# GLOBAL FORUM ON TB VACCINES

*Partnering for Progress and Innovation*

**20–23 FEBRUARY 2018**
**NEW DELHI**
**INDIA**

# PROGRAM AND ABSTRACTS

# ORGANIZERS AND SPONSORS

The Global Forum on TB Vaccines is an international convening of

Stop TB Partnership
Working Group on New TB Vaccines

## Organized by

AERAS

TBVI
TuBerculosis Vaccine Initiative

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ट्रांसलेशनल स्वास्थ्य विज्ञान एवं प्रौद्योगिकी संस्थान
TRANSLATIONAL HEALTH SCIENCE AND TECHNOLOGY INSTITUTE

Department of Biotechnology
Ministry of Science & Technology
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SERB INDIA
Science and Engineering Research Board (SERB)
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**American Thoracic Society**

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Funding for this conference was made possible in part by grant 1 R13 AI 136363 - 01 from the National Institute of Allergy and Infectious Diseases. The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government.

# CONTENTS

# WELCOME FROM CHAIRS

Dear Colleagues,

It is our pleasure to welcome you to New Delhi and to the 5th Global Forum on TB Vaccines. India's research expertise and infrastructure, its manufacturing capacity, and the important role it plays in global efforts to end the tuberculosis (TB) epidemic make it an exciting venue to host this Forum.

We are delighted to have more than 350 participants from nearly 30 countries at this conference – the largest Global Forum on TB Vaccines to date. Participants represent all sectors involved in TB vaccine research and development (R&D) - including researchers, clinicians, product developers, manufacturers, funders, policymakers, and advocates – and the program covers the full continuum of TB vaccine R&D, presented by experts from around the world. Our theme for this meeting is "Partnering for Progress and Innovation".

This Global Forum comes at a momentous time in the global effort to end TB. Just three months ago, the first "WHO Global Ministerial Conference on Ending Tuberculosis in the Sustainable Development Era: A Multisectoral Response" was convened in Moscow, resulting in a collective commitment to action on multiple fronts, including increasing investment in TB implementation and research, and advancing R&D of new tools to prevent, diagnose and treat TB. Later this year, the first ever High-Level Meeting on Tuberculosis will be held in New York, which is expected to result in a political declaration endorsed by member states that will form the basis for the future global and coordinated response to TB.

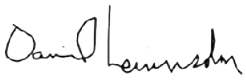
Over the years, the Global Forum has been an opportunity for the TB vaccine R&D field to come together as a community to share new data, promote innovative and transformative approaches to R&D, and to encourage partnerships and collaboration. This year's Global Forum will be no exception, and will provide a unique opportunity to discuss the state of the field and the path forward for TB vaccine R&D in the context of a global dialogue on what will be required to end this global epidemic.

Your input at this meeting will be essential and important to the success of this year's Global Forum, and we hope that you will actively participate and network in the sessions and discussions that will take place over the next three days.

We are grateful to you for attending this Forum, and for your contributions and commitment to the field of TB vaccine research and to the vision of a world without TB. We also extend a special thanks to our sponsors, whose support made this Global Forum possible.

We hope that you enjoy your time in New Delhi, and that you find the 5th Global Forum on TB Vaccines to be inspiring, informative and productive.

Sincerely,



**Dr. David Lewinsohn**
Forum Co-Chair
Chair, Working Group
on New Vaccines

**Dr. Danilo Casimiro**
Forum Co-Chair
Aeras (former)

**Dr. Nick Drager**
Forum Co-Chair
TBVI

**Dr. Soumya Swaminathan**
Forum Co-Chair
Indian Council of Medical
Research (former)

# CHAIRS AND COMMITTEES

## 5TH GLOBAL FORUM CO-CHAIRS

| | |
|---|---|
| Danilo Casimiro | Former Chief Scientific Officer, Aeras |
| Nick Drager | TuBerculosis Vaccine Initiative |
| David Lewinsohn | Stop TB Partnership Working Group on New Vaccines |
| Soumya Swaminathan | Former Secretary, Department of Health Research and former Director-General, Indian Council of Medical Research |

## ORGANIZING COMMITTEE

| | |
|---|---|
| Nisheeth Agarwal | Translational Health Science and Technology Institute (India) |
| Krishnamohan Atmakuri | Translational Health Science and Technology Institute (India) |
| Sharon Chan | Aeras (China) |
| Ann Ginsberg | Aeras (USA) |
| Willem Hanekom | Bill & Melinda Gates Foundation (USA) |
| Mark Hatherill | South African Tuberculosis Vaccine Initiative, University of Cape Town (South Africa) |
| Blessina Kumar | Global Coalition of TB Activists (India) |
| David Lewinsohn | Stop TB Partnership Working Group on New Vaccines (USA) |
| Jyoti Logani | Department of Biotechnology, Ministry of Science and Technology (India) |
| Manjula Singh | Indian Council of Medical Research (India) |
| Ramandeep Singh | Translational Health Science and Technology Institute (India) |
| Frank Verreck | TuBerculosis Vaccine Initiative (Netherlands) |
| Jennifer Woolley | Global Forum Project Director (USA) |

## INDIA ADVISORY PANEL

| | |
|---|---|
| R.R. Gangakhedkar | Indian Council of Medical Research |
| Sarala Balachandran | Council of Scientific and Industrial Research |
| K.N. Balaji | Indian Institute of Science |
| T.S. Balganesh | GangaGen Biotechnologies Private Ltd |
| Rohan Dhiman | National Institute of Technology, Rourkela, Odisha |
| Rajesh Gokhale | National Institute of Immunology |
| Randeep Guleria | All India Institute of Medical Science |
| Suresh Jadhav | Serum Institute of India |
| Manjul Joshipura | Cadila Pharmaceuticals |
| Dhiraj Kumar | International Centre for Genetic Engineering and Biotechnology |
| Jyoti Logani | Department of Biotechnology, Ministry of Science and Technology |
| Shekhar Mande | National Center for Cell Science |

