rα, when compared with the non-progressor group. In contrast, the progressor group exhibited significantly increased levels of IFNα, IFNβ, IL-6, IL-12, GM-CSF, IL-10, IL-33, CCL2, CCL11, CXCL8, CXCL10, CX3CL1, VEGF, Granzyme-B and PDL-1, when compared with the non-progressor group. The principal component analysis identified that these biomarkers could robustly discriminate between the progressor and non-progressor groups. Receiver operating characteristic analysis revealed that IFN*y*, GM-CSF, IL-1Rα, CCL2 and CXCL10 as the most promising predictive markers, with AUC ≥ 90. Further, the combinatorial analysis revealed that GM-CSF and CXCL10 exhibited high accuracy in combinations of markers.

Conclusion: Our data imply that a set of plasma biomarkers (GM-CSF and CXCL10) identify household contacts at high risk for developing TB disease.

Elevated baseline cytokine and chemokine profile in recurrent tuberculosis upon tuberculosis antigens specific stimulation

Submitting Author: Arul Nancy P

Co-authors: Nathella Pavan Kumar, Kadar Moideen, Vijay Viswanathan, Kannan T, Syed Hissar, Shanmugam Sivakumar, Ramalingam Bethunaikan, Hardy Kornfeld, Subash Babu

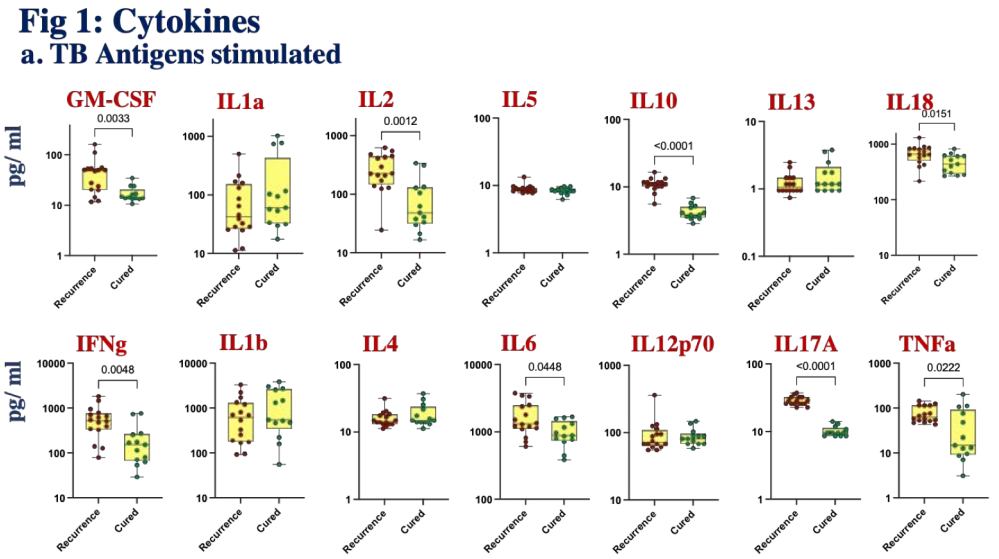
Background: Tuberculosis (TB) recurrence is defined primarily by sputum culture conversion from negative to positive after TB cure. It is important to delineate non- sputum- based biomarkers to identify predictive biomarkers for the occurrence of tuberculosis recurrence. Cytokines and chemokines are commonly used biomarkers for diagnosis of active TB. However, whether they could also serve as biomarkers for tuberculosis recurrence is unclear.

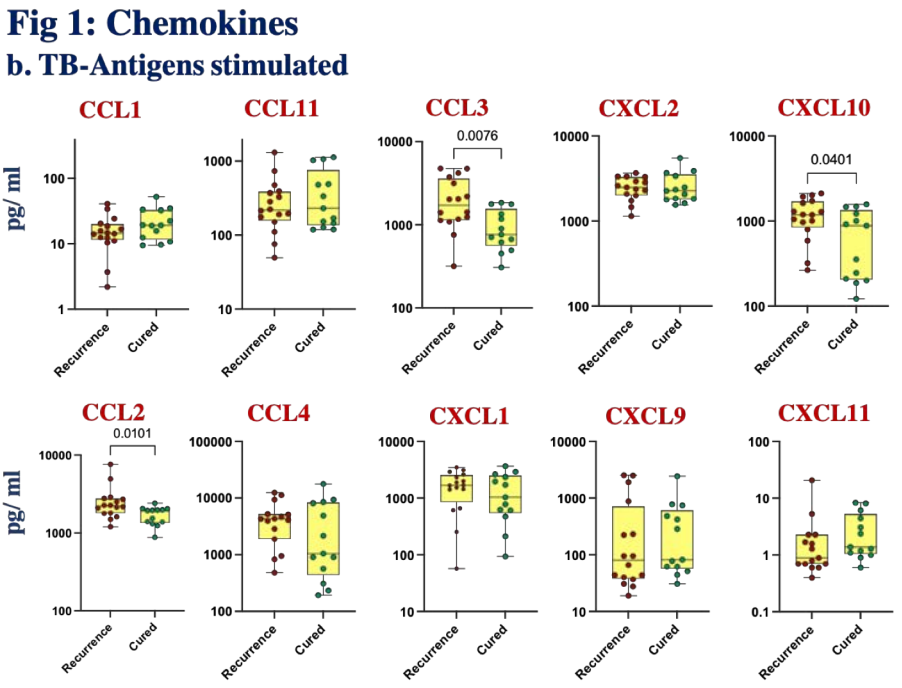
Methods: This study was performed in a clinically well characterized cohort where newly diagnosed, drug sensitive pulmonary TB patients defined by both sputum smear and culture positivity were enrolled. Our aim was to elucidate the baseline TB antigen specific cytokine and chemokine profile in TB recurrence cases (n=16) in comparison to recurrence free, microbiologically cured controls (n=13). TB antigen specific stimulation of whole blood was achieved using the QuantiFERON In-tube gold method from which plasma supernatants were used for the assay. A panel of 14 cytokines and 10 chemokines were measured in the study groups.

Elevated baseline cytokine and chemokine profile in recurrent tuberculosis upon tuberculosis antigens specific stimulation (*Continued*)

Results: In our study, eight cytokines (IL-2, IFN*y*, TNFα, IL-6, IL-10, IL17A, IL-18 and GM-CSF) and three chemokines (CCL2, CCL3 and CXCL10) (Fig:1) were significantly increased in TB recurrence cases when compared to cured controls at unstimulated as well as upon TB antigens (CFP10, ESAT6 and TB7.7) stimulation. However, no difference was seen upon mitogen stimulation between the groups, indicating that all the observed immune responses are mainly driven by TB antigens..

Conclusion: Our data suggest that TB recurrence exhibits a characteristic profile, which is immunologically distinct from TB cured individuals even before the start of the anti- TB treatment. Thus, pre-treatment level of specific cytokines and chemokines can act as an immune marker for unfavorable tuberculosis treatment outcome like recurrent TB.





Decreased IL-1 family cytokine production in patients with nontuberculous mycobacterial lung disease

Submitting Author: Bock-Gie Jung

Co-authors: Kristin Dean, Carly Wadle, Buka Samten, Deepak Tripathi, Richard J. Wallace, Jr., Barbara A. Brown-Elliott, Torry Tucker, Steven Idell, Julie V. Philley, Ramakrishna Vankayalapati

Background: Nontuberculous mycobacteria (NTM) cause pulmonary disease in individuals without obvious immunodeficiency. This study was initiated to gain insight into the immunological factors that predispose persons to NTM pulmonary disease (NTMPD).

Methods: Blood was obtained from 15 pairs of NTMPD patients and their healthy household contacts. Peripheral blood mononuclear cells (PBMCs) were stimulated with the M. avium complex (MAC). A total of 34 cytokines and chemokines were evaluated in plasma and PBMC culture supernatants using multiplex immunoassays, and gene expression in the PBMCs was determined using real-time PCR.

Results: PBMCs from NTMPD patients produced significantly less interleukin (IL)-1β, IL-18, IL-1α and IL-10 than PBMCs from their healthy household contacts in response to MAC. Although plasma RANTES levels were high in NTMPD patients, they had no effect on IL-1β production by macrophages infected with MAC. TLR2 and TWIK2 (two-pore domain K+ channel) were impaired in response to MAC in PBMCs of NTMPD patients. A TLR2 inhibitor decreased all 4 cytokines, whereas a two-pore domain K+ channel inhibitor decreased the production of IL-1β, IL-18, and IL-1α, but not IL-10, by MAC-stimulated PBMCs and monocytes. The ratio of monocytes was reduced in whole blood of NTMPD patients compared to healthy household contacts. Reduced monocyte ratio might contribute to the attenuated production of IL-1 family cytokine by PBMCs of NTMPD patients in response to MAC stimulations. Collectively, our findings suggest that attenuated IL-1 response may increase susceptibility to NTM pulmonary infection, through multiple factors including impaired expression of the TLR2 and TWIK2 and reduced monocyte ratio.

Potential miRNA biomarkers from QuantiFERON supernatants that can predict progression from Mycobacterium tuberculosis infection to active TB disease in healthy household contacts of TB patients

Submitting Author: Evangeline Ann Daniel

Co-authors: Padmapriyadarsini C, Sathyamurthi Pattabiraman, Murugesan Selvachithiram, Brindha Bhanu, Amsaveni Sivaprakasam, Manohar Nesakumar, Mandar Paradkar, Vandana Kulkarni, Rajesh Karyakarte, Shri Vijay Bala Yogendra Shivakumar, Vidya Mave, Amita Gupta, Luke Elizabeth Hanna

Background: MicroRNAs are significant regulators of TB pathogenesis and their differential expression pattern in non-TB, latent TB and active TB implies their potential to serve as useful biomarkers for different states of infection and disease. We therefore analysed differentially expressed miRNAs in TB antigen stimulated supernatants of household contacts of newly diagnosed TB patients who progressed to active TB during a 2-year follow-up period (Progressors) as compared to those did not progress to TB during follow-up (Non-progressors).

Methods: We used stored QuantiFERON supernatants of 14 progressors and 14 age and sex-matched non-progressors and performed high throughput expression analysis of 799 unique clinically relevant miRNAs in the samples using the NanoString nCounter platform. The differential expression between the groups were calculated as fold change ratio (P-value ≤ 0.05) and the significantly different miRNAs were enriched using the MicroRNA Enrichment Turned Network (MIENTURNET) online tool. Functional enrichment analysis was performed using miEAA 2.0 with the list of significant differentially expressed miRNAs to predict their involvement in biological pathways.

Results: We observed differential expression of 31 miRNAs between the Progressors and Non-progressors, among which hsa-miR-223-3p and hsa-miR-451a were significantly elevated in progressors with a maximum fold change ratio of 2.05. Additionally, hsa-miR-92a-3p (1.7-fold), hsa-miR-423-5p (1.34-fold) and hsa-miR-29a-3p (1.59-fold) were also significantly different between the groups. Target gene identification for the 31 significant miRNAs identified 66 genes implicated in TB pathogenesis; 19 miRNAs were directly involved in the TB pathway.

Potential miRNA biomarkers from QuantiFERON supernatants that can predict progression from Mycobacterium tuberculosis infection to active TB disease in healthy household contacts of TB patients *(Continued)*

Results: We observed differential expression of 31 miRNAs between the Progressors and Non-progressors, among which hsa-miR-223-3p and hsa-miR-451a were significantly elevated in progressors with a maximum fold change ratio of 2.05. Additionally, hsa-miR-92a-3p (1.7-fold), hsa-miR-423-5p (1.34-fold) and hsa-miR-29a-3p (1.59-fold) were also significantly different between the groups. Target gene identification for the 31 significant miRNAs identified 66 genes implicated in TB pathogenesis; 19 miRNAs were directly involved in the TB pathway.

Conclusions: Differential analysis of miRNA profile of TB antigen stimulated supernatants of Progressors and Non-progressors resulted in the identification of a distinct panel of miRNAs that can clearly distinguish between active TB patients and household contacts. Further validation of the candidate miRNAs in a larger independent cohort would endorse their potential as biomarkers for early detection of TB disease.

Table 1: Fold change of significant miRNAs between progressors and non-progressors

miRNA	Fold Change
hsa-miR-585-3p	1.74
hsa-miR-92a-3p	1.71
hsa-miR-33a-5p	1.68
hsa-miR-133a-5p	1.65
hsa-miR-197-3p	1.65
hsa-miR-24-3p	1.62
hsa-miR-145-5p	1.58
hsa-miR-487a-3p	1.58
hsa-miR-134-3p	1.56
hsa-miR-486-3p	1.56
hsa-miR-610	1.55
hsa-miR-370-3p	1.5
hsa-miR-888-5p	1.5
hsa-miR-128-1-5p	1.49
hsa-miR-584-3p	1.49
hsa-miR-496	1.45
hsa-miR-649	1.45
hsa-miR-365a-3p+hsa-miR-365b-3p	1.42
hsa-miR-107	1.41
hsa-miR-423-5p	1.34
hsa-miR-204-5p	-1.37
hsa-miR-199a-3p+hsa-miR-199b-3p	-1.38
hsa-miR-19b-3p	-1.5
hsa-miR-340-5p	-1.58
hsa-miR-29a-3p	-1.59
hsa-miR-20a-5p+hsa-miR-20b-5p	-1.64
hsa-miR-106b-5p	-1.71
hsa-miR-181a-5p	-1.79
hsa-miR-223-3p	-2.05
hsa-miR-451a	-2.05

Development of a four-gene host gene signature for TB diagnosis in individuals with Xpert MTB/RIF Ultra very low and trace results

Submitting Author: Kattya Lopez

Co-authors: Vaishnavi Kaipilyawar, Xutao Wang, Nisha Modi, Robert Reiss, Christie Eichberg, Lydia Nakiyingi, Chad Centner, Kimberly McCarthy, David Alland, Susan Dorman, W. Evan Johnson, Yingda Xie, Padmini Salgame

Background: The Xpert MTB/RIF Ultra assay (Ultra) is a diagnostic test for pulmonary tuberculosis (TB). However, Ultra detection of *Mycobacterium tuberculosis* at 'very low' or 'trace' semiquantitative values can be associated with negative cultures, thus making diagnosis and treatment challenging. The aim of this study was to determine whether host transcriptomic signatures can predict early TB disease when Ultra readouts are very low/trace and culture results are unavailable.

Methods: The performance of the published signatures in segregating Ultra very low and trace individuals who were culture positive from those who were negative ranged from AUC of 0.63 to 0.72. We derived a new 4-gene signature which when compared to the published signatures, demonstrated superior performance in segregating culture positive from culture negative among the Ultra very low and trace groups (AUC of 0.9). We validated our new signature in a published RNA-seq dataset of progressors and non-progressors from Brazil (AUC of 0.82).

Results: We observed differential expression of 31 miRNAs between the Progressors and Non-progressors, among which hsa-miR-223-3p and hsa-miR-451a were significantly elevated in progressors with a maximum fold change ratio of 2.05. Additionally, hsa-miR-92a-3p (1.7-fold), hsa-miR-423-5p (1.34-fold) and hsa-miR-29a-3p (1.59-fold) were also significantly different between the groups. Target gene identification for the 31 significant miRNAs identified 66 genes implicated in TB pathogenesis; 19 miRNAs were directly involved in the TB pathway.

