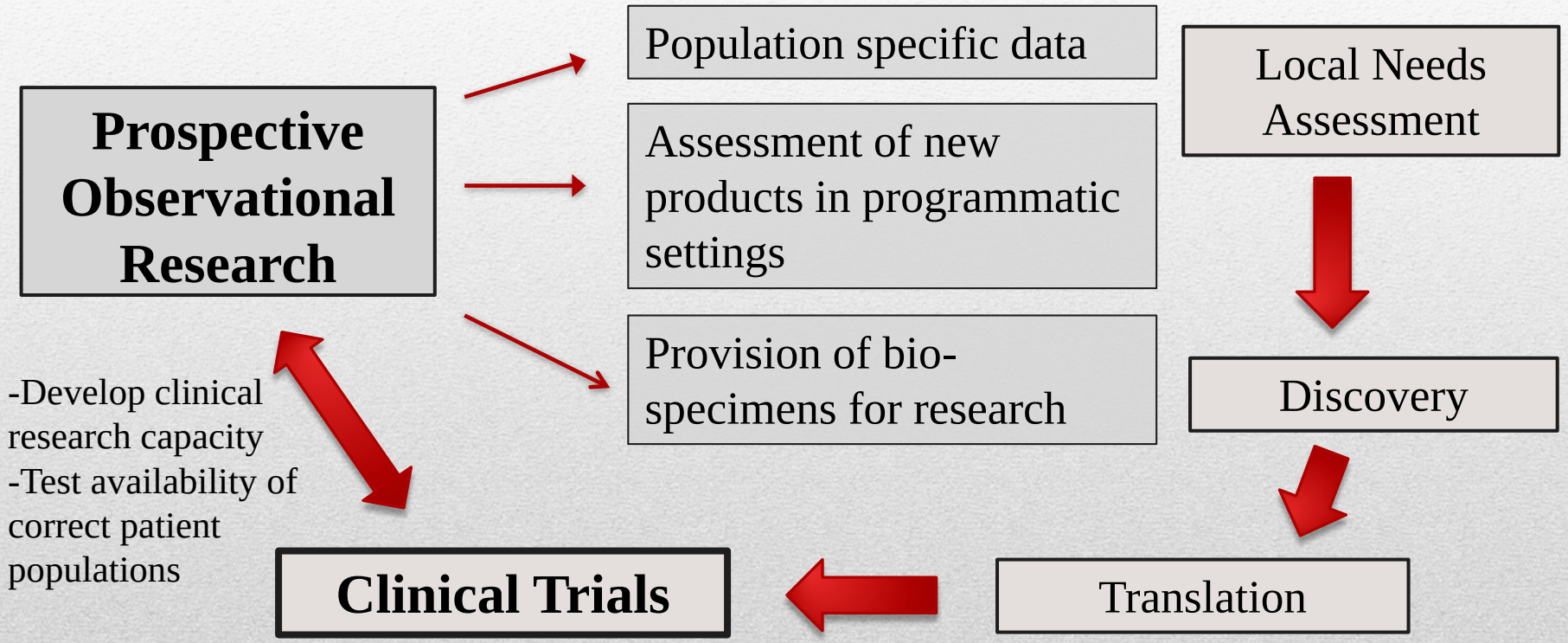
RePORT

Collaborations for improved TB and TB/HIV research

Amita Gupta MD, MHS
RePORt India US Chair and RePORT International EC Member
Associate Professor of Medicine and International Health
Deputy Director, Center for Clinical Global Health Education
John Hopkins University, USA


Prospective Observational Research
Population specific data
Assessment of new products in programmatic settings
Provision of bio-specimens for research
Local Needs Assessment
Discovery
Translation
Clinical Trials
-Develop clinical research capacity
-Test availability of correct patient populations