# CHAIRS AND COMMITTEES

| | |
|---|---|
| Amit Misra | Central Drug Research Institute |
| Anant Mohan | All India Institute of Medical Science |
| Vinay K. Nandicoori | National Institute of Immunology |
| Amit Kumar Pandey | Translational Health Science and Technology Institute |
| Kanury Rao | Translational Health Science and Technology Institute |
| Alka Sharma | Department of Biotechnology, Ministry of Science & Technology |
| Pawan Sharma | Department of Biotechnology, Ministry of Science and Technology |
| Manjula Singh | Indian Council of Medical Research |
| Rupak Singla | National Institute of Tuberculosis and Respiratory Diseases |
| Anil Tyagi | Guru Gobind Singh Indraprastha University |
| Jaya S. Tyagi | All India Institute of Medical Sciences |
| Vijaya Lakshmi Valluri | Bhagawan Mahavir Medical Research Centre |

## INTERNATIONAL ADVISORY PANEL

| | |
|---|---|
| Peter Andersen | Statens Serum Institut (Denmark) |
| Lijun Bi | Institute of Biophysics, Chinese Academy of Sciences (China) |
| Barry Bloom | Harvard T.H. Chan School of Public Health (USA) |
| Gavin Churchyard | The Aurum Institute (South Africa) |
| Keertan Dheda | University of Cape Town and Groote Schuur Hospital, (South Africa) |
| Lucica Ditiu | Stop TB Partnership (Switzerland) |
| Katrin Eichelberg | National Institute of Allergy and Infectious Diseases, National Institutes of Health (USA) |
| Helen Fletcher | London School of Hygiene and Tropical Medicine (UK) |
| JoAnne Flynn | University of Pittsburgh (USA) |
| Glenda Gray | South African Medical Research Council (South Africa) |
| Sanjay Gurunathan | Sanofi Pasteur (USA) |
| Stefan H.E. Kaufmann | Max Planck Institute for Infection Biology (Germany) |
| Luciana Leite | Instituto Butantan (Brazil) |
| Christian Lienhardt | Global TB Programme, World Health Organization (Switzerland) |
| Souleymane Mboup | Institut de Recherche en Santé, de Surveillance Epidemiologique et de Formations (Senegal) |
| Helen McShane | University of Oxford (UK) |
| Norazmi Mohd Nor | Universiti Sains Malaysia (Malaysia) |
| Ole Olesen | European & Developing Countries Clinical Trials Partnership (Netherlands) |
| Tom Ottenhoff | Leiden University Medical Centre (Netherlands) |
| Johan Vekemans | Initiative for Vaccine Research, World Health Organization (Switzerland) |

# GENERAL INFORMATION

## REGISTRATION AND INFORMATION DESK AND HOURS

The registration and information desk will be located in the conference center in the lower level at the Taj Diplomatic Enclave Hotel. The registration and information desk will be open during the following hours:
Tuesday 20 February 2018 – 08:00 - 20:00
Wednesday 21 February 2018 – 08:00 - 19:00
Thursday 22 February 2018 – 08:00 - 17:00

## NAME BADGES

Name badges must be worn at all times during the conference. Participants will not be allowed access to the conference sessions without a name badge. Participants who have lost their name badge are requested to report to the registration/information desk.

## CERTIFICATE OF ATTENDANCE

Participants who require a certificate of attendance should contact newdelhi2018@tbvaccinesforum.org.

## MEALS

The following meals will be provided to registered participants:

- Lunch and coffee/tea breaks on 20, 21 and 22 February
- Dinner on 20 February
- Cocktail reception and snacks on 21 February

Meal coupons will be provided to registered participants. You will need to present a coupon to enter the lawn area where meals are served. If you forget or lose your coupon, please see a Global Forum staff member for assistance.

All food served at meals will be halal. Gluten free options will be labelled. Kosher meals will be provided to those who requested them; please ask the conference staff for assistance.

## DAILY SHUTTLE SERVICES

Daily shuttle service to and from the conference venue will be provided from The Metropolitan Hotel & Spa and The Park New Delhi as per the schedule below. Shuttle services will be prioritized for participants who booked their accommodations through the conference registration system or notified the organizers in advance. Transportation for other participants will be provided if space is available. Participants staying in other accommodation will be responsible for arranging their own transportation.

### Tuesday 20 February 2018:

09:00 - Pickup from hotels to the Taj Diplomatic Enclave Hotel (conference venue)
20:15 - Transfer from Taj Diplomatic Enclave Hotel to hotels for those not attending the Forum Dinner
21:30 - Transfer from Taj Diplomatic Enclave Hotel to hotels following the Forum Dinner

### Wednesday 21 February 2018:

08:15 - Pickup from the hotels to the Taj Diplomatic Enclave Hotel
18:30 -Transfer from Taj Diplomatic Enclave Hotel to conference hotels for those not attending the Networking Reception
20:15 - Transfer from Taj Diplomatic Enclave Hotel to hotels following the Networking Reception

### Thursday 22 February 2018:

06:45 - Pick up from hotels to the Taj Diplomatic Enclave Hotel for the Satellite Session
08:15 - Pick up from hotels to the Taj Diplomatic Enclave Hotel for morning session
17:00 - Transfer from the Taj Diplomatic Enclave Hotel to hotels

## Friday 23 February 2018 (Site Visits):

08:00 - Pick up from The Park Hotel to Taj Diplomatic Enclave Hotel for THSTI site visit
09:00 - Pick up from The Metropolitan Hotel for NITRD site visit
08:30 - Pick up from The Park Hotel for ICGEB and NITRD site visit
Return transfers to hotels following the site visits will be the participant's responsibility