Conclusions: Our data indicate that the new 4-gene host biomarker test in combination with the Ultra assay may confirm paucibacillary TB diagnosis among Ultra very low and trace samples.

Immune cell phenotypes in HIV-infected children

Submitting Author: Kamakshi Prudhula Devalraju

Co-authors: Venkata Sanjeev Kumar Neela1, Deepak Tripathi, Anvesh Kumar Bogam, Vara Lakshmi Mallidi, Mohammad Soheb Ansari, Ramakrishna Vankayalapati, Vijaya Lakshmi Valluri

Background: HIV infection markedly increases the likelihood of latent tuberculosis (TB) infection progressing to active TB. TB is the leading cause of death in HIV-infected persons and more than half a million coinfected people die annually. Children are more susceptible to TB infection, due to an immature immune system. It is difficult to diagnose TB in children and early diagnosis of TB infection and identification of HIV+ children who are at increased risk for development of TB would allow treating only high-risk children and preventing future development of TB. To develop diagnostic markers, it is important to understand the immune responses of children to Mtb and human cohort studies provide important information.

Methods: HIV- and HIV+ children in the ages between (2-18 years) were recruited. Peripheral blood mononuclear cells (PBMCs) were isolated and flow cytometry was used to identify various immune cell population (NK, macrophage and T-cell subpopulations including T-regulatory cells (Tregs)) flow cytometry was performed on some freshly isolated PBMC. Remaining PBMC were cultured with ESAT-6 and CFP-10. The culture supernatants were collected to measure cytokine and chemokine levels by multiplex ELISA.

Results: We determined the number various immune cell populations and expression of activating inhibitory receptor expression in freshly isolated PBMCs of age and sex matched HIV+ and HIV- children. We found that PBMCs of HIV+ children had significantly high number of $CD4^+CD8^+$ T cells and CTLA4 and PD1 expressing $CD4^+CD25^+FoxP3^+$ Tregs compared to HIV- healthy children. We also found that NK cells from the PBMC of HIV+ children express higher level of inhibitory receptor TIM3 and CTLA4 compared to the NK cells from age matched HIV- children. ESAT-6 and CFP-10-stimulated PBMCs from HIV+ children produced significantly high TNF-α and IL-10 but low MIP-1α, IL-4, GRO-α compared to HIV- children.

Conclusions: HIV infection in children enhanced the expression of various inhibitory receptors on Tregs and NK cells and dysregulate the production of inflammatory and anti-inflammatory cytokines which might lead to progression to active TB.

Mtb antigen-specific $CD4^+$ memory T cell subsets demonstrate distinct immunometabolic pathways

Submitting Author: Vaishnavi Kaipilyawar

Co-authors: Samantha Leong, Arianne Lovey, Lorenzzo Stringari, W. Evan Johnson, Reynaldo Dietze, Jerrold J. Ellner, Rodrigo Ribeiro-Rodrigues, Padmini Salgame

Background: Memory $CD4^+$ T cells play a crucial role in mediating long-lasting protective immunity against Mtb; however, their functional roles remain largely unexplored. In this study, we characterized the transcriptomic profiles and effector responses of $CD4^+$ T stem cell memory (T-SCM), central memory (T-CM), transitional memory (T-TM), and effector memory (T-EM) subsets, to provide a broader understanding of the memory response in latent TB infection (LTBI) and to support the development of novel vaccination strategies..

Methods: Following in-vitro Mtb-antigen stimulation of PBMC from 5 asymptomatic, long-term IGRA+ individuals, $CD4^+$ T cell memory subsets (T-SCM, T-CM, T-TM and T-EM) were isolated using fluorescence-sorting. Global gene expression patterns of all memory subsets were visualized using Principal Component Analysis and Mtb-specific functional responses were quantified using flow cytometry and Mtb-growth restriction assays. NanoString analysis and Ingenuity Pathway Analysis of differentially expressed genes of subsets identified shared, differential, and uniquely expressed immunometabolism pathways. Finally, Met-Flow analysis was performed to quantitate protein expression of key metabolic pathway regulators.

Mtb antigen-specific CD4+ memory T cell subsets demonstrate distinct immunometabolic pathways *(Continued)*

Results: Gene expression data demonstrated that Mtb-stimulated memory T cell subsets segregated into discrete clusters and suggested a model of progressive memory cell differentiation among CD4+ T cells. T-SCM and T-CM subsets exhibited increased protein expression of metabolic regulators and activation of pathways including glycolysis, mitochondrial respiration, and cell cycle signaling, indicating rapid repopulation capacity. In contrast, T-TM and T-EM subsets secreted the most IFN-γ and showed greater Mtb growth-restriction.

Conclusions: Our analyses show that during a recall response, distinct metabolic profiles of Mtb antigen-specific T memory subsets induce unique effector functions that modulate durable protective immunity in LTBI. Findings and techniques developed from this study will further provide key insights to the RePORT India platform in characterizing CD4+ T memory cell responses associated with various clinical stages along the TB spectrum.

Tuberculosis risk signatures and differential gene expression predict individuals who fail treatment

Submitting Author: Arthur VanValkenburg

Co-authors: Padmini Salgame, W. Evan Johnson, Jerrold J Ellner

Background: Although Tuberculosis (TB) remains the second leading infectious disease killer, it is treatable. However, some individuals fail treatment protocols after 5-6 months, and these remain potentially contagious. Identifying early those who fail treatment could help retain the spread of TB and adapt therapy to those individuals. Those who fail treatment may have differentially expressed genes (DEGs) compared to treatment responders. However, only a few studies have searched for a predictive gene signature in these patients. Furthermore, existing signatures designed to predict the risk of TB progression might help differentiate treatment failures from treatment success.

Methods: RNA-seq data from individuals with TB at baseline and two months of treatment were analyzed for differences in gene expression between those who benefited from treatment and those who did not. DEGs were analyzed with Qiagen's Ingenuity Pathway Analysis to determine relevant pathways involved in treatment failure. In addition, several TB signatures were scored with ssGSEA using the TBSignatureProfiler. DEGs were subjected to machine learning to identify genes for potential biomarkers for treatment failure.

Results: DEGs from the RNAseq data separated treatment failures and controls using dimension reduction and clustering with limma. Several TB signatures were enriched in the treatment failure group at baseline and month two. The DEGs were associated with several immune pathways, including the T and B cell Receptor Signaling pathways, Estrogen Receptor Signaling (upregulated in the treatment failure group), and Oxidative Phosphorylation Signaling (decreased in the treatment failure group). We identified two signatures, with four and fourteen genes, with the potential to differentiate between treatment failures and controls in the data.

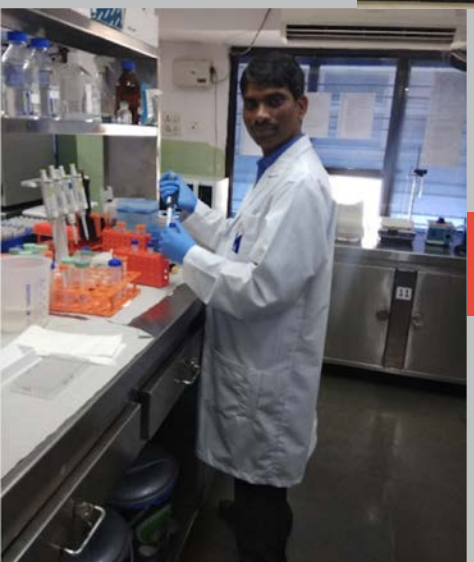
Conclusion: These results suggest that gene signatures may identify treatment failure at either baseline or month two and present potential pathways leading to treatment failure.

CMC Vellore

ICER Lab

NIRT

JIPMER



BMMRC

REPORT INDIA

Related Grants & Substudies

BJGMC

JIPMER

CMC

RePORT International & CFAR Supplemental Funded Projects

TITLE	PARTNERS	CRDF#	START DATE	INVESTIGATORS
Innovative Modelling for Predicting TB Treatment Outcomes in Global Cohorts	JHU FIOTEC Vanderbilt U		2022	
Impact of Latent TB Infection and Trained Immunity on Susceptibility to SARS-CoV-2 Infection in India and the Philippines	Rutgers, JIPMER, University of the Philippines Manila		2021	
Associative BRICS Research in COVID-19 and Tuberculosis (ABRICOT)	FIOTEC, Wits Health Consortium		2021	
T Cell Biomarkers and T-Regulatory Responses to Pediatric TB	Emory, JHU, BJGMC, NIRT	65373	2020	Rengarajan J, Kagal A, Kinikar A, Mave V, Padmapriyadarsini C, Hanna L, Paradkar M
Pregnancy Associated Immune Responses to TB and HIV in India and South Africa (PARTHISA study)	JHU, BJGMC, Wits Health Consortium, Cornell	65344	2020	Gupta A, Martinson N, Mathad J, Bhosale R, Kagal A, Alexander M, Kulkarni V
Pharmacokinetic Assessment of MDR-TB Drugs in the Treatment of TB Meningitis	JHU, PD Hinduja, Beijing Chest Hospital, BJGMC, Wits Health	65351	2020	Tornheim JA, Ashavaid T, Rodrigues C, Udwadia Z, Duan H, Sangle S, Varaiava E, Dooley K, Ignatius E, Mave V, Gupta A, Shivakumar SVBY, Chawla P, Patil S, Kulkarni V
Inflammasome Genetics and TB Treatment Outcomes	UPenn, JHU, UMass, NIRT, MVDRC, BGJMC	65375	2020	Bisson G, Gupte A, Viswanathan V, Gupta A, Kornfeld H, Hanna L, Babu S, Andrade B, Dhanasekaran M
Host RNA Expression for Diagnosis and Monitoring of Pediatric TB in Africa and India	NIRT, BGJMC, JHU, Univ. Cape Town, Imperial College, London	64080	2019	Kinikar A, Paradkar M, Hissar S, Workman L, Dawre R, Gupte N, Tornheim JA, Kulkarni V
Determination of Efficacy of Xpert PCR Ultra And Transcriptional Signatures In The Diagnosis of Pleural Tuberculosis	CMC, Vellore & University of Cape Town, SA	64074	2018	Christopher DJ, Keertan Dheda
Validation of Transcriptional Signature to Predict Active TB Disease among Advanced HIV Patients	RePORT Brazil, BMC, BJGMC, JHU	63158	2017	Mave V, Rolla V, Salgame P, Kadam D, Andrade B, Gupta A, Meshram S, Kulkarni V, Ellner J

RePORT International & CFAR Supplemental Funded Projects

TITLE	PARTNERS	CRDF #	START DATE	INVESTIGATORS
Molecular Signatures of Tuberculosis-Diabetes Interaction (MSTDI) Study	JHU, UMass, BJGMC, NIRT, MVDRC	63459	2017	Kornfeld H, P Chandrasekaran, Gupte A, Mave V, Bharadwaj R, Golub J, Andrade B, Paradkar M, Luke H, Kulkarni V, Gupte N, Shivakumar SVBY, Gupta A
Biomarkers for TB Diagnosis and Treatment Response	BJGMC, NIRT, Emory, JHU	63069	2016	Rengarajan J, Hanna LE, Mave V, Padmapriyadarsini C, Thiruvengadam K, Toidi A, Gupte N, Kulkarni V, Gupta A and CTRIUMPH team
Impact of HIV and Diabetes Mellitus on TB Drug Resistance and Recurrence	BJGMC, NIRT, JHU, MVDRC, UMass, Rutgers	63221	2016	Mave V, Devi U, Padmapriyadarsini C, Mathema B, Vishwanathan V, Kornfeld H, Kreiswirth B, Golub J, Gupte N, Shivakumar SVBY, Gupta A
MDR-TB and HIV at RePORT Sites India	BJGMC, NIRT, JIPMER, JHU, BMC	63076	2016	Horsburg R, Padmapriyadarsini C, Mave V, Gupta A, Sarkar S
Validation and Fine Tuning of the Computer Aided Diagnosis of Pulmonary Tuberculosis Model for the Indian Subcontinent	CMC	62922	2016	Christopher DJ, Thangakunam B, Lal B, Agrawal A
Extracranial Involvement as Detected by Positron Emission Tomography Scan in Patients with Tubercular Meningitis	CMC	62906	2016	Thangakunam B, Christopher DJ
Inflammatory Biomarkers as a Triage Test for Screening Symptomatic TB	JIPMER, Rutgers, BMC	63466	2016	Ellner J, Salgame P, Sarkar S, Pleskunas J
Characterization of Monocyte Responses in Pulmonary TB Patients with or without Type 2 Diabetes	NIRT-NIH – ICER, MVDRC	62911	2016	Kumar P
Effect of Malnutrition on Latent TB	Approved: JIPMER, Rutgers, BMC	23719	2016	Hochberg NS, Negi VS, Mahalakshmy T, Johnson WE, Salgame P, Pleskunas J
Determining Barriers to TB Care	JIPMER, BMC/BU	64020	2016	Sabin L, Sarkar S, Hochberg NS, Fernandes P, Pleskunas J, Amsaveni
TH17 Cell Subsets as Potential Risk Markers of Latency and Active TB Infection in Household Contacts	BMMRC, UT	62916	2016	Devalraju KP, Neela VSK, Valluri VL, Vankayalapati K
Comparison of Available Purified-Protein Derivative (PPD) Tuberculin Skin Test (TST) Antigen Solutions in Detecting Latent Tuberculosis Infection in India	CMC, BJGMC, JIPMER, BMMRC, NIRT, JHU, BMC	61783	2015	Christopher DJ, Shankar D, Roy G, Sarkar S, Prakash Babu S, Gupta A, Deluca A, Cox SR, Hochberg NS, Horsburgh R

Grants Awarded

TITLE	PARTNERS	GRANT SOURCE	START DATE
Microbiome-Associated Effects of Diabetes and BMI on Tuberculosis Severity	MVDRC, UMass	NIH	Submitted 2020 - *Pending*
Learning Effect of Parasites and Reinforcing Diets on TB (TB-LEOPARD)	JIPMER, BU	Burroughs-Wellcome Fund	2022
Dynamics and Immune Mechanisms of QFT Response in Close Contacts of TB Cases	JIPMER, BU	NIH/NIAID Supplement	2022
Rapid Research for Diagnostics Development in TB Network	CMC Vellore, UCSF	NIH/NIAID R01	2021
Innate Immune Response of LTBI+HIV+ Children	BMMRC, UT	NIH/NIAID R01	2021
Impact of Latent TB Infection and Trained Immunity on Susceptibility to SARS-CoV-2 Infection in India and the Philippines	Rutgers, JIPMER (Approved), University of the Philippines-Manila College of Medicine	RICC	2021
Learning about Experience with Nutritional Supplementation in Tuberculosis (LENS): An Exploratory Study	JIPMER, BU	Boston University of India (Seed Grant)	2021
Understanding Mycobacterium tuberculosis Mediated Host Metabolomics in Pulmonary Tuberculosis: Correlation with Disease Severity and Treatment Course	JIPMER IISER, Pune	PEER Women in Science SEED Grants 2021: National Academies	2021
The Regional Prospective Observational Research for Tuberculosis (RePORT) India Phase II Common Protocol	CMC Vellore	EC Approved	2020
Hybrid Trial for Alcohol Reduction among People with TB and HIV in India (HATHI)	BJGMC, JHU, London School of Hygiene and Medicine, DY Patil	NIH NIAAA R01	2020
Signature of Profiling and Staging the Progression of TB from Infection to Disease		NIH R01	2020
VITAL TB (Vitamins And Latency in Tuberculosis)	JIPMER, BU	U.S. Department of State's Partnership 2020 educational initiative	2020
Thyroxine (T4) Hormone Inhibits Expansion of Immunosuppressive CD4CD25+Foxp3+ (Tregs) Cells (Administrative Supplement for current R01 "IFN- independent inhibition of MTB growth in human macrophages")	BMMRC, UT	R01	2020
Host and Microbiome Transcriptional Profiling in the Upper Airways for TB Susceptibility	JIPMER	CTSI Pilot Grant, BU, US	2020