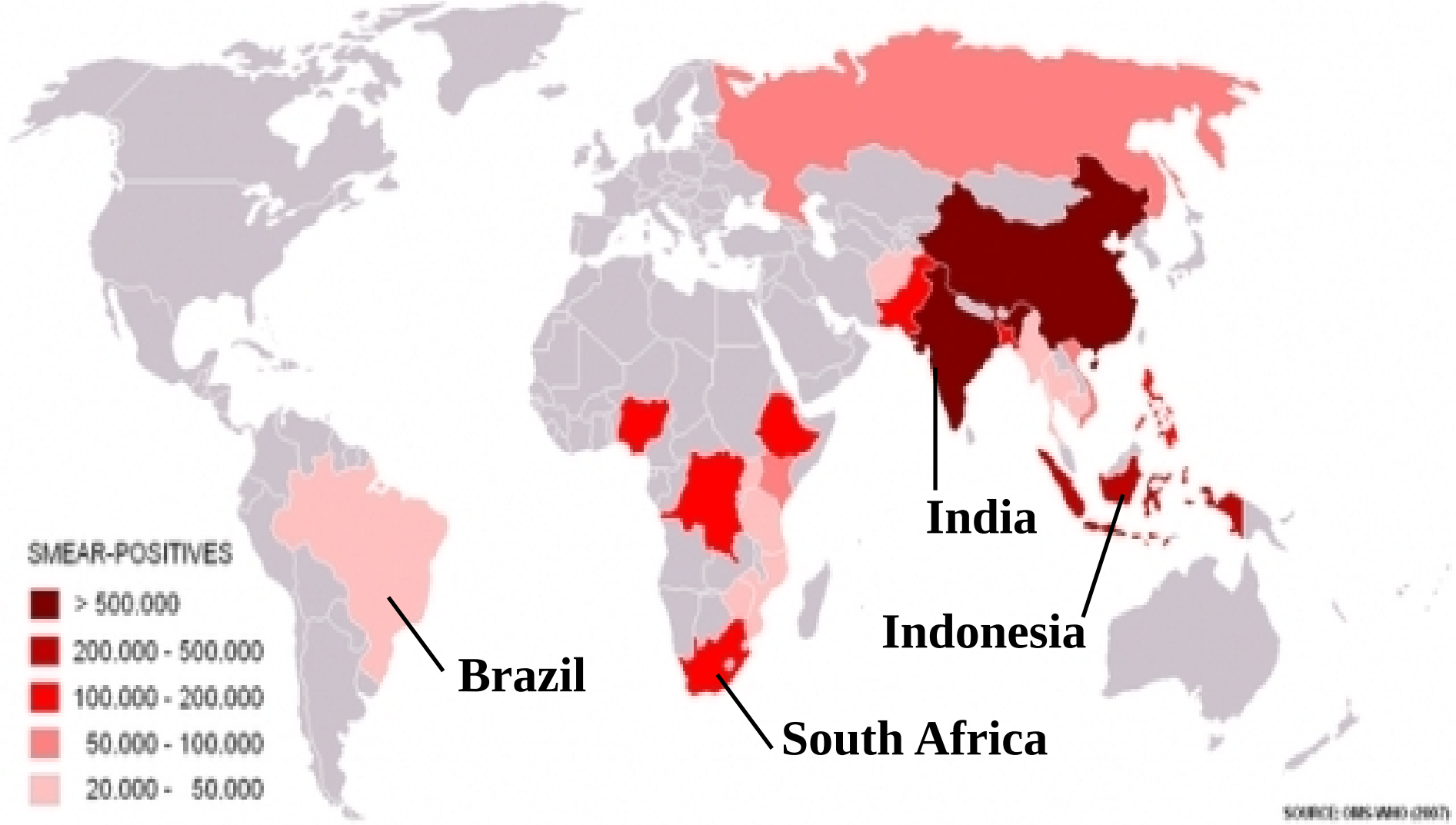
- Consortium of independent Regional Prospective Observational cohorts for TB research
- Independently funded and organized but coordinated through utilization of standardized common protocol for data and specimen collection