## NETWORKING AND SPECIAL EVENTS

**Inaugural Ceremony and Forum Dinner**
Tuesday 20 February, Taj Diplomatic Enclave Hotel
17:45 - 18:30: Networking and Refreshments (Rani Bagh Lawn)
18:30 - 20:00: Inaugural Ceremony (Shahjehan)
20:00 - 21:30: Dinner (Rani Bagh Lawn)

**Networking Reception and Poster Viewing**
Wednesday 21 February, Taj Diplomatic Enclave Hotel
18:15 - 18:45 Cultural Entertainment (Shahjehan)
18:45 - 20:00 Cocktails, Snacks and Poster Viewing
*Drink and food stations will be set up in Shahjehan and Roshanara. Posters will be set up in Mumtaz Mahal, Roshanara, and Sheesh Mahal.*

## PRESENTATIONS

Speakers must provide their presentation to the conference staff in the Speaker Ready Room (Alamgir Hall) at least two hours prior to the session in which they will speak.

## POSTER REGISTRATION AND SET-UP

Poster presenters should check-in at the designated registration desk. A poster number and location will be provided at registration. Poster presenters must hang their poster on the poster board associated with their poster number. Any posters hung on an incorrect poster board will be removed by the organizers.

Poster set up begins at 09:00 on 20 February. All posters should be set up by 15:30 on 20 February.

Posters must be taken down by 14:00 on 22 February. Posters that have not been removed by this time will be discarded.

## EMERGENCY CONTACT NUMBERS

Police - 100 | Ambulance - 101 | Global Forum Secretariat : +91 9650694449

## WIFI AND SOCIAL MEDIA

Wifi is complimentary for all guests staying at the Taj Diplomatic Enclave, and is available throughout the hotel and in the meeting rooms. If you are staying at Taj Diplomatic Enclave, please use this wifi service.

Wifi will be available in the meeting rooms for participants staying at other hotels, with a limit of one device per person. To ensure that wifi can be available to all participants, please do not login with more than one device.

The 5th Global Forum on TB Vaccines welcomes social media activity from participants. Please review the social media guidelines before posting or disseminating information on any social media platform, and honor any speakers' requests to refrain from posting unpublished data or other information from presentations.

## SITE VISITS

Four site visits will be offered on 23 February, offering participants an opportunity to see first-hand how TB research and care is provided in a variety of facilities and settings.

Pre-registration is required for site visits. Participants who are interested in a site visit but who have not pre-registered can inquire about availability at the information desk.

Busses for all site visits will depart from the main lobby of Taj Diplomatic Enclave Hotel. Transfers will be provided from The Metropolitan Hotel & Spa and The Park New Delhi. See "Daily Shuttle Service" above for departures from other hotels.

Return times are estimates and may vary based on traffic conditions and time spent at the site.

### Operation ASHA

Location: Tekhand, Okhla, New Delhi
Distance from Venue: 20 km (approx. 1 hour)
Departure from Taj Diplomatic Enclave: 08:30
Estimated Return: 12:30

### Translational Health Science and Technology Institute (THSTI)

Location: NCR Biotech Science Cluster, 3rd Milestone, Faridabad – Gurgaon Expressway, Faridabad
Distance from Venue: 40 km (approx. 1 hour 15 min)
Departure from Taj Diplomatic Enclave: 08:30
Estimated Return: 14:00
*Lunch will be provided at THSTI*

### International Centre For Genetic Engineering And Biotechnology (ICGEB)

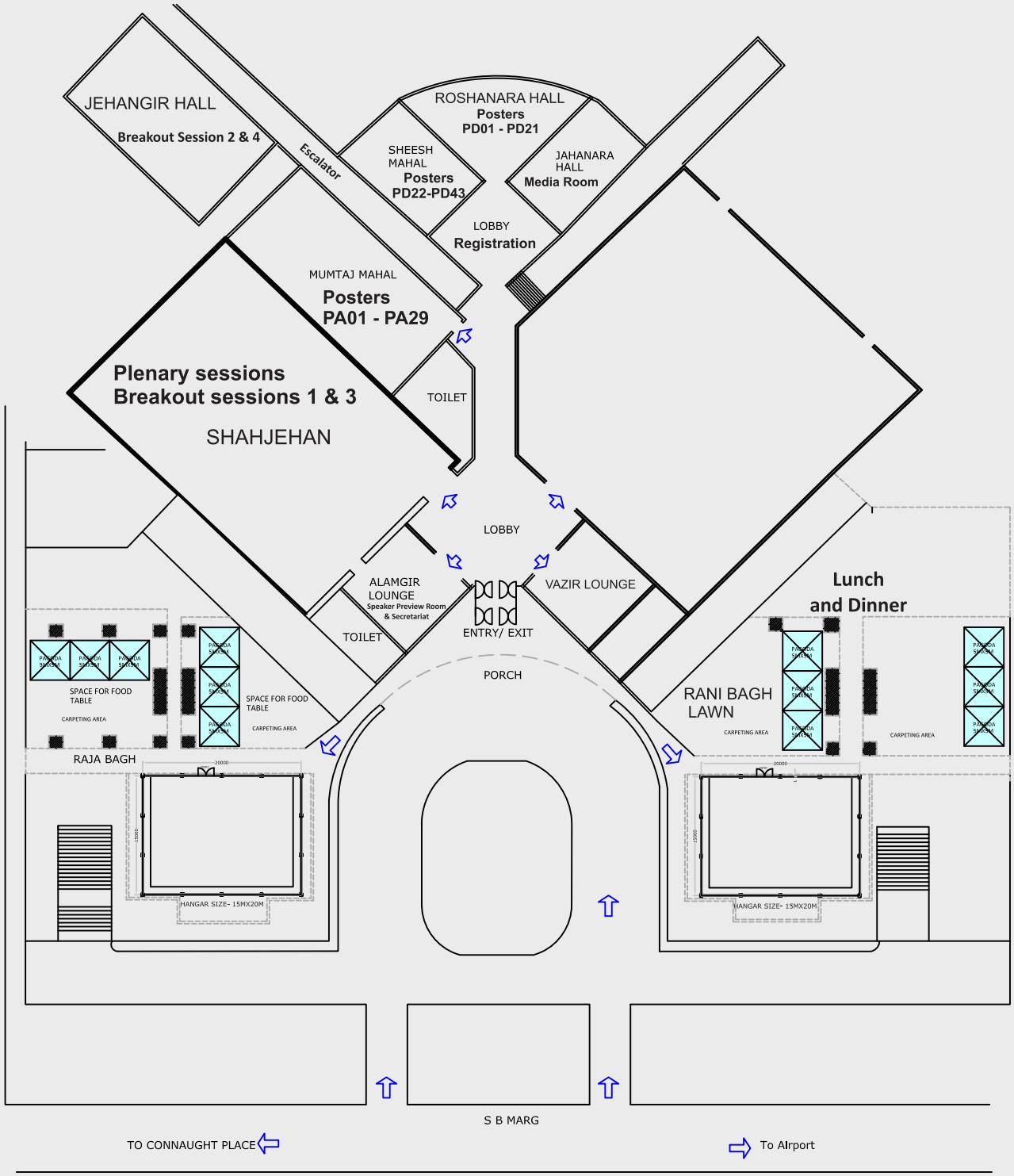
Location: ICGEB New Building, Jawaharlal Nehru University, New Delhi
Distance from Venue: 10 km (approx. 30 min)
Departure from Taj Diplomatic Enclave: 09:00
Estimated Return: 11:00