Grants Awarded

TITLE	PARTNERS	GRANT SOURCE	START DATE
Immune Responses and Effect of Disulfiram on MTB Infected PBMCs as a Potential Host Directed Therapy	BJGMC, NIRT, JHU, THSTI	Funding from Translational Health Sciences and Technology (THSTI)	2019
Dried Plasma Spots as a Simple Sampling Strategy to Measure Rifampicin Concentration to Facilitate this Service In Resource Limited Settings	CMC	Internal fluid research grant	2019
Evaluation of Diagnostic Potential of Aptamer-based Assays for Pulmonary Tuberculosis: A Pilot Study	CMC	THSTI	2019
Tuberculosis: Learning the Impact of Nutrition (TB LION)	JIPMER, BMC, Rutgers, Tufts, NIRT	Warren Alpert Foundation	2018
Whole Genome Sequencing of Drug Resistant Tuberculosis in India: Genotype-Phenotype Correlation, Clinical Impact of Resistance, and Sequencing Directly from Sputum	Hinduja, JHU	NIH/NIAID K23	2018
Validating a Th17 Switch as a Novel Correlate of Protective Immunity to TB	NIRT, BJMC, IISc, Bangalore, JHU	DBT/ IISc	2018
Characterization of Genomics and Metabolomics among Individuals (TB-GWAS)	Emory, JHU, BJGMC, JIPMER, BMMRC, NIRT, PHRU, McGill	NIH/NIAID R01	2018
Prevalence of Latent Tuberculosis in Rheumatoid Arthritis and Ankylosing Spondylitis	CMC	Internal fluid research grant	2018
The Effect of Appropriate Anti Tuberculous Treatment on Recovery of Pulmonary And Pleural Tuberculosis and the Impact of Tuberculosis on Lung Function and Quality of Life in Newly Diagnosed Patients	CMC	Internal fluid research grant	2018
Validation of Indigenously Developed Technology (TruNat MTB) for Diagnosis of Extra-pulmonary Tuberculosis: Multi-centric Validation	CMC, Hinduja, NIRT, AIIMS	ICMR	2018
Multicenter Phase II/III Double-Blind, Randomized, Placebo Controlled Study to Evaluate the Efficacy and Safety of VPM1002 in the Prevention of TB Recurrence in Pulmonary TB Patients after Successful TB Treatment.	RePORT India Sites	Serum Institute of India	2017-2022
Predictors of Resistance Emergence Evaluation in MDR-TB Patients on Treatment - (PREEMPT)	JIPMER, NIRT, BJGMC, Brazil, Vanderbilt, Rutgers, CDC, JHU, BMC, Hinduja	NIH/NIAID: R01	2017-2022
Transcriptomic and Metabolomic Analysis of Microbiologically Confirmed Pediatric Tuberculosis Patients and Uninfected Household Contacts	BJGMC, JHU	Ujala Foundation Wyncote Foundation BWI-CTU C-TRIUMPH	2017
Therapeutic Outcomes with Second-Line Drug Exposures in a Cohort of South African and Indian Patients with Drug Resistant TB: A Pharmacokinetic-Pharmacodynamic Assessment	Hinduja, PHRU, JHU	DBT/South Africa MRC	2017
Association of Lipid Mediators of Inflammation with TB Treatment Outcomes	JHU, NIRT, BJGMC	CTRIUMPH and Gilead Foundation	2017

Grants Awarded

TITLE	PARTNERS	GRANT SOURCE	START DATE
The Role of Innate Immunity in the Acquisition of Sterile Protection Against TB Infection	U Colorado, JHU, BJMC	NIH R21	2017
IFN-γ Independent Inhibition of MTB Growth in Human Macrophages	BMMRC, UT	NIH/NIAID R01	2017
MDR-TB Free: Monitoring Adverse Effects, Utilizing Resources Optimally, Knowing Resistance Patterns, and Treatment Strategy (MDR TB – MUKT)	Hinduja, JHU	Hinduja	2017
The Role of Monocyte Subpopulation in HIV+LTB+ Individuals and Development of Active TB	BMMRC, UT	NIH R21 Indo-US Vaccine Program, RePORT India Cohort	2016-2018
Measuring TB Drugs in Hair as a Tool to Monitor Adherence, Exposure and Response	BJGMC, NIRT, JHU	NIH/NIAID: R21	2016-2018
Role of Iron Deficiency in Resistance of Women of Child-Bearing Age to Tuberculosis	JIPMER, BMC	NIH	2016-2017
Studying T cell Memory Responses for Understanding Protective Immune Response in Tuberculosis (TB)	CMC, NIRT, Saint Louis U	American Society of Tropical Medicine and Hygiene/ Burroughs Wellcome Fund)	2016
Impact of Immune Changes of HIV and Stages of Pregnancy on TB	BJGMC, NIRT, JHU	NIH/NICHD R01	2015-2020
Impact of Pregnancy on Tuberculosis	JIPMER, BMC	NIH/NIAID R01	2015-2018
Residual Respiratory Impairment Following Pulmonary Tuberculosis: The Lung Health Sub-Study	BJGMC, NIRT, JHU	UJALA/ Gilead Foundation/ RePORT India	2015-2017
D4GDI-mediated Immune Responses in LTBI+HIV+ Individuals	BMMRC, UT	NIH R21 Indo-US Vaccine Program, RePORT India	2015-2017
Understanding of Tuberculosis Infection and Preventive Therapy Among Skin-Test Positive Household Contacts of Tuberculosis Cases	BJGMC, NIRT, JHU	NIH CFAR Fogarty D43	2015
T-regs Mediated Immune Responses in LTBI+HIV+ Individuals	BMMRC, UT	UT	2015
Compare Drug Levels in Newly Diagnosed or Relapsed PTB/ EPTB Following Daily ATT vs DOTS Regimen	CMC	Internal fluid research grant	2015
Impact of Personal Exposure to Black Carbon on Pulmonary Tuberculosis Severity	JIPMER BMC	Potts Memorial Foundation	2014-2018
Yield of TB using GeneXpert (Xpert MTB-Rif) by Induced Sputum Compared to Standard Sputum Samples	CMC	Internal fluid research grant	2014

Substudies

Childhood 'Omics' and Mycobacterium tuberculosis-derived BIOsignatures (COMBO) for TB Diagnosis

Principal Investigators
Adithya Cattamanchi (UCSF)
Joel Ernst (UCSF)
Devan Jagannath (UCSF)
Aarti Kinikar (BJGMC)
Mandar Paradkar (BJGMC-JHU CRS)

Population
BJGMC Pune site will contribute stored samples (plasma, urine) of eligible pediatric participants enrolled in the CTRIUMPH, RICC Pediatric, and TB Elispot studies.

Funding
NIAID: R

Design: We will utilize banked blood and urine specimens among children being evaluated for TB in India, Uganda, South Africa, The Gambia, and Peru. We will measure Mtb-specific proteins and host proteins, and metabolites in the discovery and initial validation set of banked samples from 150 children with Confirmed TB, 150 children with Unconfirmed TB, and 300 children with Unlikely TB per NIH consensus definitions with and without HIV infection.

Aims

1. Quantify levels of known Mtb proteins using an Electrochemiluminescence (ECL)-based assay ultra-sensitive
2. Perform an untargeted, shotgun proteomic and metabolomic approach to identify host proteins and metabolites that can serve as biomarkers for detection of childhood TB
3. Derive and validate the diagnostic accuracy of Mtb and/or host biosignatures for childhood TB.

Validating a th17 Switch as a Novel Functional Correlate of Immune Protection of Tuberculosis

Principal Investigators
Annapurna Vyakarna (Indian Institute of Science, Bangalore & USA St. Johns National Academy of Health Sciences)
Amita Gupta (JHU)
Vidya Mave (BJGMC-JHU CRS)
Padmapriyadarsini Chandrasekaran (NIRT)
Rajesh Karyakarte (BJGMC)

Sites
NIRT
BJGMC
St. Johns National Academy of Health Sciences

Population
Cohort I: TB Progressors among adults (>1 15 years household contacts: Longitudinal PBMC samples archived from a minimum of N=12 (maximum of 20) adults disease free for TB before and after they progress to TB.

Cohort 2: TB Non-Progressors among adults (>1 15 years household contacts: Longitudinal PBMC samples, age and sex-matched archived from a minimum of N=12 (maximum of 20) adults disease free for TB over the same time frame as cohort I.

Funding
RePORT India
DBT

Design: Longitudinal assessment of PBMC samples of progressors and non-progressors among adult household contacts of active TB patients

Aims

1. Validate using advanced 16-color flow cytometry in CTRIUMPH longitudinal samples, if TB-free adults who progress to TB (cohort 1), is associated with loss of DosR antigen-specific Th17 regulatory CD4 T cell responses with a concomitant increase in DosR antigen-specific Th17 proinflammatory CD4 T cells.
2. Further validate using advanced 16-color flow cytometry in cTRIUMPH longitudinal samples of adults who do not progress to TB in the same time frame as cohort I (cohort 2), are associated with preservation of DosR antigen-specific, Th17 regulatory CD4 T cell responses.
3. Undertake a comparative analysis of the DosR antigen-specific Th17 regulatory and proinflammatory response in cohorts I and 2 with responses to the Mycobacterium tuberculosis (Mtb) immunodominant secretory antigen ESAT6/CFP10 as well as recall response to stimulation with BCG vaccine, which can stimulate responses to multiple T cell epitopes of Mtb antigens.

Duration: Anticipated study start date- October 2018 | Length of study - 2 years

Markers of Lung Impairment in HIV-TB Coinfected Indian Adults

Principal Investigators
Akshay Gupte (BU)
Amita Gupta (JHU)
Sanjay Gaikwad (BJGMC)
Rajesh Karyakarte (BJGMC)

Sites
BJGMC

Population
1. Adults (>18 years) with drug-susceptible pulmonary TB and HIV co-infection (HIV-TB group).
2. Adults with drug-susceptible pulmonary TB without HIV co-infection (TB group).

Funding
TREAT Asia
NIAID/amfAR
DBT

Design: A retrospective cohort study of already collected clinical samples and data from the CTRIUMPH study at BJGMC. BJGMC, Pune, India

Aims

1. We will compare the degree of lung impairment between HIV-TB and TB participants at the completion of TB therapy. Lung impairment will be measured by pre-and post-bronchodilator spirometry. The primary outcome will be z-score standardized FEVI using the Global Lung Initiative (GLI) reference equations. Secondary outcomes will include z-score standardized FVC and FEV1/FVC ratio. We will use linear regression to compare the degree of lung impairment in TB cases with and without HIV, adjusting for potential confounders. With 15 HIV-TB and 30 TB participants, we will have 80% power at 5a % significance level to detect a 4.5 or higher percentile difference in lung function parameters between the two groups.
2. We will compare concentrations of inflammatory and metabolomic markers between HIV-TB and TB participants during TB therapy. Marker concentrations will be measured at individual time-points

Substudies

Inflammasome Genetics and Tuberculosis Treatment Outcomes

Principal Investigators	Sites	Population	Funding
Gregory Bisson (UPenn) Amita Gupta (JHU) Akshay Gupte (BU) Luke Hanna (NIRT) Subash Babu (NIH-NIRT-ICER) Vijay Vishwanathan (MVDRC) Sanjay Gaikwad (BJGMC) Rajesh Karyakarte (BJGMC)	BJGMC NIRT MVDRC	Adults (>18 years) with drug-susceptible pulmonary TB enrolled in the CTRIUMPH or EDOTS studies.	RICC

Design: Retrospective case-cohort analysis of already collected clinical samples and data from the CTRIUMPH and EDOTS studies.

Aims

1. To determine the association between single nucleotide polymorphisms (SNPs) in candidate genes related to inflammasomes and microbiologic treatment outcomes in adults being treated for drug-susceptible pulmonary TB.
2. To determine the association between SNPs in candidate genes related to inflammasomes and pulmonary involvement in adults who successfully complete treatment for a new diagnosis of drug-susceptible pulmonary TB.

Duration: 2 years

Molecular Signatures of Tuberculosis-Diabetes Interaction (MSTDI) Study—Metabolomics

Principal Investigators	Sites	Population	Funding
Amita Gupta (JHU) Akshay Gupte (BU) Hardy Kornfeld (UMass) Rajesh Karyakarte (BJGMC) Padmapriyadarsini Chandrasekaran (NIRT) Vidya Mave (BJGMC-JHU CRS) Bruno Andrade (RePORT Brazil)	NIRT BJGMC MVDRC RePORT Brazil	1. TB with DM (TBDM) 2. TB without DM (TB) 3. DM without TB (DM) 4. Healthy controls (HC)	RICC

Design: We will conduct a retrospective cohort study using collected demographic and clinic data and archived whole blood samples in the CTRIUMPH study as well as a small cross-sectional study of MTB uninfected adults with DM.

Aims

1. Compare baseline metabolomic signatures between newly diagnosed drug-sensitive PTB patients with and without DM.
2. Characterize and compare longitudinal change in metabolomic signatures in response to A TT between newly diagnosed drug-sensitive PTB patients with and without DM.

Molecular Signatures of Tuberculosis-Diabetes Interaction (MSTDI) Study—Transcriptomics

Principal Investigators	Sites	Population	Funding
Amita Gupta (JHU) Akshay Gupte (BU) Hardy Kornfeld (UMass) Rajesh Karyakarte (BJGMC) Padmapriyadarsini Chandrasekaran (NIRT) Vidya Mave (BJGMC-JHU CRS) Bruno Andrade (RePORT Brazil)	NIRT BJGMC MVDRC RePORT Brazil	1. TB with DM (TBDM) 2. TB without DM (TB) 3. DM without TB (DM) 4. Healthy controls (HC)	RICC

Design: We will conduct a retrospective cohort study using collected demographic and clinic data and archived whole blood samples in the RePORT India and RePORT Brazil study.