- Benefits
  - Maximize research resources by sharing where appropriate
  - Ensure that key research needs are addressed
  - Increase opportunities for large research projects
  - Help fill research gaps that are not able to be addressed by a single group

RePORT International

Regional Prospective Observational Research for TB

International Observational Research: RePORT Consortium



RePORT-India

Regional Prospective Observational Research in TB

Background

- Research needs in TB are enormous and collaborations are needed to ensure efficiency and rapidity of research progress

- The RePORT-India Initiative represents collaboration on multiple levels
  - Funding: Indian DBT, ICMR, NIAID, OAR, CRDF Global
  - Research: U.S. and Indian Investigators, basic scientists and clinical researchers

- Administered under the Indo-U.S. Vaccine Action Program

Background

- India 40% latently infected with Mtb
- 2.3 million active cases per year, 24% of global burden
- Poses $23.7 billion annual economic burden
- Multiple host and microbial factors associated with TB treatment outcome, progression and transmission
- Studies to date have not included a prospective comprehensive assessment to accurately examine independent and combined attributable impact

RePORT-India

- Consortium of 5 distinct observational cohort studies in India to evaluate TB infection and TB disease in Indian context
- Each cohort linked by:
  - Common Protocol
    - central SDMC and
    - central repository
  - enable each research team to maintain unique research interests while facilitating collaborative research
- All of the cohorts will be coordinated via a leadership group
  - Composed of PIs, funder representatives, SDMC and CR representatives
- Key partnerships:
  - U.S. and India based scientists
  - clinical and basic science researchers

RePORT
Indian Principal Investigators' Institution, City and Corresponding U.S. Partner

- Gautam Roy
  JIPMER, Pondicherry
  - Jerry Ellner, Boston Medical Center
- Vijaya Valluri
  LEPRA Society – Blue Peter, Hyderabad
  - Ramakrishna Vankayalapati, Univesity Texas Health Center
- Vijay Viswanathan
  Diabetes Research Centre, Chennai
  - Hardy Kornfeld, University of Massachusetts Medical School
- Soumya Swaminatha
  National Institute of Research in Tuberculosis & BJ Medical College, Chennai/Pune
  - Amita Gupta, John Hopkins University
- Devasahayam Christopher
  Christian Medical College, Vellore
  - Lalita Ramakrishnan , University of Washington

Common Protocol

- Minimum set of data and specimens to be collected across all cohorts
- Establish harmonized standards, definitions, and processes for data and specimen collection
- Managed by leadership group and serviced by central DMC and repository
- Enable cross cohort analyses and lab based research projects
- Facilitate collaborations with other research programs

Statistical and Data Management Center

- SAS-CHRDF chosen by DBT and ICMR
- Will work in collaboration with Westat/FHI
- Will develop and maintain common protocol database and associated CRFs
  - Based on CDISC standard
- Perform analyses as needed for cross cohort RePORT-India projects
- Serve as consultative resource for cohorts as needed
- Work with sites to ensure GCP standards established and maintained
- Serve as coordinating center for RePORT-India

Common Repository

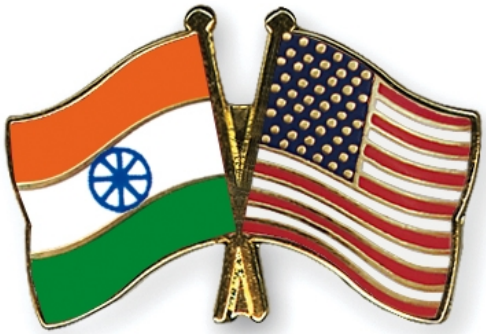
- NIRT, Chennai chosen by DBT/ICMR
- Will work in collaboration with Westat/FHI
- Coordinate and maintain specimens collected under Common Protocol
- Establish standards and SOPs for specimen collection and processing
- Work with site labs to establish and maintain GLP standards