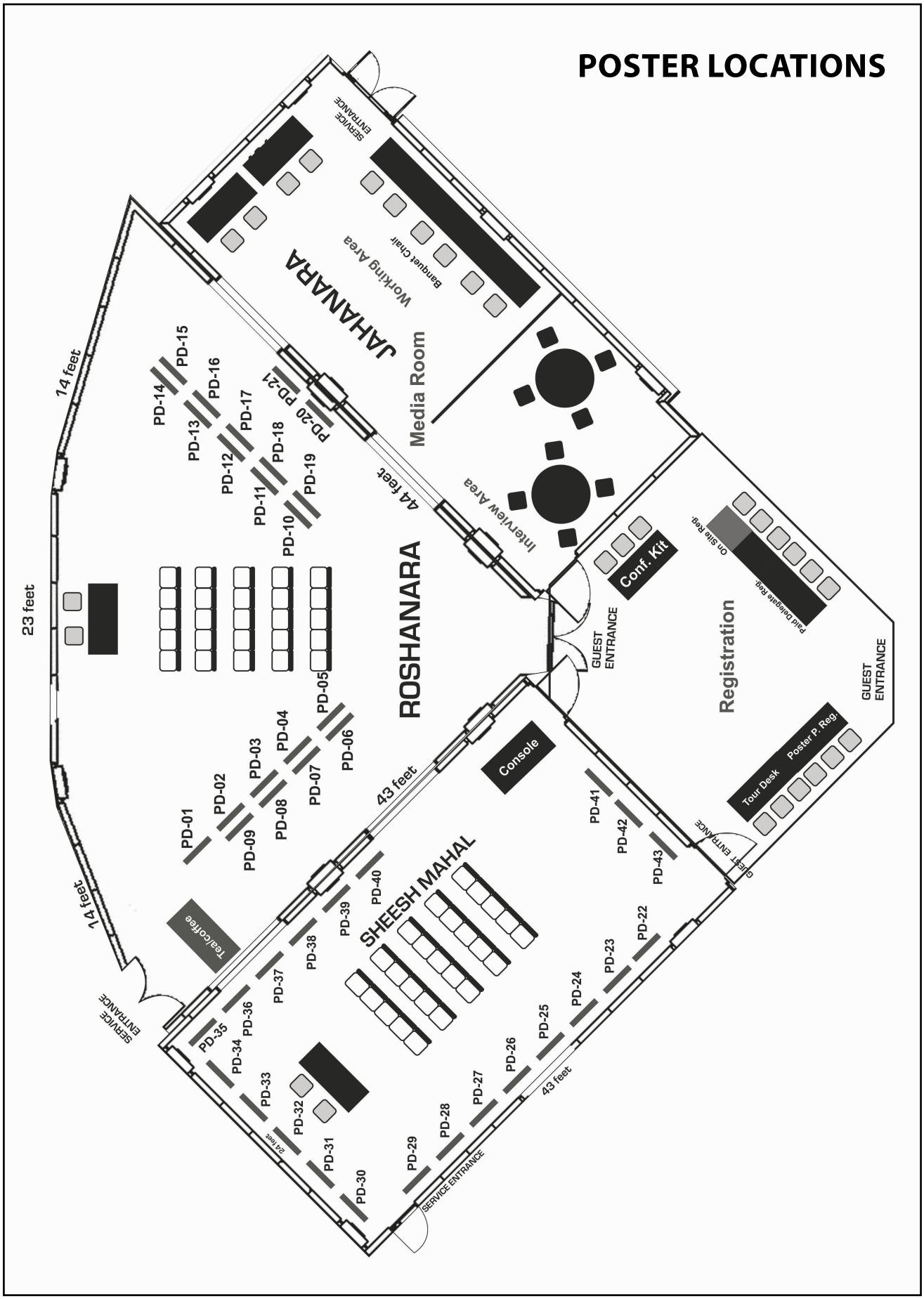
### National Institute For Tuberculosis And Respiratory Diseases (NITRD)