Aims

1. Compare baseline whole blood RNA-seq transcriptional signatures between newly diagnosed drug-sensitive PTB patients with and without DM in Pune and Chennai, India and Salvador, Brazil.
2. Characterize and compare longitudinal change in transcriptional signatures in response to A TT between newly diagnosed drug-sensitive PTB patients with and without DM in Chennai, India.

Substudies

Evaluation of a Urinary Biomarker Assay for Diagnosis and Test of Cure for Tuberculosis

Principal Investigators
Jeffrey Tornheim (JHU)
Sanjay Gaikwad (BJGMC)
Rajesh Karyakarte (BJGMC)
Aarti Kinikar (BJGMC)
Vidya Mave (BJGMC-JHU CRS)

Population
Stored samples

Funding
NIH
CFAR

Design: We will conduct a case-control diagnostic study nested within the CTRIUMPh cohort study using stored urine samples to identify positive results by the urine FujiLAM, conventional LAM, and the LAM and ESAT-6 nanocage assays. Samples have been collected from patients at multiple time points during treatment, and we will evaluate samples at enrollment (start of treatment), 2 months into treatment, and at the end of treatment (6 months).

Aims

1. To assess the ability of the FujiLAM kit and a urine lipoarabinomannan glycan (LAM) nanocage assay and a urine ESAT-6 nanocage assay to diagnose tuberculosis (TB) among Indian adults and children with HIV and CD4 counts >100 as well as among age-matched Indian TB patients without HIV,
2. To compare the TB treatment response as measured by urine LAM and ESAT-6 nanocage assays to TB treatment response as measured by sputum conversion, radiographic improvement, and clinical improvement among Indian TB patients with HIV and CD4 counts> 100 as well as among age-matched Indian TB patients without HIV.
3. (Exploratory): To assess the ability of FujiLAM kits and urine LAM and ESAT-6 nanocage assays to diagnose pediatric TB in Indian children with confirmed and unconfirmed TB.

A Nanopore Biosensor for Leveling MTB Antigens in Blood

Principal Investigators
Tony Ye Hu (Tulane U)
Robert C Bollinger (JHU)
Amita Gupta (JHU)
Rajesh Karyakarte (BJGMC)

Sites
BJGMC
Tulane U
JHU

Population
The purpose of the CTRIUMPH study was to evaluate the risk factors for TB among adults and children < 15 in India. Three cohorts were established:

1. Active TB cohort included adults with newly diagnosed active pulmonary TB (PTB) and children with TB
2. Household contacts cohort enrolling household members of active TB cases

Stored plasma samples from participants enrolled in these three cohorts at the Pune site will be utilized for the proposed study for assessment and the performance of the portable prototype system of the protein-based nanopore technology to quantify Mtb target peptides. These CTRIUMPH samples, as well as their linked clinical and microbiological data, will be analyzed to evaluate the performance of the peptide detection assay.

Funding
NIH R01

Design: This ROI will employ components of our current platform in a study to develop and optimize a robust and portable protein nanopore-based platform (QuantiPep) that meets WHO guidelines for new TB diagnostics and which can sensitively detect Mtb antigens in adult and pediatric blood samples. Shifting the assay from a mass spectrometry- to a nanopore-based system will allow rapid, sensitive and cost-effective TB detection and management in leaner clinical environments worldwide. Single channel recording technology is sensitive, specific, fast and affordable alternative to mass spectrometry. Nanopore ion currents are very sensitive to target molecule interactions as they occupy and translocate through the pore, and such interactions can generate signatures (current-time relationships) that are characteristic for a given target.

Aims

1. Develop a sensitive and specific QuantiPep TB assay suitable for resource-limited settings:
2. Validate Mtb antigen-derived peptides for TB diagnosis in a well-characterized cohort of adults and children with serially collected clinical, radiological and bacteriological data.
3. Evaluate how serum levels of Mtb antigens change in adult PTB cases in during anti-TB therapy.

Duration: 5 years

Substudies

Identification of Biomarkers that Can Predict Progression from Latent TB Infection to Active TB Disease

Principal Investigators	Sites	Population	Funding
Subash Babu (NIH-NIRT-ICER) Rajesh Karyakarte (BJGMC) Vidya Mave (BJGMC-JHU CRS) Luke Hanna (NIRT) Padmapriyadarsini Chandrasekaran (NIRT) Amita Gupta (JHU)	NIRT BJGMC NIH-NIRT-ICER	Adult and child household contacts of adult PTB cases from India enrolled in CTRIUMPh study: 1. HHCs of adult PTB cases, who progressed to active TB disease 2. HHCs of adult PTB cases, who did not progress to active TB disease	ICMR DBT NIH

Design: Case-control analysis of stored specimens and associated data between progressors and non-progressors

Aims

1. To measure the plasma biomarker profiles at baseline in HHC who progress versus those who do not.
2. To profile microRNAs at baseline in HHC who progress versus those who do not.
3. To measure the unstimulated, TB-antigen, and mitogen-stimulated cytokine and chemokine responses at baseline in HHC who progress versus those who do not.
4. To measure the unstimulated, TB-antigen, and mitogen-stimulated growth factors and other immune factors at baseline in HHC who progress versus those who do not.

Duration: 2 years

Biomarkers for Tuberculosis Diagnosis and Treatment Response

Principal Investigator	Sites	Population	Funding
Jyothi Rengarajan (Emory)	NIRT BJGMC JHU Emory	Stored samples of participants enrolled in the Active TB cohort and Household contact cohort in the CTRIUMPh study	RePORT India

Design: Cross-sectional longitudinal study

Aims

1. To evaluate biomarker performance on PBMCs from confirmed pulmonary TB and difficult-to–diagnose cases such as sputum smear-negative and HIV-infected individuals, extrapulmonary and pediatric TB patients.
2. To assess the ability of our biomarkers to monitor treatment response by selecting PBMCs from a subset of adult ATB patients, obtained at Time O (pre-treatment) and 1, 2, 6, and 12 after treatment initiation.
3. To use comprehensive immune profiling by mass cytometry (CyTOF) and multiparameter flow cytometry on a subset of ATB and control samples, to generate antigen-specific signatures of Adult TB, with the goal of discovering new markers that could further increase the sensitivity of our candidate biomarkers, particularly for difficult-to diagnose TB cases.

Duration: 12-18 months

T-Cell Biomarkers and T-Regulatory Responses to Pediatric TB

Principal Investigators	Sites	Population	Funding
Jyothi Rengarajan (Emory) Vidya Mave (BJGMC-JHU CRS) Anju Kagal (BJGMC) Aarti Kinikar (BJGMC)	BJGMC	Stored samples of participants enrolled in the CTRIUMPh Pediatric Active TB cohort and RICC Pediatric study.	RICC

Design: We will use cryopreserved PBMC samples from CTRIUMPH cohorts: pediatric unconfirmed TB, confirmed TB, latent TB and no TB controls. We will also be leveraging the data and specimens from the RePORT International Coordinating Centre (RICC) Pediatric Diagnostic Cohort study at BJGMC, Pune and analyze PBMCs isolated from pediatric TB suspects.

Aims

1. Validate host T cell biomarkers for diagnosis of pediatric TB
2. Aim 2: Investigate the phenotype and functions of T-regulatory cells in pediatric TB

Substudies

Host RNA Expression for Diagnosis & Monitoring of Pediatric TB in Africa & India RICC Pediatric Transcriptomic Study

Principal Investigators	Sites	Population	Funding
Lesley Workman (U of Cape Town) Aarti Kinikar (BJGMC) Mandar Paradkar (BJGMC-JHU CRS) Syed Hissar (NIRT)	Cape Town BJGMC NIRT	Baseline samples from 365 South African children will be tested as part of the existing Levin biomarker validation study and are not budgeted here. Follow up samples from a subset of 200 South African children will be included as part of the proposed study.	RICC

Design: This study involves the collaboration of two RePORT consortia, South Africa and India, both high burden TB and TB-HIV settings with well-established pediatric cohorts of children with TB disease, together with the Imperial College group leading the current NIH-supported pediatric TB biomarker validation study.

Aims

- Primary Objectives: To derive and validate a global RNA expression signature for the diagnosis of pulmonary TB, and extra-pulmonary TB in children; and to identify longitudinal changes in RNA expression with TB treatment in children who have microbiologically confirmed or clinically diagnosed TB, using bio-banked samples from the South Africa and Indian cohorts and clinical information from the TB RePORT Common Protocol (CP) and India parent protocol databases.
- Secondary Objectives: To establish a biorepository of samples that can be used for future pediatric TB diagnostic and pathogenesis studies.

Duration: 2 years

Residual Respiratory Impairment Following Pulmonary Tuberculosis: The Lung Health Sub-Study

Principal Investigators	Sites	Population	Funding
Rahul Lokhande (BJGMC) Shashikala Sangle (BJGMC) Sriram Selvaraju (NIRT) Akshay Gupte (BU) Amita Gupta (JHU)	BJGMC NIRT	1. Active TB cohort comprising 400 new adult pulmonary TB (PTB) cases. 2. Reference cohort comprising 400 adults without TB. 3. Cohort of 200 adults with chronic obstructive pulmonary disease (COPD) Each study site will enroll approximately 50% of the total sample size. COPD controls will be enrolled at BJGMC only.	NHLBI K99

Design: Prospective cohort study nested within the CTRIUMPH study.

Aims

1. To characterize trends in respiratory impairment among new adult PTB cases undergoing anti-tuberculous treatment (ATT) in India.
2. To identify host factors measured during the first 2 months of ATT initiation that are associated with respiratory impairment at ATT completion among new adult PTB cases in India.
3. To explore the impact of TB disease; alone and in combination with smoking exposure, indoor air pollution (IAP) exposure, HIV infection and diabetes mellitus (DM); on respiratory impairment up to 42 months following ATT completion among successfully treated adult PTB cases in India.
4. Characterize the chronicity and progression of lung impairment, and its responsiveness to bronchodilator therapy, in successfully treated PTB cases

Characterization of Genomics and Metabolomics among Individuals Highly–Exposed, but Resistant to Mtb Infection (TB-GWAS)

Principal Investigators	Sites	Population	Funding
Neel Gandhi (Emory) Yan Sun (Emory) Sanjay Gaikwad (BJGMC) Rajesh Karyakarte (BJGMC) Amita Gupta (JHU) Vidya Mave (BJGMC-JHU CRS) Padmapriyadarsini Chandrasekharan (NIRT) Neil Martinson (Perinatal HIV Research Unit, SA)	BJGMC JIPMER BMMRC	Household contacts of adult pulmonary TB cases from parent protocols study, RePORT India Common Protocol phase I at all sites; and Prospective TB GWAS study enrollments at BJGMC, Pune site.	NIH R01

Aims

1. To characterize a phenotype for resistance to Mtb infection using TST and IGRA results among household contacts recently exposed to TB.
2. To determine genetic predictors for resistance to Mtb infection.
3. To identify metabolomic markers associated with resistance to Mtb infection.

Substudies

Immune Responses & Effect of Disulfiram on MTB Infected PBMCs: Disulfiram as a Potential Host Directed Therapy

Principal Investigators
Amit Singhal (Singapore Immunology Network, Agency for Science, Technology and Research [A*STAR])
Ramandeep Singh (NCR Biotech Science Cluster)
Rajesh Karyakarte (BJGMC)
Amita Gupta (JHU)
Padmapriyadarsini Chandrasekaran (NIRT)
Vidya Mave (BJGMC-JHU CRS)

Sites
NIRT
BJGMC

Population
1. Adult PTB patients on TB treatment with an AUDIT score ≥ 8 (n = Up to 20)
2. Adult PTB patients on TB treatment with an AUDIT score < 8 (n = Up to 40)
3. Adult healthy contacts (n=Up to 20)

Funding
DBT
NIH

Design: We will conduct a cross-sectional study using already collected CTRIUMPh and RePORT India common protocol data (baseline demographic, clinical) and archived whole blood PBMC samples from the baseline visit to assess those with and without harmful use of alcohol as assessed by AUDIT scores 2::8. immunophenotyping will be performed by flow cytometry. Additional plasma cytokine and chemokine will also be considered.

Aims
1. To assess immune responses among adult PTB patients with harmful alcohol use defined by an AUDIT score >=8 compared to those with AUDIT scores < 8 at the time of treatment initiation.
2. Aim 2: To assess the effects of disulfiram on Mtb growth in PBMCs of alcoholic and non–alcoholic individuals

Identifying TB Treatment Response Biomarkers Using qRT-PCR Signature for TB Treatment Response and TB NanoString for Tx

Principal Investigators
Hardy Kornfeld (UMass)
Padmini Salgame (Rutgers)

Funding
RICC

Design: To validate five signatures (RESPONSE5, ACS6, RISK4, Khatri 3-gene, and Maertzdorf4-gene) as blood biomarkers in predicting TB treatment response to favorable and unfavorable treatment outcomes in the RePORT cohorts

Aims
To develop a promising blood biomarker for identifying response to TB treatment among active TB cases

Proteomic Discovery of Protein-based TB Recurrence and Death Signatures (IIT-M Proteomics Study)

Principal Investigators
Sanjeeva Srivastava (IIT-Bombay)
Sonia Krishnan (JHU)
Amita Gupta (JHU)
Mandar Paradkar (BJGMC-JHU CRS)
Rajesh Kayakarte (BJGMC)
Vandana Kulkarni (BJGMC-JHU CRS)

Funding
DBT
NIH
Phase 2

Aims
To identify markers of TB recurrence/death by mass spectrometry

The Role of Innate Immunity in the Acquisition of Sterile Protection Against TB Infection

Principal Investigators
Adriana Weinberg (University of Colorado)
Vandana Kulkarni (BJGMC-JHU CRS)
Rajesh Kayakarte (BJGMC)

Funding
NIH R21

Design: To identify potential targets for new TB vaccines by characterizing the immune responses that distinguish individuals with sterilizing protection against TB (TB-resisters), defined by presence of TB-specific immune responses and absence of latent infection, from individuals with latent TB infection (LTBI-participants)

Substudies

Epidemiologic Factors Associated with TB Treatment Outcomes across RePORT International Consortia

Principal Investigators
Bruno Andrade (RePORT Brazil)
Timothy Sterling (RePORT Brazil)
Mark Hatherill (RePORT South Africa)
Thomas Scriba (RePORT South Africa)
Amita Gupta (RePORT India)
Sonali Sarkar (RePORT India)
Retna Mustika Indah (RePORT Indonesia)
Muhammad Karyana (RePORT Indonesia)
Yuhong Liu (RePORT China)
Jingtao Gao (RePORT China)
Marrissa Alejandria (RePORT Philippines)
Ray (Sang Nae) Cho (RePORT Philippines)

Funding
RICC

Design: Analysis of data collected from a prospective multi-site cohort study to determine the Impact of key non-communicable and communicable diseases on tuberculosis treatment outcomes and recurrence using data from multiple RePORT International consortia

Aims

1. To create a harmonized analytical dataset from multiple RePORT International consortium sites
2. To determine the Impact of non-communicable diseases, including prediabetes and diabetes mellitus, and communicable diseases, including HIV, on tuberculosis treatment outcomes and recurrence, both globally and regionally

Validation of Transcriptional Signature to Predict Active TB Disease among Advanced HIV Patients

Principal Investigators
Vandana Kulkarni (BJGMC-JHU CRS)
Vidya Mave
Shashikala Sangale
Valeria Rolla

Funding
RICC

Design: The 1:1 case-control study to assess the performance of the 15 gene signature to detect TB among patients with advanced HIV. The cases would be advanced HIV patients (CD4 <100 cells/ul) with confirmed active TB and controls would be advanced HIV patients without any clinical and microbiologic evidence for active TB. The study was performed at BJGMC, Pune, India, Rio de Janeiro and Manaus at Brazil.