Leadership Group

- Coordinate research across cohorts
- Oversee implementation of common protocol
- Develop and implement the scientific agenda of the RePORT Consortium
  - Establish scientific working groups as appropriate
  - Facilitate sharing of data
  - Oversee trans-cohort research projects
  - Develop collaborative partnerships with other research programs as beneficial
- Regularly scheduled conference calls
- Bi-annual in-person meetings (U.S. and India)

RePORT India: Four Guiding Principles

- Enhance existing global clinical research resources for TB and TB/HIV
- COMMUNICATION, COORDINATION AND COLLABORATIONS at all levels to improve efficiency of research investment
- Develop highly efficient/nimble clinical research groups able to quickly address key questions
- Foster transformative innovation and development of new tools against TB and TB/HIV



C-TRIUMPh
Cohort for TB Research by the Indo-US Medical Partnership

PI - India: Dr. Padmapriya Darsini, MD

Director, NIRT, Chennai, India

PI - USA: Dr. Amita Gupta, MD, MHS

Associate Professor of Medicine and International Health

John Hopkins University, USA

Scientific objectives

- **Factors associated with poor TB Treatment outcomes**
  - Modifiable host factors - e.g. HIV, DM, smoking, indoor air pollution, lung health, under nutrition, low BMI, household food insecurity
- **Factors associated with progression to active TB**
  - Modifiable factors such as under nutrition, smoking & alcohol misuse associated with↑ risk of progression to active TB
  - Non-modifiable host factors such as age, sex, and host genetics polymorphisms (LTR4 genetic variants or PGYRP) host proteins
- **Factors associated with TB acquisition & transmission**
  - Host Factors such as genetics, smoking & alcohol misuse, environmental factors such as proximity to the index case, characteristics of the household & duration of exposure, pathogen factors such as M.tb strain and resistance profile

Study design

- Study Type: Prospective Observational Study
- Study Sites: BJMC and NIRT-affiliated field site
- Study Duration: 5 years
- Study Population: 3 Prospective Cohorts.
  - Active TB Cohort (800 PTB+ 200EPTB, 200 peds TB)
  - Household (HH) Contact Cohort (800 households with 1800 contacts)
  - Control Cohort (100-150 adults and children)

Active TB Enrollment Clinics

SOE for *Active TB cohort*

	Entry	2W	1M	2M	4M	6M	12M	18M	24M	End of Tx[a]	TB Recurrence
Consent/Enrollment	x										
Medical History/Medication History	x										
Psychosocial Interview	x			x		x	x	x		x	x
Clinical Assessment (TB and Lung Health Assessment, Physical Examination, Diagnoses/AEs etc)	x	x	x	x	x	x	x	x	x	x	x
TB Medication Adherence	x	x	x	x	x	x				x	
IAP and Nutrition Assessment	x			x						x	x
Anthropometrics	x	x	x	x	x	x	x	x	x	x	x
Chest Radiograph	x			x							x
Sputum AFB and Culture X2 (DST if culture +ve)	x	x	x	x	x	x		x		x	x

SOE for *Active TB cohort*

	Entry	2W	1M	2M	4M	6M	12M	18M	24M	End of Tx[a]	TB Recurrence
Sputum for GeneXpert X2	X										X
Extrapulmonary TB sample for AFB and culture/histopathology	X[b]										X
Hematology (CBC)	X			X							X
HIV Test (if not already known)	X										X
CD4 count if HIV +ve	X										X
Hemoglobin A1c (Adults)	X										
Chemistry (Renal panel, LFT, electrolytes, glucose)	X		X	X	X	X				X	X
Urinalysis	X										X
PFT (Adults), Spirometry (Child) [random subset]	X									X	X

Biorepository samples: *Active TB cohort*

	Entry	2W	1M	2M	4M	6M	12M	18 M	24M	End of Tx	TB Recurrence
Stored Plasma for PK			X		X	X					
Stored Serum	X		X	X		X				X	X
Whole Blood for DNA	X		X			X					
Stored Sputum	X	X	X	X		X				X	X
Stored Urine	X		X	X		X				X	X
Stored Hair	X		X		X	X				X	X
Stored Mtb isolate	X			X	X	X					X
Stored Host mRNA (PAXgene)	X		X	X		X				X	X
Stored PBMC	X		X	X		X				X	X
QGIT	X	X	X	X	X	X				X	X