Location: Sri Aurobindo Marg, Near Qutub Minar, Mehrauli, New Delhi
Distance from Venue: 11 km (approx. 25 min)
Departure from Taj Diplomatic Enclave: 09:30
Estimated Return: 13:00

# MAP OF VENUE

## TAJ CONVENTION CENTRE LAYOUT PLAN




POSTER LOCATIONS
JAHANARA
Working Area
Banquet Chair
SERVICE ENTRANCE
Media Room
Interview Area
ROSHANARA
Conf. Kit
GUEST ENTRANCE
Registration
On Site Reg.
Paid Delegate Reg.
GUEST ENTRANCE
Tour Desk
Poster P. Reg.
GUEST ENTRANCE
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SHEESH MAHAL
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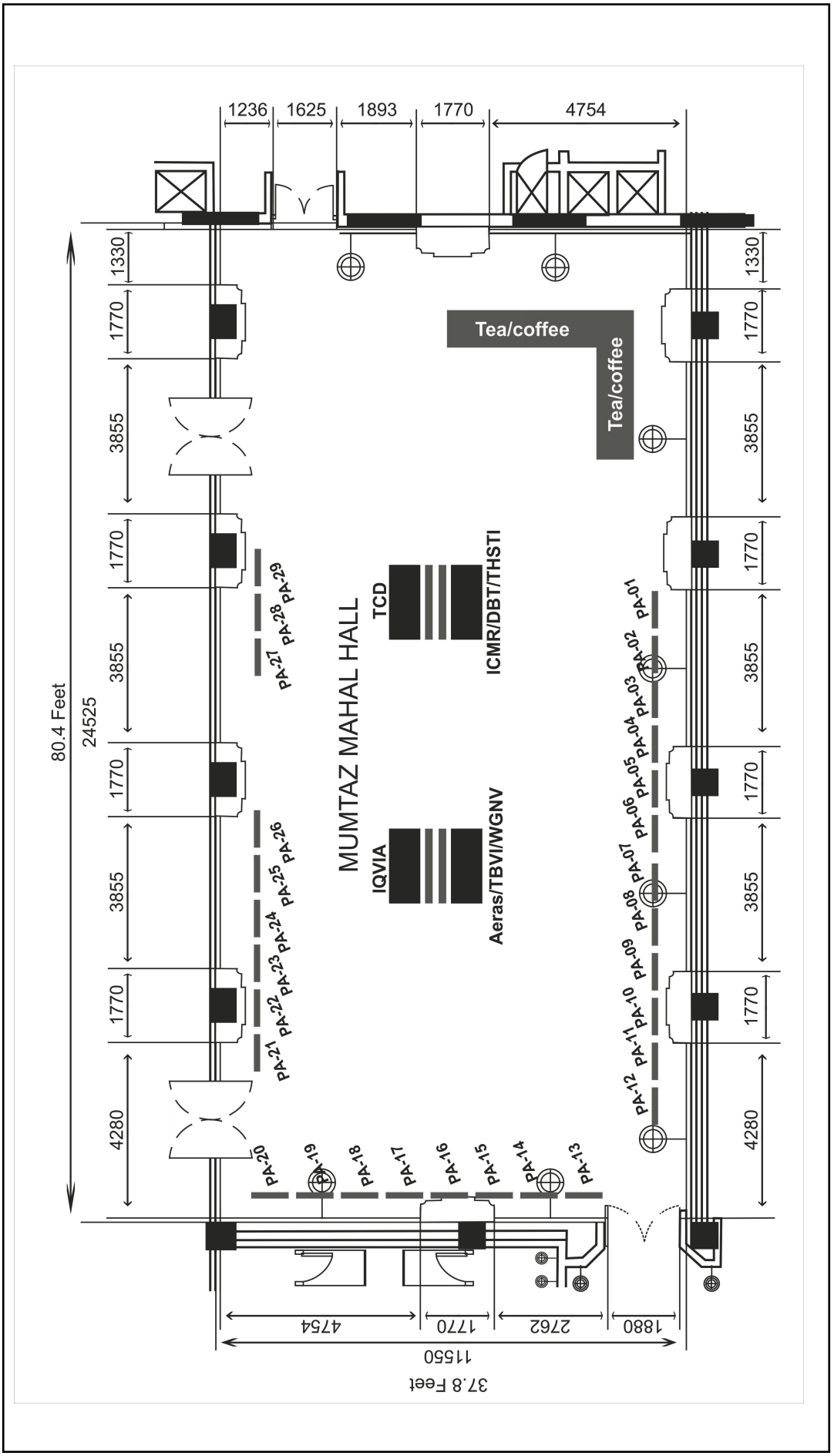
# MAP OF VENUE

## POSTER LOCATIONS



# PROGRAM-AT-A-GLANCE

| | 20 February | 21 February | 22 February | 23 February |
|---|---|---|---|---|
| 09:00 - 11:00 | **Registration / Poster setup** | Plenary 2 - TB Vaccines in Clinical Development | Plenary 4 - The Cutting Edge: Translating Scientific Advances into New TB Vaccines | Site Visits |
| | Opening Session (10:30) | | | |
| **11:00 - 11:30** | | **Coffee/Tea Break (poster area)** | **Coffee/Tea Break (poster area)** | |
| 11:30 - 13:00 | | Breakout 1 - Basic Science Research | Breakout 3 - Novel Vaccine Concepts and Preclinical Research | |
| | Keynote Address | | | |
| | | Breakout 2 - Clinical Research | Breakout 4 - Biomarkers, Correlates, and Epidemiology | |
| **13:00 - 14:00** | **Lunch** | **Lunch** | **Lunch** | |
| 14:00 - 16:00 | Plenary 1 - Increasing Probability for Success and Maximizing Impact | Plenary 3 - Novel Approaches to TB Vaccine R&D | Plenary 5 - Partnering for Progress and Innovation (panel discussion) | |
| 16:00 - 16:30 | Poster Discussions/Poster Viewing (16:15 - 17:45) | **Coffee/Tea Break (poster area)** | Closing Session | |
| 16:30 - 18:00 | | Poster Discussions/Poster Viewing | | |
| 18:00 - 18:30 | **Networking and Refreshments (17:45 - 18:30)** | Networking Reception and Poster Viewing | | |
| 18:30 - 20:00 | Inaugural Ceremony | | | |
| 20:00 - 21:30 | Forum Dinner | | | |