Aims

Study Exploratory objectives -To assess and compare changes in the T cell activation of HLA-DR+ and CD38+ T cell subsets, cytokine profiles of inflammatory markers and co-relate blood transcriptional and cytokine signatures of TB among advanced HIV patients with or without TB.

Aim 1: To conduct testing and validation of the 15-gene signature to predict active TB disease among advanced HIV patients with CD4 <100 cells/ul.

Aim 2: To assess and compare the cytokine/chemokine signature that may be predictive for active TB among advanced TB-HIV and HIV patients in India and Brazil.

Understanding Mycobacterium tuberculosis mediated host metabolomics in pulmonary tuberculosis: correlation with disease severity and treatment course

Principal Investigators	Sites	Population
Senbagavalli Prakash Babu	JIPMER	Adult participants enrolled in the Active TB cohort (Cohort A)
Sonali Sarkar	IISER	and Household contact (Cohort B) of common protocol phase I

Design: We will use plasma samples collected from common protocol cohorts to measure the metabolomic markers; active pulmonary TB (n=20) grouped as per disease severity (mild and severe) and their household contacts (n=10). For cohort A participants, samples will be analyzed at baseline, Month 1 and End of treatment; for cohort B at baseline

Aims

1. To study the differences in MTB influenced host metabolomics in mild and severe disease groups.
2. To study the dynamic changes of host metabolites at baseline, during and at the end of the standard anti-TB treatment regimen.
3. To examine whether there is a correlation between host metabolomics with disease severity and course of standard anti-TB treatment.

Substudies

Impact of Latent TB Infection and Trained Immunity on Susceptibility to SARS-CoV- 2 Infection in India and the Philippines

Principal Investigators	Sites	Population	Funding
Padmini Salgame Sonali Sarkar Alejandria Marcelo Marissa	JIPMER University of the Philippines	HHCs of pulmonary TB patients from RePORT India Phase I studies; Index COVID cases and their HHCs (Philippines)	RICC

Design: About 300 household contacts of pulmonary TB patients enrolled through RePORT Phase 1 studies will be reconsented and stratified into 4 groups based on the presence of LTBI +/- and SARSCoV +/-. About 300 SARS-CoV-2 positive patients identified from the hospital database (index cases) and an additional 250 of their household contacts will be enrolled in Philippines. For each of the 4 groups, 20 subjects will be selected and the trained immunity of their monocytes and NK cells will be examined.

Aims

1. Examine whether there is a correlation between LTBI and SARS-CoV-2 IgG seroconversion and/or COVID-19 disease severity
   a. In India, determine the seroprevalence of COVID-19 in healthy household contacts of prior active PTB cases stratified according to the presence of LTBI
   b. In the Philippines, determine the prevalence of LTBI in patients with confirmed COVID-19 infection and in their household contacts; and the association of LTBI with disease severity
2. Examine in a subset if enhanced trained immunity in LTBI positively correlates with protection from SARS-CoV-2 infection

Abdominal and Thoracic Ultrasound for the Diagnosis of Pulmonary and Extra-pulmonary Tuberculosis. Assessing the Accuracy of Point-of-care Ultrasound for the Diagnosis and Therapy Monitoring in Patients with Presumed Tuberculosis in India and Germany

Principal Investigators	Sites	Population
D.J. Christopher (India) Claudia M. Denkinger (Germany)	CMC Vellore, India Heidelberg University, University Clinics Cologne University Clinics Frankfurt, Germany	Patients aged **18** years or older presenting with: clinical constellation compatible with Pulmonary (PTB) and extra-pulmonary TB (EPTB)

Design: A prospective, multicentre study (Germany, India), we will enroll patients with presumed active TB of any anatomic site and in both in- and outpatient settings.

Objectives:

- To assess the accuracy of the FASH-protocol for diagnosing TB in extra-pulmonary sites (i.e. abdominal lymph nodes, splenic micro-abscesses, pleural or pericardial effusions, liver micro-abscesses) using a microbiological reference standard (MRS), an extended microbiological (eMRS) and composite reference standard (CRS) in presumptive adult TB-patients in Germany and separately in India
- To assess the accuracy of lung ultrasound for the diagnosis of pulmonary tuberculosis (unilateral large pleural effusion, especially with stranding, subpleural nodules (SUN) pattern, consolidation with an additional sign of TB (SUN, abdominal nodes, splenic lesions, pericardial effusions)) using a microbiological (MRS), extended microbiological (eMRS) and composite reference standard (CRS) in presumptive adult TB-patients in Germany and separately in India

Duration: Study start date – 18 April 2022 | Length of study – 36 Months

Rapid Research in Diagnostics Development for TB Network (R2D2 TB Network) Study

Principal Investigators	Sites	Population	Funding
D.J. Christopher (India) Adithya Cattamanchi (USA) Payam Nahid (USA) Claudia Denkinger (Germany)	CMC Vellore, India Hanoi Lung Hospital, Vietnam De La Salle Medical and Health Sciences Institute, Philippines Stellenbosch University, South Africa Makerere University College of Health Sciences, Uganda	Adult outpatients (age ≥18 years) with cough ≥2 weeks' duration, a commonly accepted criterion for identifying patients with presumed pulmonary TB	NIH

Design: For the novel TB triage and diagnostic tests, we will conduct large-scale evaluation of design-locked tests in a cohort of adults with presumed TB, with nested feasibility/pilot studies of early and late prototype tests. The large-scale evaluation is a *prospective cross-sectional study of 3,000 participants (600/clinical study site)*.

Objectives:

1. To conduct pilot studies of the diagnostic accuracy and usability of early and late prototypes of novel TB tests in settings of intended use to inform their further development.
2. To conduct large-scale validation studies of the diagnostic accuracy and usability of design-locked novel TB tests to inform policy development.

Our study hypotheses are:

1. Early and late prototypes of novel TB tests will meet pre-specified decision thresholds for advancement to the next phase of assessment.
2. Design-locked novel TB tests will meet updated WHO target product profile (**TPP**) requirements for minimum diagnostic accuracy.

Duration: study start date- 16 Aug 2021 | Length of study - 2 Years

Substudies

MDR-TB Free: Monitoring Adverse Effects, Utilizing Resources Optimally, Knowing Resistance Patterns, and Treatment Strategy (MDR TB MUKT)

Principal Investigators
Zarir F. Udwadia (Hinduja)
Camilla S. Rodrigues (Hinduja)
Tester F. Ashavaid (Hinduja)
Amita Gupta (JHU)
Jeffrey A Tornheim (JHU)

Sites
Hinduja

Population
1. Cohort A: Adults and adolescents ≥15 years of age with MDR-TB (n=200).
2. Cohort B: Adult and child household contacts of MDR-TB Cohort A participants with pulmonary TB (n=60).

Funding
Hinduja Foundation
RePORT India
NIH: K23

Design: This study is comprised of two prospective observational cohorts. Cohort A will enroll adults and adolescents ≥15 years with active multidrug resistant tuberculosis (MDR-TB). Cohort B will enroll adult and child household contacts of participants in Cohort A pulmonary MDR-TB cases.

Aims: To establish well-characterized prospective cohorts of active MDR-TB cases and their household contacts with associated biorepositories.

Cohort A Primary Objectives: To document participant outcomes including early treatment response, MDR-TB treatment-associated adverse events, mortality, and loss to follow-up.

Cohort B Primary Objectives: To assess rates of prevalent and incident TB infection and disease in household contacts of MDR-TB cases.

Cohort A Secondary Objectives

1. To evaluate the impact of comorbid diseases including diabetes mellitus, prediabetes, HIV, COPD, smoking status, alcoholism, depression, quality of life, and malnutrition on treatment outcomes and TB treatment-associated adverse events.
2. To assess the genotype-phenotype correlation among resistant TB isolates through MIC-based phenotypic drug susceptibility testing and next generation sequencing of TB isolates, including assessment of strain evolution, drug susceptibility pattern changes during treatment, and impact of strain on treatment outcomes.
3. To derive pharmacokinetic parameters of second-line agents in participants receiving multidrug treatment regimens with particular attention to linezolid, clofazimine, high-dose moxifloxacin, aminoglycosides, and any new drugs that become available including bedaquiline and delamanid.
4. To assess host biomarkers of treatment response and correlates of progression from exposure to TB disease using multiomics approaches (e.g. transcriptomics, metabolomics, cellular markers, and immunity- and inflammation-associated soluble biomarkers).
5. To assess microbial markers of treatment response including smear and culture conversion, quantitative burden, and the time to conversion.
6. To assess standard and novel imaging approaches to monitor treatment responses.
7. To assess the impact of TB on the quality of life and mental health of subjects with MDR-TB, and in turn their impact on treatment adherence and outcomes.
8. To assess host immune responses to and inflammation following TB exposure and TB treatment and correlate these responses with clinical outcomes.
9. To ascertain true outcomes and self-reported barriers to treatment retention of MDR-TB participants lost to follow-up (>=2 consecutive months of missed visits) during treatment through prospective phone follow-up and/or home visits.

Cohort B Secondary Objectives

1. To determine the feasibility of enrolling household contacts of index adult MDR TB cases.
2. To explore the proportion of contacts with prevalent TB disease and infection, what proportion develop new TB disease and infection during follow-up, and what are prevalent comorbidities (diabetes mellitus, prediabetes, HIV, COPD, smoking status, alcoholism, depression, quality of life, and malnutrition) among the household contacts.
3. To contribute samples to a global repository for the study of biomarkers of incident TB and progression from exposure to TB disease using multiomics approaches (e.g. transcriptomics, metabolomics, cellular markers, and immunity- and inflammation-associated soluble biomarkers).

Substudies

Therapeutic Outcomes with Second Line Drug Exposures in a Cohort of Patients with Drug Resistant TB: A Pharmacokinetic-Pharmacodynamic Assessment

Principal Investigators	Sites	Population	Funding
Tester F. Ashavaid (Hinduja) Camilla S. Rodrigues (Hinduja) Neil Martinson (PHRU, SA) Ebhrahim Variava (PHRU, SA)	Hinduja (India) PHRU (South Africa)	Cohort A: Adults and adolescents ≥15 years of age with MDR-TB (n=200)	SA MRC DBT

Design: The study is designed to study the pharmacokinetic (PK) and pharmacodynamics (PD) profiles of second line TB drugs and develop PK-PD models to help understand efficacy of these drugs.

Aims

1. To determine the pharmacokinetic parameters of second-line agents in South African and Indian patients receiving DR-TB treatment regimens with particular attention to moxifloxacin, linezolid, clofazimine, bedaquiline and SLI (Kanamycin, Amikacin)
2. To assess the MIC of these drugs using Thermoscientific Fisher Sensititre panels.
3. To characterize the population pharmacokinetics of these drugs in the study population and determine factors associated with low drug exposures
4. To study the association between drug exposures of second-line TB drugs and therapeutic outcomes in a pharmacokinetic-pharmacodynamic analysis among patients with DR-TB

Predictors of Resistance Emergence Evaluation in Multidrug Resistant-Tuberculosis Patients on Treatment (PREEMPT)

Principal Investigators	Sites	Population	Funding
Zarir F. Udwadia (Hinduja) Camilla S. Rodrigues (Hinduja) Tester F. Ashavaid (Hinduja) C. Robert Horsburgh (BU)	NIRT (India) BJGMC (India JIPMER (India) Hinduja (India) NEGRIMS (India) YRJCARE (India) INI – FIOCRUZ (Brazil) UFRJ (Brazil)	Adult PTB MDR patients on TB treatment (N=400 for India and 200 for Brazil)	NIH: R01

Design: In this observational cohort study, we propose to study the contribution of potential causes to resistance and develop the knowledge base required to stop resistance from developing by analyzing AUC and sputum samples.

Aims

1. Determine whether low serum antimycobacterial drug concentrations are associated with the clinical emergence of drug resistance in MDR-TB patients.
2. Determine whether HIV seropositivity is a risk factor for low serum drug concentrations.
3. Determine the contribution of increased DNA mutation to clinical emergence of drug resistance in patient isolates.
4. Determine the earliest time at which mutations responsible for drug resistance can be detected during treatment

Whole Genome Sequencing of Drug Resistant Tuberculosis in India: Genotype-Phenotype Correlation, Clinical Impact of Resistance, and Sequencing Directly from Sputum (K23)

Principal Investigators	Sites	Population	Funding
Camilla S. Rodrigues (Hinduja) Jeffery A. Tornheim (JHU)	Hinduja	Cohort A (MDR-TB MUKT): Adults and adolescents ≥15 years of age with MDR-TB (n=200)	NIH: K23

Design: The K23 analysis will correlate mutations identified by whole genome sequencing with both MGIT and MIC drug susceptibility test results, correlate those results with plasma drug levels and participant outcomes, and compare the results obtained by sequencing the isolates without culture to those obtained by sequencing MGIT cultures and solid cultures.

Aims

1. To characterize MIC distribution for mutations identified on WGS in Indian MDR-TB strains and compare the frequency and predictive value of WGS-derived mutations in Mtb isolates from Indian MDRTB patients with those from South African MDR-TB patients in the ReSeqTB Data Platform.
2. To assess the impact of partial resistance (identified by WGS and MIC-testing) and drug exposures (using PK-PD analysis) on patient outcomes in a cohort of MDR-TB patients.
3. To assess a new direct-from-sputum method for WGS compared to culture-based WGS for DST.

Substudies

Pharmacokinetic Assessment of MDR-TB Drugs in the Treatment of TB Meningitis (MDR-TBM PK)

Principal Investigators	Indian Sites	Population	Funding
Jeffrey A Tornheim (JHU) Tester F. Ashavaid (Hinduja) Hongfei Duan (Beijing Chest Hospital) Ebrahim Variava (Perinatal HIV Research Unit) Rohidas Tanku Borse (BJGMC)	BJGMC Hinduja **International Sites** Johns Hopkins Beijing Chest Hospital PHRU	Adult MDR TBM patients on TB treatment (N=70 all sites) - (Hinduja site n=20)	RICC

Design: Patient suspected of TBM will be screened for the eligibility of enrolment in the study. Eligible participants will be consented, enrolled and followed up for a 6-month period after enrollment with a total of 8 clinical encounters each. On enrolment, a baseline lumbar puncture (LP) will be performed to confirm the diagnosis of TBM. If suspected patients have already undergone an LP, the sample will be retrieved from the labs and stored for biorepository. This LP will be a part of standard of care (SOC). For the PK studies, participants will be followed up for Week 1 & Week 4 with repeat LP. These LP may be as a part of SOC or for research use only for PK studies.