Household Contact Visit

SOE for *HH* Contact Cohort

Time	Entry	3M	6M	12M	18M	24M	Q6M	Active TB
Consent/Enrollment	H							
Medical History/Medication History	H							
Brief Psychosocial Interview	H			H		H		F
Clinical Assessment (i.e. TB and Lung Health Assessment, Concomitant Meds)	H	H	H	H	H	H	H	F
IAP & Nutrition Assessment [3]	H	H	H	H	H	H	H	F
Targeted Physical Exam and Anthropometrics[4]	H	H	H	H	H	H	H	F
Chest radiograph	F	(F)						F
Sputum AFB and culture x 2 (DST if culture +)	H	H						F
TT Skin Test	H	H		H		H		
Quantiferon Gold in Tube	H	H		H		H		F
Hemoglobin Point of Care	H							
Rapid HIV Test[6]	H							F
Hemoglobin A1c Point of care (Adults)	H			H				F
PFT (Adults), Spirometry (Child) (random subset)	H			H				F
Household Air Sample	H[1]	H[1]		H[1]				

Biorepository samples:
HH contact cohort

	Entry	6M	12M	24M	Q6M	Active TB
Stored Serum	H	H	H	H		F
Stored DNA	H	H	H	H		F
Stored Sputum	H	H		H		F
Stored Urine	H	H	H	H		F
Stored Hair	H	H	H	H		F
Stored MTB isolate	H					F
Stored QGIT supernatant	H	H	H	H		F
Stored Host mRNA (Paxgene)	H	H[1]	H[1]	H[1]		F
Stored PBMC	H	H[1]	H[1]	H[1]		F

F=Facility, H=household

Summary Storage CTRIUMPH

	Cohort A				Cohort B			
No of Participants	Total Aliquots Expected	Actual Aliquots stored	BJMC storage	NIRT storage	Total Aliquots Expected	Actual Aliquots stored	BJMC Storage	NIRT storage
Plasma for PK	678	967	697	270				
Stored Plasma	12752	13487	8519	4976	10512	9914	4706	5224
DNA	283	252	142	110	646	599	273	325
Stored Sputum	7492	2511	1233	1278	4924	2298	600	1698
Stored Urine	11784	9116	6916	2200	10512	6159	3879	2280
Stored Hair	1368	750	749	1	1314	499	498	1
Mtb isolate		813	84	729		66	8	58
PAXgene	1594	1478	859	620	1314	1139	488	655
PBMC	3188	3059	1592	1467	2628	2698	965	1733
QGIT	19126	15146	12470	2676	15768	12082	6462	6120

Selected analyses of interest
CTRIUMPH Methods Paper
Yield of screening in Cohort B to assess prevalence of TBI and active disease
Socio-behavioral aspects of TB
Estimating PK-PD-PG relationship of ATT with TB treatment Outcome
Response treatment of Mono- resistant (non-MDR) TB patients treated with RNTCP Category I regimen under programmatic conditions
Blood levels of macro & micronutrients and its relation to treatment response and progression of infection to disease
LTBI in children of Cohort B contacts and its progression to disease
Decision Tree Modeling to predict progression of TB Infection to Disease
Identification of biomarkers on T cells and in QGIT supernatants for early diagnosis of active TB
Using Urine as Biomarker for TB - Proteomics
Determination of transmission patterns among TB Index and Contact cohorts using Spoligotyping
Characterize trends and patterns of respiratory impairment (RI) among adult PTB cases.
Measure the correlation between Spirometry, SGRQ, 6MWT and MMRC scale.

Thank You

NIH Program officers: Sudha rinivasan, Peter Kim
DBT: Jyoti Logani
ICMR: Soumya Swaminathan, Rashmi Arora
BJMC-NIRT-JHU research partnership & study participants