# SESSION PROGRAM

## Tuesday
## 20 February 2018

| | |
|---|---|
| **08:00** | **REGISTRATION OPENS** |
| **09:00 - 10:30** | **COFFEE/TEA BREAK** |
| **10:30 - 12:15** | **OPENING SESSION** |
| Shahjehan | Co-Chairs: Danilo Casimiro, former Chief Scientific Officer, Aeras (USA) \| Soumya Swaminathan, former Director General, Indian Council of Medical Research (India) \| David Lewinsohn, Chair, Stop TB Partnership Working Group on New Vaccines(USA) \| Nick Drager, Executive Director, TuBerculosis Vaccine Initiative (Netherlands) |
| | **Overview of the TB epidemic globally and in India** |
| | Soumya Swaminathan, Deputy Director General of Programmes, World Health Organization (Switzerland) |
| | **Civil society perspective on the need for new TB vaccines** |
| | Blessina Kumar, Global Coalition of TB Activists (India) |
| | **Access and affordability for new TB vaccines** |
| | Hendrik Bekedam, World Health Organization Representative to India, WHO Country Office (India) |
| PS-01 | **The potential public health impact of new TB vaccines** |
| | Richard White, Professor, London School of Hygiene and Tropical Medicine and Director, TB Modelling and Analysis Consortium (UK) |
| | **Partnerships and collaboration in TB vaccine R&D** |
| | Renu Swarup, Senior Advisor, Department of Biotechnology, Ministry of Science & Technology (India) |
| | **India's commitment to end TB** |
| | Manoj Jhalani, Additional Secretary and Mission Director, National Health Mission, Ministry of Health & Family Welfare (India) |
| **12:15 - 13:00** | **KEYNOTE ADDRESS** |
| Shahjehan | **Why we need a vaccine to control TB and what we need to learn to develop an effective vaccine**<br>Barry R. Bloom, Joan L. and Julius H. Jacobson Research Professor of Public Health, Harvard University (USA) |
| **13:00 - 14:00** | **LUNCH - RANI BAGH LAWN** |
| **14:00 - 16:00** | **PLENARY SESSION 1: INCREASING PROBABILITY OF SUCCESS AND MAXIMIZING IMPACT** |
| Shahjehan | Co-Chairs: Willem Hanekom, Bill & Melinda Gates Foundation (USA) \| Gagandeep Kang, Translational Health Science and Technology Institute (India) |
| | **Vaccine strategies to address drug-resistant tuberculosis**<br>Gavin Churchyard, The Aurum Institute (South Africa) |
| PS-02 | **Decision-making in TB vaccine development: the stage-gate process**<br>Georges Thiry, Aeras/TuBerculosis Vaccine Initiative Joint Working Group on Stage-Gates (France) |
| PS-03 | **Can biomarkers advance the development of new TB vaccines?**<br>Hazel M. Dockrell, London School of Hygiene and Tropical Medicine (UK) |
| PS-04 | **Human TB Challenge - you can do that?**<br>Eric J. Rubin, Harvard T.H. Chan School of Public Health (USA) |
| PS-05 | **Enriching cohorts for smaller, quicker, more efficient TB vaccine studies**<br>Dereck Tait, Aeras (South Africa) |
| **16:15 - 17:45** | **POSTER DISCUSSION/POSTER VIEWING SESSIONS** |
| Roshanara | Poster Discussion 1: Basic Vaccine Concepts and Correlates of Protective Immunity |
| Sheesh Mahal | Poster Discussion 2: Diagnostics and Epidemiology |
| Mumtaz Mahal | Poster Viewing: Novel Vaccine Concepts; Chemistry, Manufacturing and Controls |
| | See Poster Program for additional details |
| | Coffee/tea to be served by the session rooms |

| | |
|---|---|
| **17:45 - 18:30** | **NETWORKING AND REFRESHMENTS, RANI BAGH LAWN** |
| **18:30 - 20:00** | **INAUGURAL CEREMONY** |
| Shahjehan | Co-Chairs: Nick Drager, Executive Director, TuBerculosis Vaccine Initiative (Netherlands) \| Lucica Ditiu, Executive Director, Stop TB Partnership (Switzerland) |
| | **Prevention is better than cure: A survivor story**<br>Mona Balani, Touched by TB (India) |
| | **Regional efforts to bending the curve**<br>Poonam Khetrapal Singh, WHO Regional Director for South-East Asia (India) |
| | **Translating rhetoric into action: Transforming the global TB response**<br>Soumya Swaminathan, Deputy Director General of Programmes, World Health Organization (Switzerland) |
| | **India's mission to strengthen vaccine research**<br>Anupriya Patel, Honourable Minister of State, Ministry of Health & Family Welfare (India) |
| | **Research, innovation and partnerships as the pathway to success**<br>Harsh Vardhan, Honourable Union Minister, Ministry of Science & Technology and Earth Sciences, Ministry of Environment, Forest & Climate Change (India) |
| **20:00 - 21:30** | **FORUM DINNER - RANI BAGH LAWN** |