Aims

1. Penetration coefficient of each drug into the CSF
2. Relationship between PK parameters, survival, and functional status.

Baseline pRescription According to Direct from Sputum Sequencing and TArgeted drug Concentration Strategy (BRASS TACS)

Principal Investigators	Site	Population	Funding
Tester F. Ashavaid (Hinduja) Camilla S. Rodrigues (Hinduja) Zarir F. Udwadia (Hinduja) Jeffrey A. Tornheim (JHU)	Hinduja	Adult with Pulmonary RR/MDR-TB (n=210)	NIH: R01

Design: This study is an observational study of a combined treatment strategy informed by NGS, TDM, and MIC testing. The study will enroll adults starting treatment at Hinduja Hospital for RR/MDR-TB of the lungs. All data will be provided to clinicians to help personalize therapy. Outcome and side effect data will be compared to data from historical controls with MDR-TB enrolled in previous RePORT-India associated cohort studies at Hinduja Hospital using propensity score matching by disease severity and resistance to assess the impact of the BRASS TACS treatment strategy to outcomes among similar patients treated without this strategy.

Aims

1. To determine the proportion of patients with MDR-TB in Mumbai, India with resistance-associated mutations that would prevent treatment with moxifloxacin, linezolid, bedaquiline, clofazimine, or cycloserine using culture-free NGS.
2. To identify the proportion of cohort participants with MDR-TB that achieve model-derived steady-state plasma levels meeting efficacy and toxicity targets.
3. To assess the time to final regimen, frequency of treatment-associated side effects, time to culture conversion, and final outcome of cohort participants who complete culture-free NGS and TDM.

Identification of M. tuberculosis and Prediction of Drug-resistance among Adults with Pulmonary Tuberculosis Using a Novel Urine Collection and Target Concentration Device, Followed by Cartridge-based Nucleic Acid Amplification Testing (Urigami and CBNAAT Study)

Principal Investigators	Site	Population	Funding
Tester F. Ashavaid (Hinduja) Camilla S. Rodrigues (Hinduja) Jeffrey A. Tornheim (JHU)	Hinduja	1. Adult PTB MDR patients on TB treatment (N=400 for India and 200 for Brazil) 2. Adult healthy contacts (n=Up to 20)	CFAR NIH: R21

Design: We will transfer the novel urine capture and affinity bait method developed at the Liotta Lab in the USA to the PD Hinduja National Hospital and Medical Research Centre in Mumbai, India where it will be used to assess the baseline and 6-month urine samples collected from newly diagnosed adults with drug susceptible pulmonary tuberculosis, as well as the de-identified baseline and 6-month urine samples collected from participants in the MDR-TB MUKT cohort with pulmonary MDR-TB and fluoroquinolone resistance stored in the MDR-TB MUKT biorepository. Specificity will be assessed by repeating the assay among de-identified samples collected from household contacts of pulmonary TB patients stored in the MDR-TB MUKT biorepository.

Aims

1. To assess the diagnostic accuracy of the combination of a collapsible urine collection device with hydrogel nanocage affinity baits for Mtb cfDNA and the Xpert MTB/RIF and Xpert Ultra for the detection of pulmonary Mtb and rifampin resistance from freshly collected urine.
2. To assess the accuracy of this combination method to identify resistance to isoniazid, fluoroquinolones, and second-line injectable drugs using the Xpert XDR cartridge on de-identified samples in a well-characterized biorepository.
3. To implement this novel concentration technology in a high burden setting by transferring technology developed in a US laboratory to the Indian context. To achieve an analytical sensitivity for genomic DNA of 10 pg/mL in urine matrix.

RePORT INDIA

Publications

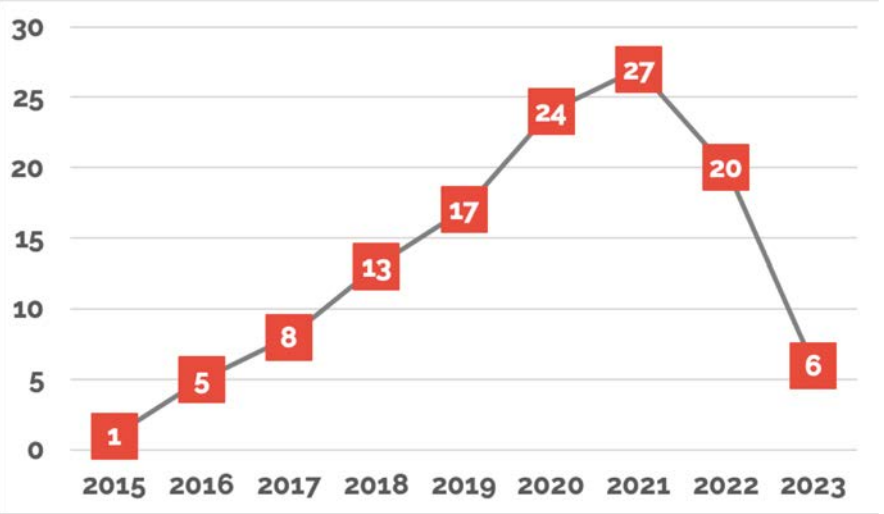
BMMRC

Hinduja

BJGMC

JIPMER

Publications 2015-2023



2022-23 Publications

Bhagwan Mahavir Medical Research Centre
University of Texas Health Science Center at Tyler (CRU 107)

1. **Metabolites enhance innate resistance to human Mycobacterium tuberculosis infection**
   Tripathi D, Devalraju KP, Neela VSK, Paidipally P, Radhakrishnan RK, Mukherjee T, Dozmorov I, Bogam AK, Mallidi V, Ansari MS, Valluri VL, Vankayalapati R. JCI Insight. 2022 Nov 22;7(22):e152357. doi: 10.1172/jci.insight.152357. PMID: 36509283; PMCID: PMC9746823.

Byramjee Jeejeebhoy Government Medical College
National Institute for Research in Tuberculosis
Johns Hopkins University (CRUs 106 & 105)

1. **Characterising cause of death among people treated for drug- susceptible TB in India**
   Cox SR, Padmapriyadarsini C, Mave V, Seth B, Thiruvengadam K, Gaikwad S, Sahasrabudhe TR, Sane M, Tornheim JA, Shrinivasa BM, Lokhande R, Barthwal MS, Shivakumar VBY, Krishnan S, Santhappan R, Kinikar A, Kakrani AL, Paradkar M, Bollinger RC, Sekar K, Gupte AN, Hanna LE, Gupta A, Golub JE, on behalf of the CTRIUMPH and TBDM Study Teams. Int J Tuberc Lung Dis. 2023;27(1):78-80. http://dx.doi.org/10.5588/ijtld.22.0454
2. **Predictive performance of interferon-gamma release assays and the tuberculin skin test for incident tuberculosis: an individual participant data meta-analysis**
   Hamada Y, Gupta RK, Quartagno M, Izzard A, Acuna-Villaorduna C, Altet N, Diel R, Dominguez J, Floyd S, Gupta A, Huerga H, Jones-López EC, Kinikar A, Lange C, van Leth F, Liu Q, Lu W, Lu P, Rueda IL, Martinez L, Mbandi SK, Muñoz L, Padilla ES, Paradkar M, Scriba T, Sester M, Shanaube K, Sharma SK, Sloot R, Sotgiu G, Thiruvengadam K, Vashishtha R, Abubakar I, Rangaka MX. EClinicalMedicine. 2023 Jan 5;56:101815. doi: 10.1016/j.eclinm.2022.101815. PMID: 36636295; PMCID: PMC9829704.

Byramjee Jeejeebhoy Government Medical College
National Institute for Research in Tuberculosis
Johns Hopkins University (CRUs 106 & 105)

3. **QuantiFERON supernatant-based host biomarkers predicting progression to active tuberculosis disease among household contacts of tuberculosis patients**
Daniel EA, Thiruvengadam K, Rajamanickam A, Chandrasekaran P, Pattabiraman S, Bhanu B, Sivaprakasam A, Paradkar M, Kulkarni V, Karyakarte R, Shivakumar SVBY, Mave V, Gupta A, Babu S, Hanna LE. Clin Infect Dis. 2022 Dec 30:ciac979. doi: 10.1093/cid/ciac979. Epub ahead of print. PMID: 36582115.

4. **Sex differences in tuberculosis clinical presentation, drug exposure, and treatment outcomes in India**
Deshmukh S, Sane M, Gaikwad S, Sahasrabudhe T, Barthwal M, Lokhande R, Raskar S, Kagal A, Dharmshale S, Pradhan N, Gupte A, Alfarisi O, Gupta A, Dooley KE, Gupte N, Golub JE, Mave V. Chest. 2022 Sep 26:S0012-3692(22)03893-4. doi: 10.1016/j.chest.2022.09.024. Epub ahead of print. PMID: 36174745.

5. **Whole genome sequencing assessing impact of diabetes mellitus on tuberculosis mutations and type of recurrence in India**
Mave V, Chen L., Ranganathan U D, Kadam D, Vishwanathan V, Lokhande R, S, S. K., Kagal A, Neeta, Shivakumar SVBY, Paradkar MS, Deshmukh S, Tornheim JA, Kornfeld H, Farhat M, Gupta A, Padmapriyadarsini C, Gupte N, Golub JE, Mathema B, & Kreiswirth BN. Clin Infect Dis. 2022 Sep 14;75(5):768-776. doi: 10.1093/cid/ciab1067. PMID: 34984435; PMCID: PMC9477453.

6. **Baseline IL-6 is a biomarker for unfavourable tuberculosis treatment outcomes: a multisite discovery and validation study**
Gupte AN, Kumar P, Araújo-Pereira M, Kulkarni V, Paradkar M, Pradhan N, Menon P, Padmapriyadarsini C, Hanna LE, Yogendra Shivakumar SVB, Rockwood N, Du Bruyn E, Karyakarte R, Gaikwad S, Bollinger R, Golub J, Gupte N, Viswanathan V, Wilkinson RJ, Mave V, Babu S, Kornfeld H, Andrade BB, Gupta A. Eur Respir J. 2022 Apr 21;59(4):2100905. doi: 10.1183/13993003.00905-2021. PMID: 34711538; PMCID: PMC7612881.

7. **Concomitant pulmonary disease is common among patients with extrapulmonary TB**
Shivakumar SVBY, Padmapriyadarsini C, Chavan A, Paradkar M, Shrinivasa BM, Gupte A, Dhanasekaran K, Thomas B, Suryavanshi N, Dolla CK, Selvaraju S, Kinikar A, Gaikwad S, Kohli R, Sivaramakrishnan GN, Pradhan N, Hanna LE, Kulkarni V, DeLuca A, Cox SR, Murali L, Thiruvengadam K, Raskar S, Ramachandran G, Golub JE, Gupte N, Mave V, Swaminathan S, Gupta A, Bollinger RC. Int J Tuberc Lung Dis. 2022 Apr 1;26(4):341-347. doi: 10.5588/ijtld.21.0501. PMID: 35351239; PMCID: PMC8982647.

8. **Host lipidome and tuberculosis treatment failure**
Shivakoti R, Newman JW, Hanna LE, Queiroz ATL, Borkowski K, Gupte AN, Paradkar M, Satyamurthi P, Kulkarni V, Selva M, Pradhan N, Shivakumar SVBY, Natarajan S, Karunaianantham R, Gupte N, Thiruvengadam K, Fiehn O, Bharadwaj R, Kagal A, Gaikwad S, Sangle S, Golub JE, Andrade BB, Mave V, Gupta A, Padmapriyadarsini C. Eur Respir J. 2022 Jan 6;59(1):2004532. doi: 10.1183/13993003.04532-2020. PMID: 34375300; PMCID: PMC9625841.

9. **The kynurenine/tryptophan ratio is a sensitive biomarker for the diagnosis of pediatric tuberculosis among Indian children**
Tornheim JA, Paradkar M, Zhao H, Kulkarni V, Pradhan N, Kinikar A, Kagal A, Gupte N, Mave V, Gupta A, Karakousis PC. Front Immunol. 2022 Jan 12;12:774043. doi: 10.3389/fimmu.2021.774043. PMID: 35095848; PMCID: PMC8790563.

Christian Medical College, Vellore
University of Cambridge–University of Washington (CRU 101)

1. **Accuracy of Xpert MTB/RIF Ultra for the diagnosis of tuberculosis in adult patients: a retrospective cohort study**
   Kaswala C, Schmiedel Y, Kundu D, George MM, Dayanand D, Devasagayam E, S AM, Kumar SS, Michael JS, Ninan MM, Chacko G, Zachariah A, Sathyendra S, Hansdak SG, Iyadurai R, Christopher DJ, Gupta R, Karthik R, Abraham OC, Varghese GM. Int J Infect Dis. 2022 Sep;122:566-568. doi: 10.1016/j.ijid.2022.07.016. Epub 2022 Jul 8. PMID: 35811084.
2. **Semantic segmentation of bone structures in chest X-rays including unhealthy radiographs: A robust and accurate approach**
   Singh A, Lall B, Panigrahi BK, Agrawal A, Agrawal A, Thangakunam B, Christopher DJ. Int J Med Inform. 2022 Sep;165:104831. doi: 10.1016/j.ijmedinf.2022.104831. Epub 2022 Jul 18. PMID: 35870303.
3. **Impact of undernutrition on tuberculosis treatment outcomes in India: A multicenter prospective cohort analysis**
   Sinha P, Ponnuraja C, Gupte N, Babu SP, Cox SR, Sarkar S, Mave V, Paradkar M, Cintron C, Govindarajan S, Kinikar A, Priya N, Gaikwad S, Thangakunam B, Devarajan A, Dhanasekaran M, Tornheim JA, Gupta A, Salgame P, Christopher DJ, Kornfeld H, Viswanathan V, Ellner JJ, Horsburgh CR, Gupte AN, Padmapriyadarsini C, Hochberg NS. Clin Infect Dis. 2022 Nov 25:ciac915. doi: 10.1093/cid/ciac915. Epub ahead of print. PMID: 36424864.

Jawaharlal Institute of Postgraduate Medical Education & Research
Boston Medical Center/Boston University
Rutgers (CRU 102)

1. **Psychometric properties of the Household Food Insecurity Assess Scale among households with tuberculosis patients in South India**
   (Accepted in Progress in Nutrition) Yuvaraj Krishnamoorthy, Sathish Rajaa, Komala Ezhumalai, Selby Knudsen C, Robert Horsburgh Jr., Natasha S. Hochberg, Padmini Salgame, Jerrold Ellner, Senbagavalli PB, Sonali Sarkar
2. **Comparison of IGRA and TST in the diagnosis of latent tuberculosis among women of reproductive age in South India**
   Senbagavalli Prakash Babu, Komala Ezhumalai, Kalaivani Raghupathy, Madhusudanan Sundaresan, Komal Jain, Prakash Babu Narasimhan, Selby Knudsen, Robert Horsburgh, Natasha Hochberg, Padmini Salgame, Jerrold Ellner, Sonali Sarkar. Indian Journal of Tuberculosis https://doi.org/10.1016/j.ijtb.2022.03.011.
3. **Effect of treatment adherence on the association between sex and unfavourable treatment outcomes among tuberculosis patients in Puducherry, India: a mediation analysis**
   Barathi A, Krishnamoorthy Y, Sinha P, Horsburgh C, Hochberg N, Johnson E, Salgame P, Govindarajan S, Senbagavalli PB, Lakshinarayanan S, Roy G, Ellner J, Sarkar S. J Public Health (Oxf). 2022 Jun 11:fdac062. doi: 10.1093/pubmed/fdac062. Epub ahead of print. PMID: 35692180.
4. **Development of prognostic scoring system for predicting 1-year mortality among pulmonary tuberculosis patients in South India**
   Krishnamoorthy Y, Ezhumalai K, Murali S, Rajaa S, Majella MG, Sarkar S, Lakshminarayanan S, Joseph NM, Soundappan G, Prakash Babu S, Horsburgh C, Hochberg N, Johnson WE, Knudsen S, Pentakota SR, Salgame P, Roy G, Ellner J. J Public Health (Oxf). 2022 Aug 27:fdac087. doi: 10.1093/pubmed/fdac087. Epub ahead of print. PMID: 36038507.
5. **Malnutrition leads to increased inflammation and expression of tuberculosis risk signatures in recently exposed household contacts of pulmonary tuberculosis**
   VanValkenburg A, Kaipilyawar V, Sarkar S, Lakshminarayanan S, Cintron C, Prakash Babu S, Knudsen S, Joseph NM, Horsburgh CR, Sinha P, Ellner JJ, Narasimhan PB, Johnson WE, Hochberg NS, Salgame P. Front Immunol. 2022 Sep 28;13:1011166. doi: 10.3389/fimmu.2022.1011166. Erratum in: Front Immunol. 2022 Oct 20;13:1064883. PMID: 36248906; PMCID: PMC9554585.

Jawaharlal Institute of Postgraduate Medical Education & Research
Boston Medical Center/Boston University
Rutgers (CRU 102)

6. **Predictors of weight loss during the intensive phase of tuberculosis treatment in patients with drug-susceptible pulmonary tuberculosis in South India**
   Kalva J, Babu SP, Narasimhan PB, Raghupathy K, Ezhumalai K, Knudsen S, Horsburgh CR, Hochberg N, Salgame P, Roy G, Ellner J, Sarkar S. J Public Health (Oxf). 2022 Nov 30:fdac141. doi: 10.1093/pubmed/fdac141. Epub ahead of print. PMID: 36451280.
7. **Impact of Undernutrition on Tuberculosis Treatment Outcomes in India: A Multicenter Prospective Cohort Analysis.**
   Sinha P, Ponnuraja C, Gupte N, Babu SP, Cox SR, Sarkar S, Mave V, Paradkar M, Cintron C, Govindarajan S, Kinikar A, Priya N, Gaikwad S, Thangakunam B, Devarajan A, Dhanasekaran M, Tornheim JA, Gupta A, Salgame P, Christopher DJ, Kornfeld H, Viswanathan V, Ellner JJ, Horsburgh CR, Gupte AN, Padmapriyadarsini C, Hochberg NS. Clin Infect Dis. 2022 Nov 25:ciac915. doi: 10.1093/cid/ciac915. Epub ahead of print. PMID: 36424864.
8. **Development and validation of a parsimonious TB gene signature using the digital NanoString nCounter platform**
   Kaipilyawar V, Zhao Y, Wang X, Joseph NM, Knudsen S, Babu SP, Muthaiah M, Hochberg NS, Sarkar S, Horsburgh CR, Jr., Ellner JJ, Johnson WE, Salgame P. Clin Infect Dis. 2022. Epub 2022/01/12. doi:10.1093/cid/ciac010. PubMed PMID: 35015839.

MVDRC, NIRT-ICER, UMass

1. **Chitinase and indoleamine 2, 3-dioxygenase are prognostic biomarkers for unfavourable treatment outcomes in pulmonary tuberculosis**
   Kumar NP, Nancy A, Viswanthan V, Shanmugam S, Thiruvengadam K, Ahamed SF, Hissar S, Kornfeld H, Babu S. Frontiers in Immunology. *In press*
2. **Longitudinal Trends in Glycated Hemoglobin During and after Tuberculosis Treatment**
   Kornfeld H, Procter-Gray E, Kumpatla S, Kane K, Li W, Magee MJ, Babu S, Viswanathan V. Diabetes Res Clin Pract. 2023 Jan 7:110242. doi: 10.1016/j.diabres.2023.110242. Online ahead of print.. PMID: 36627027
3. **Heightened microbial translocation is a prognostic biomarker of recurrent tuberculosis**
   Kumar NP, Moideen K, Viswanathan V, Sivakumar S, Ahamed SF, Ponnuraja C, Hissar S, Kornfeld H, Babu S. Clin Infect Dis. 2022 Nov 14;75(10):1820-1826. doi: 10.1093/cid/ciac236. PMID: 35352112; PMCID: PMC9662171.

P.D. Hinduja National Hospital & Medical Research Center
Johns Hopkins University (CRU 108)

1. **Pharmacokinetic analysis of linezolid for multidrug resistant tuberculosis at a tertiary care centre in Mumbai, India**
   Resendiz-Galvan JE, Arora PR, Abdelwahab MT, Udwadia ZF, Rodrigues C, Gupta A, Denti P, Ashavaid TF, Tornheim JA. Front Pharmacol. 2023 Jan 4;13:1081123. doi: 10.3389/fphar.2022.1081123. PMID: 36686664; PMCID: PMC9846493.
2. **Cycloserine did not increase depression incidence or severity at standard dosing for multidrug-resistant tuberculosis**
   Tornheim JA, Udwadia ZF, Arora PR, Gajjar I, Gupte N, Sharma S, Karane M, Sawant N, Kharat N, Blum AJ, Shivakumar SV. Eur Respir J. 2022 Mar 24;59(3):2102511. doi: 10.1183/13993003.02511-2021. PMID: 34949698; PMCID: PMC8943271.

RePORT INDIA

Data

CMC

BJGMC

BMMRC

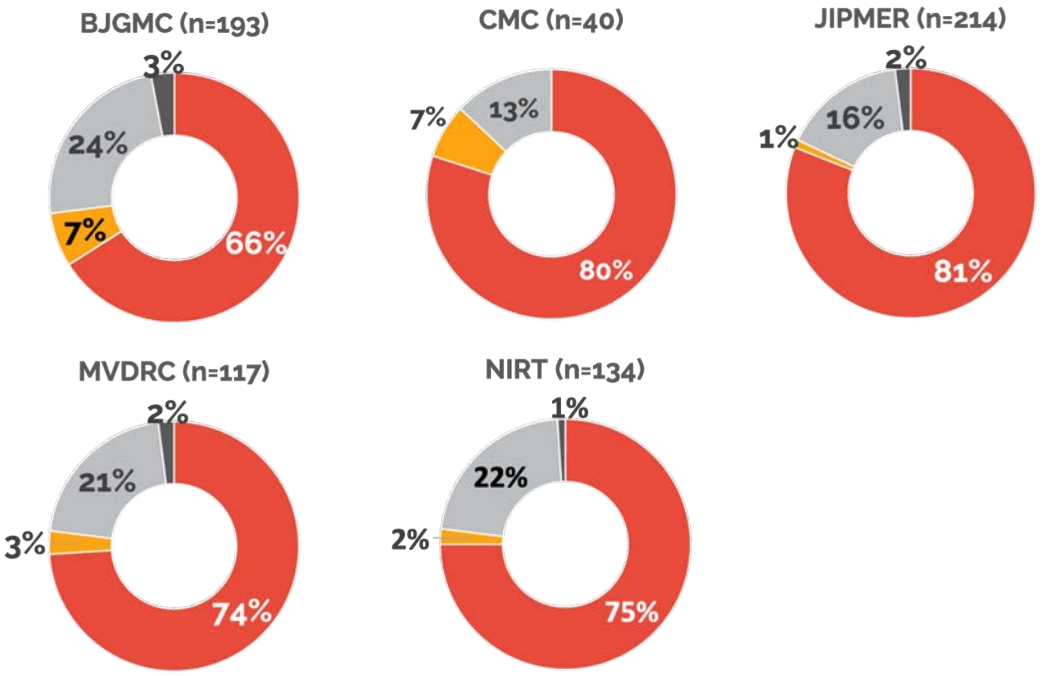
JIPMER

Prof. M. Viswanathan Diabetes Research Centre

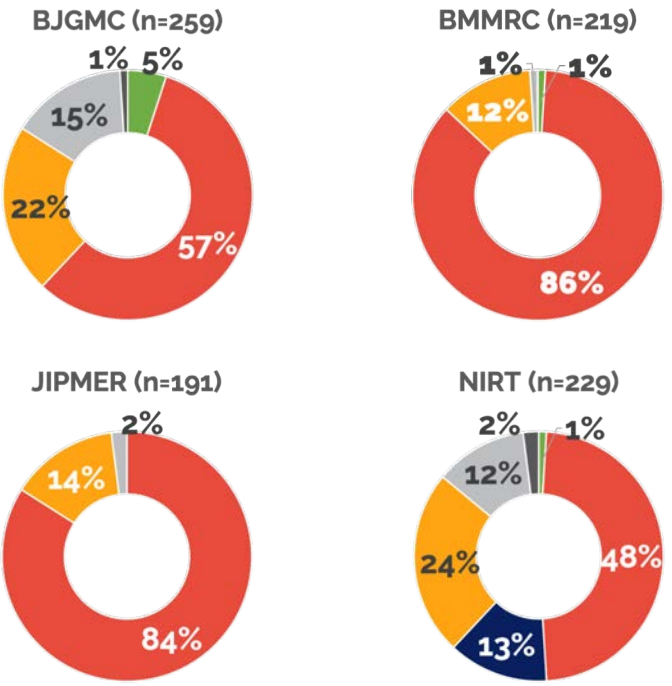
Hinduja

NIRT

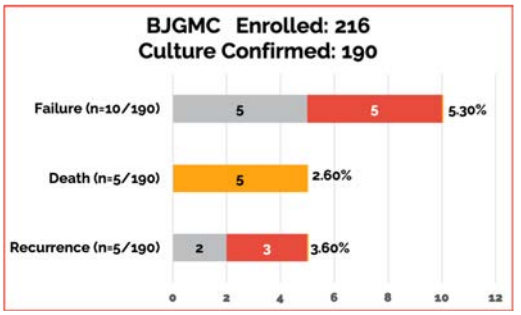
Phase 1: Common Protocol Cohort A: Accrual

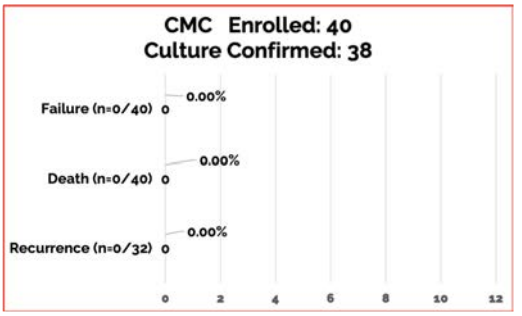


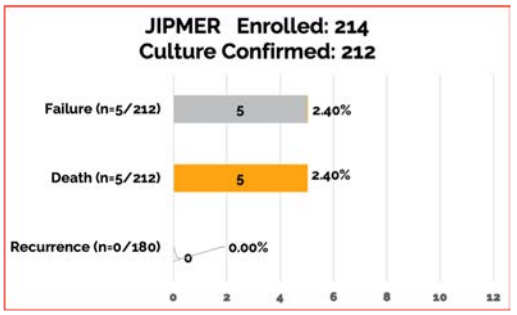
Phase 1: Common Protocol Cohort B: Accrual