## Wednesday
## 21 February 2018

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|---|---|
| **09:00 - 11:00** | **PLENARY SESSION 2: CLINICAL DEVELOPMENT OF NEW TB VACCINES** |
| Shahjehan | Co-Chairs: Souleymane Mboup, Institut de Recherche en Santé, de Surveillance Epidemiologique et de Formations (Senegal) \| Sanjay Mehendale, Indian Council of Medical Research (India) |
| PS-06 | **A critical juncture in tuberculosis vaccine clinical development: overview of progress**<br>Ann M. Ginsberg, Aeras (USA) |
| PS-07 | **Community engagement and Good Participatory Practice guidelines for TB vaccine research and development**<br>Moses Zimba, Centre for Infectious Disease Research in Zambia (Zambia) |
| PS-08 | **Evaluating potential of vaccine(s) in preventing disease in healthy household contacts of TB patients**<br>Kavita Singh, Multi Vaccines Development Program (India) |
| PS-09 | **A new TB vaccine on the horizon**<br>Umesh Shaligram, Serum Institute of India Ltd Pvt (India) |
| PS-10 | **Prevention of infection with Mycobacterium tuberculosis by H4:IC31 vaccination or BCG revaccination in healthy adolescents: results of a randomized controlled trial**<br>Mark Hatherill, South African Tuberculosis Vaccine Initiative, University of Cape Town (South Africa) |
| **11:00 - 11:30** | **COFFEE/TEA BREAK** |
| **11:30 - 13:00** | **BREAKOUT SESSION 1: BASIC SCIENCE RESEARCH** |
| Shahjehan | Co-Chairs: Katrin Eichelberg, National Institute for Allergy and Infectious Diseases, National Institutes of Health (USA) \| Rajesh Gokhale, National Institute of Immunology (India) |
| OA-01 | **How EsxH controls host cellular responses to Mycobacterium tuberculosis?**<br>Ekansh Mittal, Washington University School of Medicine (USA) |
| OA-02 | **Elevated cyclic AMP inhibits Mycobacterium tuberculosis-stimulated T cell IFN-γ secretion through type I protein kinase A**<br>Buka Samten, University of Texas Health Science Center at Tyler (USA) |
| OA-03 | **A TOLLIP deficiency allele, rs5743854, is associated with decreased lncRNA TOLLIP-AS1 expression, BCG-specific T-cell memory phenotypes, and increased TB susceptibility**<br>Javeed Ali Shah, University of Washington (USA) |
| OA-04 | **Pulmonary mucosal BCG vaccination shows protection of infection in a novel repeated ultra-low dose challenge model in rhesus macaques**<br>Frank A.W. Verreck, Biomedical Primate Research Centre (Netherlands) |

# SESSION PROGRAM

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|---|---|
| OA-05 | **Memory, activation and functional profiles of Mycobacterium tuberculosis-specific CD4 T cells in recent QFT converters**<br>Cheleka Anne-Marie Mpande, South African Tuberculosis Vaccine Initiative, University of Cape Town (South Africa) |
| OA-06 | **Protein kinase G confers survival advantage to Mycobacterium tuberculosis during latency like conditions**<br>Mehak Zahoor Khan, National Institute of Immunology (India) |
| Jehangir | **BREAKOUT SESSION 2: CLINICAL RESEARCH** |
| | Co-Chairs: Sanjay Gurunathan, Sanofi Pasteur (USA) \| Randeep Guleria, All India Institute of Medical Sciences (India) |
| OA-07 | **DAR-901: an inactivated whole cell NTM booster vaccine**<br>C. Fordham von Reyn, Geisel School of Medicine at Dartmouth (USA) |
| OA-08 | **A randomized, double-blind, dose-escalation clinical trial of MTBVAC compared to BCG Vaccine SSI, in newborns living in a tuberculosis endemic region**<br>Michele Tameris, South African Tuberculosis Vaccine Initiative, University of Cape Town (South Africa) |
| OA-09 | **Clinical development of ID93+GLA-SE as a prophylactic or therapeutic vaccine for tuberculosis**<br>Tracey Ann Day, Infectious Disease Research Institute (USA) |
| OA-10 | **Use of oral inactivated Mycobacterium manresensis to reduce the risk of TB**<br>Pere-Joan Cardona, Institute Germans Trias i Pujol (Spain) |
| OA-11 | **Phase III, placebo-controlled, 2:1 randomized, double-blinded trial of tableted immunotherapeutic TB vaccine (V7) containing 10 microgram of heat-killed M. vaccae**<br>Aldar S. Bourinbair, Immunitor LLC (Mongolia) |
| OA-12 | **Randomized open phase 1 trial of TB/FLU-01L vaccine administrated intranasally or sublingually for immunotherapy of pulmonary tuberculosis**<br>Marina Stukova, Research Institute of Influenza (Russia) |
| **13:00 - 14:00** | **LUNCH - RANI BAGH LAWN** |
| **14:00 - 16:00** | **PLENARY SESSION 3: NOVEL APPROACHES TO TB VACCINE RESEARCH & DEVELOPMENT** |
| Shahjehan | Co-Chairs: JoAnne Flynn, University of Pittsburgh (USA) \| Anil Tyagi, Guru Gobind Singh Indraprastha University (India) |
| PS-11 | **The route of BCG vaccination determines immunity and protection against Mycobacterium tuberculosis infection in non-human primates**<br>Robert Seder, National Institute of Allergy and Infectious Diseases, National Institutes of Health (USA) |
| PS-12 | **Vaccination following mycobacterial exposure**<br>Thomas J. Scriba, South African Tuberculosis Vaccine Initiative (SATVI), University of Cape Town (South Africa) |
| PS-13 | **Cytomegalovirus (CMV)-based TB vaccines**<br>Aurelio Bonavia, Vir Biotechnology (USA) |
| PS-14 | **Nucleic acid vaccines for tuberculosis**<br>Jeffrey B. Ulmer, GSK Vaccines (USA) |
| PS-15 | **Protective potential of Mycobacterium indicus pranii (MIP) and the underlying mechanisms in animal models of tuberculosis**<br>Sangeeta Bhaskar, National Institute of Immunology (India) |
| **16:00 - 16:30** | **COFFEE/TEA BREAK** |
| **16:30 - 18:00** | **POSTER DISCUSSION SESSIONS** |
| Roshanara | Poster Discussion 3: Preclinical Research |
| Sheesh Mahal | Poster Discussion 4: Clinical Research and Community Engagement |
| Mumtaz Mahal | Poster Viewing: Basic Science Research, Biomarkers and Correlates, Epidemiology |
| | See Poster Program for additional details |
| **18:00 - 20:00** | **NETWORKING RECEPTION AND POSTER VIEWING** |
| | Cultural performance followed by networking and poster viewing<br>Posters on display in Mumtaz Mehal, Sheesh Mahal, and Roshanara<br>Food and drink stations will be located in Shahjehan and Roshanara |