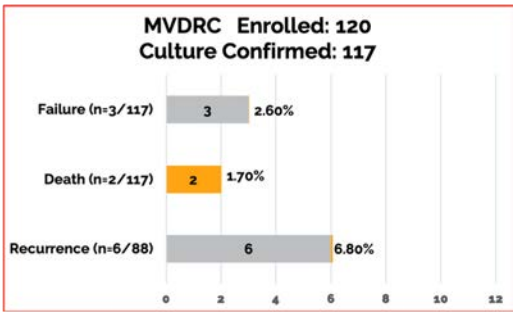


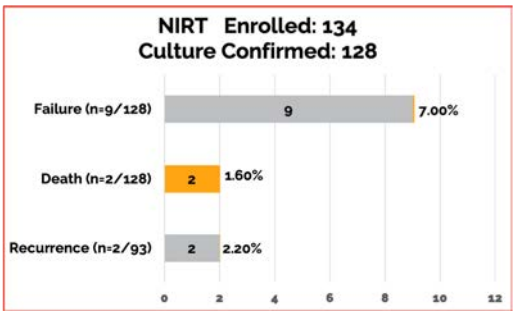
Phase 1: Cohort A Treatment Outcomes

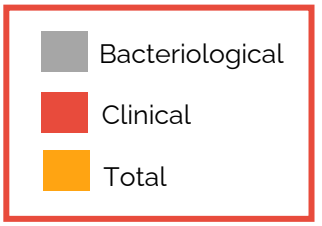




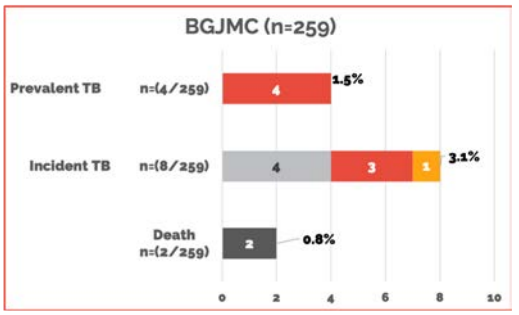


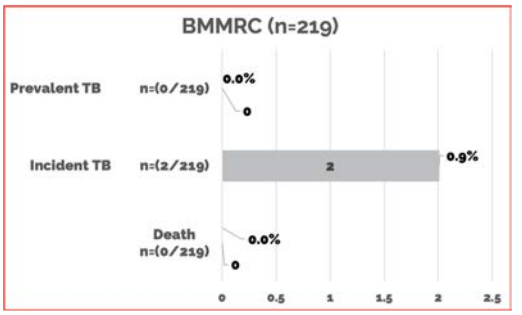


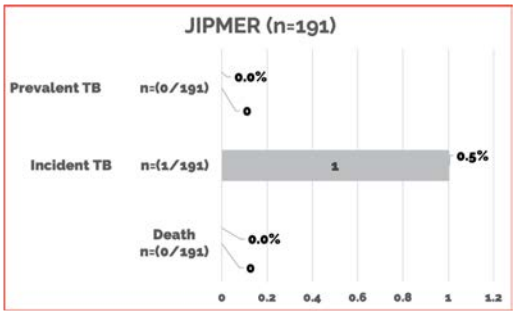


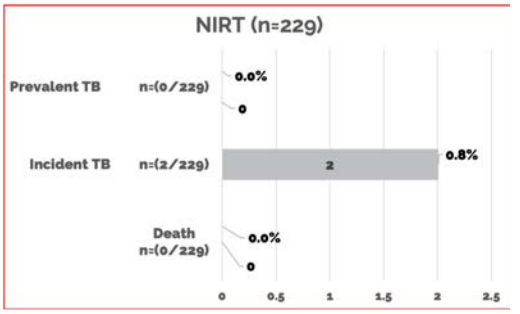


Phase 1: Cohort B Study Outcomes







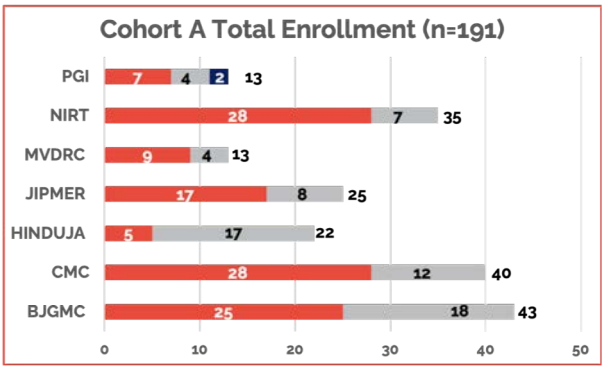


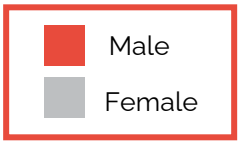
Outcomes

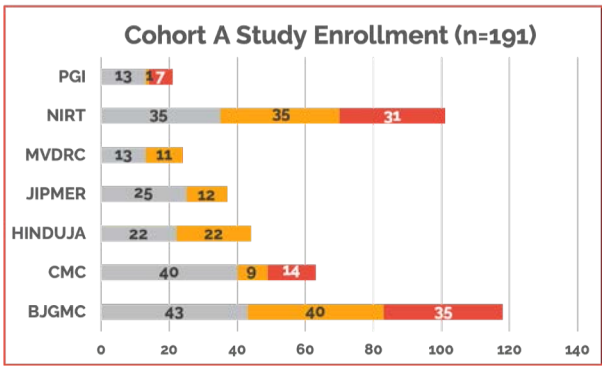
Participants

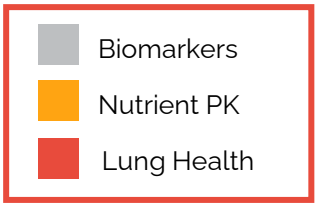
Phase 2 Common Protocol

Cohort A Enrollment

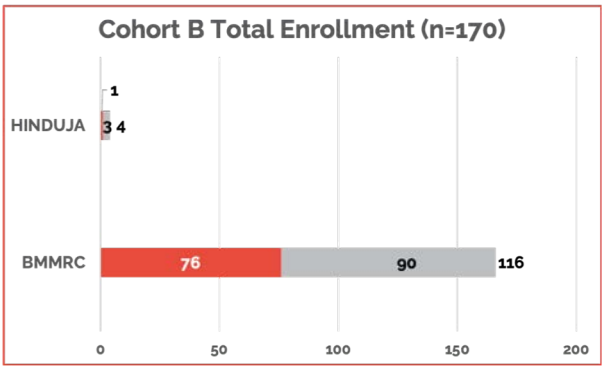


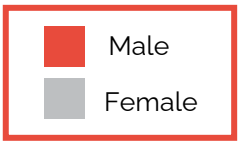


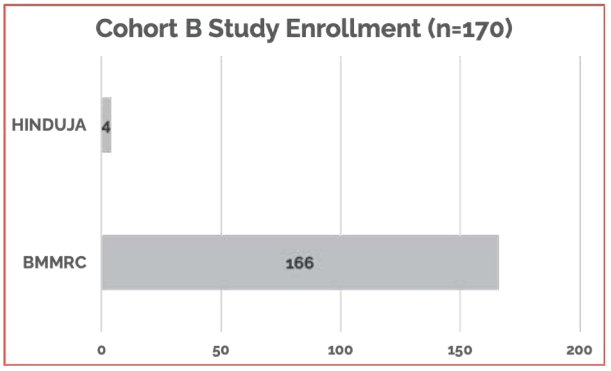




Cohort B Enrollment

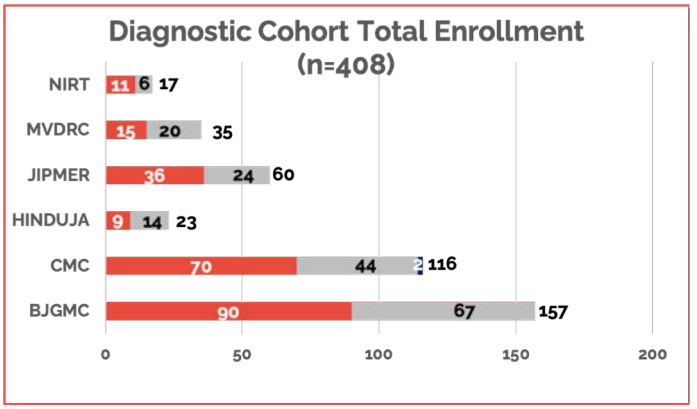


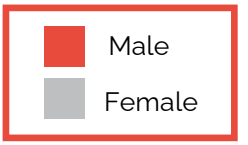


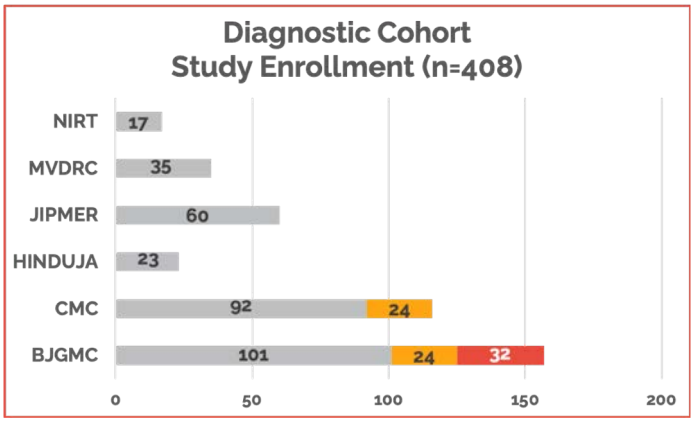


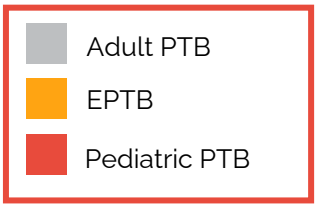
Phase 2 Common Protocol

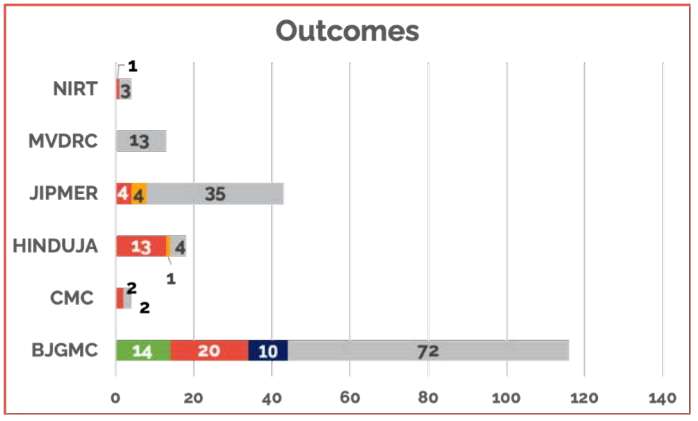
Diagnostic Cohort Enrollment & Outcomes

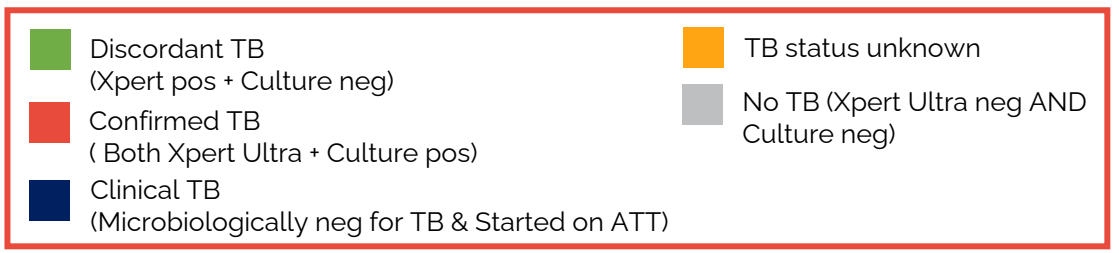






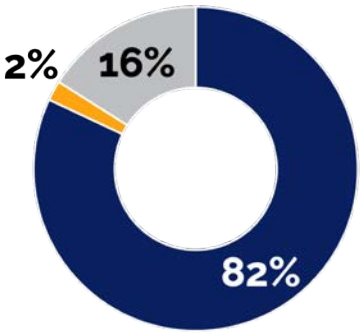




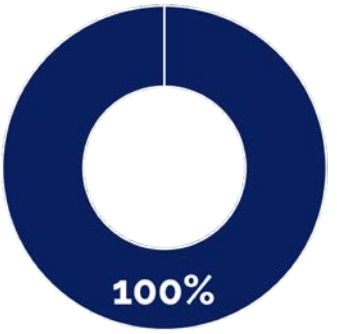


Phase 2 Common Protocol: Accrual Status Cohort A

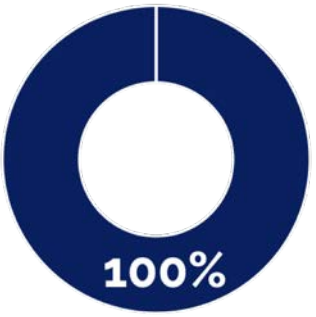
BJGMC (n=43)



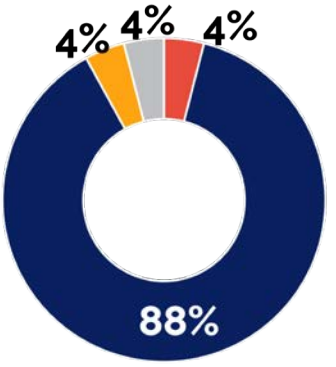
CMC (n=41)



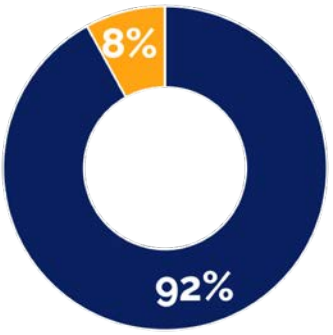
Hinduja (n=22)



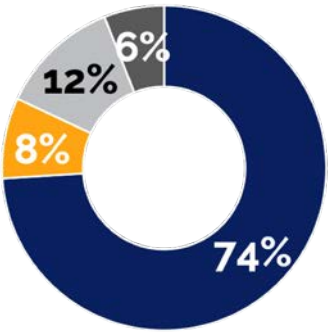
JIPMER (n=26)



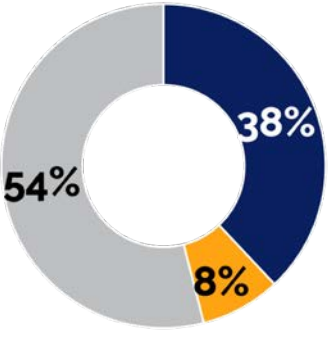
MVDRC (n=13)



NIRT (n=35)



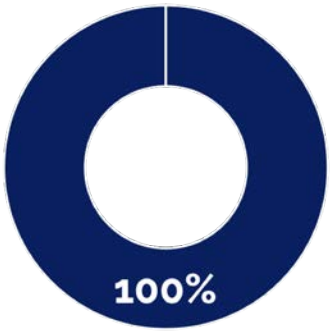
PGI (n=13)



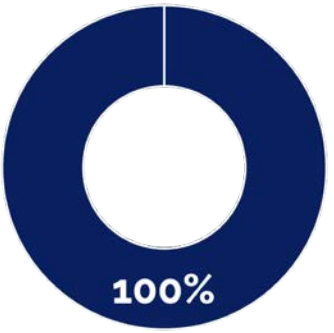
Phase 2 Common Protocol: Accrual Status

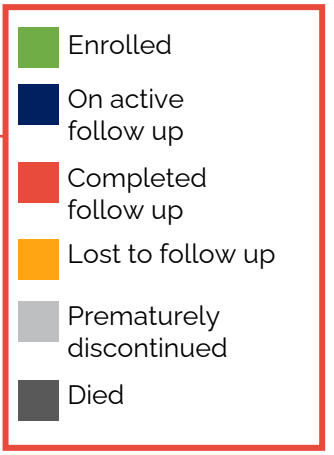
Cohort B

BMMRC (n=169)



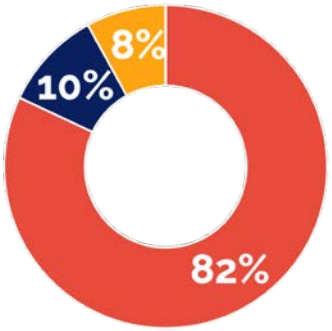
Hinduja (n=4)



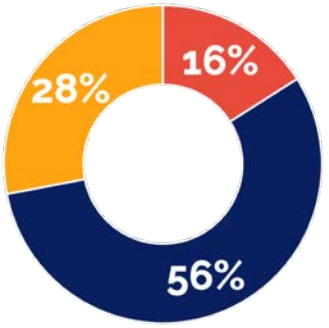


Diagnostic Cohort

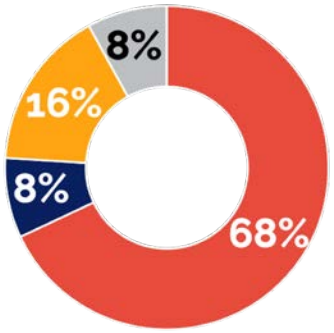
BJGMC (n=157)



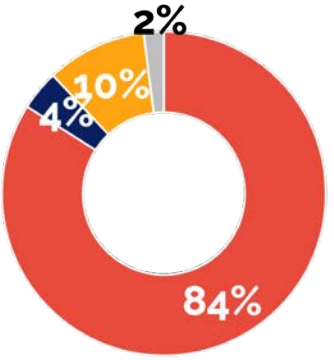
CMC (n=119)



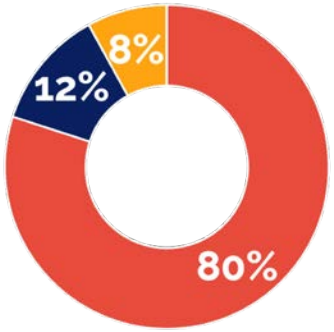
MVDRC (n=35)



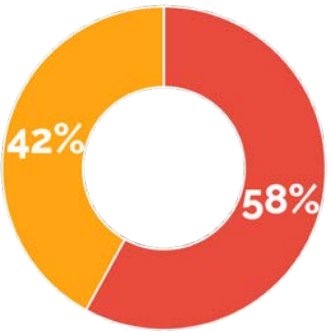
JIPMER (n=60)



Hinduja (n=24)



NIRT (n=17)



So lovely to see you again!




Wishing You Happiness & Good Health

RePORT INDIA

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