## Thursday
## 22 February 2018

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|---|---|
| **07:15 - 08:45** | **SATELLITE SESSION: PANEL DISCUSSION AND AUDIENCE Q&A ON THE H4:IC31®/BCG REVACCINATION POI TRIAL RESULTS** |
| Jehangir | Organized by Sanofi Pasteur and Aeras<br>Speakers/content to be announced<br>Coffee/tea and light snacks provided |
| **09:00 - 11:00** | **PLENARY SESSION 4: THE CUTTING EDGE: TRANSLATING SCIENTIFIC ADVANCES INTO NEW TB VACCINES** |
| Shahjehan | Co-Chairs: Peter Andersen, Statens Serum Institute (Denmark) \| G.P. Talwar, Talwar Research Foundation (India) |
| PS-16 | **Predictive biosignatures to improve tuberculosis vaccine development**<br>Stefan H.E. Kaufmann, Max Planck Institute for Infection Biology (Germany) |
| PS-17 | **Harnessing the power of innate immunity in vaccines against TB**<br>Maziar Divangahi, McGill University (Canada) |
| PS-18 | **Donor unrestricted T-cells (DURTS)**<br>David Lewinsohn, Oregon Health & Science University (USA) |
| PS-19 | **Tissue-resident memory T-cells in infection and inflammation**<br>Chang Ook Park, Yonsei University College of Medicine (South Korea) |
| PS-20 | **Targeting checkpoint inhibitor-PD-1 for enhancing efficacy of therapeutic vaccines in tuberculosis**<br>Dipendra K. Mitra, All India Institute of Medical Sciences (India) |
| **11:00 - 11:30** | **COFFEE/TEA BREAK** |
| **11:30 - 13:00** | **BREAKOUT SESSION 3: NOVEL VACCINE CONCEPTS AND PRECLINICAL RESEARCH** |
| Shahjehan | Co-Chairs: Luciana Leite, Instituto Butantan (Brazil) \| Seyed E. Hasnain, Jamia Hamdard (India) |
| OA-13 | **Stress-response deficient attenuated Mycobacterium tuberculosis as next-gen TB vaccines**<br>Deepak Kaushal, Tulane National Primate Research Center (USA) |
| OA-14 | **Mechanisms of attenuation and protection of MTBVAC, a live attenuated tuberculosis vaccine moving to efficacy clinical trials**<br>Carlos Martin, University of Zaragoza (Spain) |
| OA-15 | **Increased efficacy of chemotherapy against Mycobacterium tuberculosis by additive immunotherapy using a multistage MVA vaccine**<br>Stéphane Leung-Theung-Long, Transgene (France) |
| OA-16 | **Immunogenicity and efficacy evaluation of multiple ChAd3-5Ag ± MVA-5Ag prime-boost vaccine regimens in rhesus macaques**<br>Agnes Laurence Chenine, Aeras (USA) |
| OA-17 | **Recombinant BCG expressing ESX-1 of Mycobacterium marinum combines low virulence with cytosolic immune signaling and improved tuberculosis protection**<br>Matthias I. Gröschel, Institute Pasteur, Paris (France); University Medical Center Groningen (Netherlands) |
| OA-18 | **Novel mucosal TB vaccine candidates generated by EMI-TB consortium**<br>Rajko Reljic, St. George's Medical School, University of London (UK) |
| Jehangir | **BREAKOUT SESSION 4: BIOMARKERS, CORRELATES AND EPIDEMIOLOGY** |
| | Co-Chairs: Gerald Voss, TuBerculosis Vaccine Initiative (Belgium) \| Vijaya Lakshmi Valluri, Bhagwan Mahavir Medical Research Centre (India) |
| OA-19 | **NK cells and memory-like NK cells as immunological markers of protection against latent TB conversion in household contacts of TB patients**<br>Kamakshi Prudhula Devalraju, Bhagwan Mahavir Medical Research Centre (India) |
| OA-20 | **Gene expression profiles of pediatric tuberculosis patients and exposed controls from India**<br>Jeffrey A Tornheim**,** Johns Hopkins University School of Medicine (USA) |
| OA-21 | **Evaluating immune correlates of risk of Mycobacteria tuberculosis infection in humans**<br>Iman Satti, University of Oxford (UK) |

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| OA-22 | **Maximising impact of the TB vaccine pipeline - mathematical modelling to inform target product profiles**<br>Rebecca Claire Harris, London School of Hygiene and Tropical Medicine (UK) |
| OA-23 | **Incidence of tuberculosis disease among household contacts of adult pulmonary tuberculosis patients in India - a multi centric cohort study**<br>Sriram Selvaraju, National Institute for Research in Tuberculosis (India) |
| OA-24 | **High risk for tuberculosis infections among medical and nursing trainees in India**<br>Aarti Avinash Kinikar, Byramjee Jeejeebhoy Government Medical College and Sassoon General Hospital (India) |
| **13:00 - 14:00** | **LUNCH - RANI BAGH LAWN** |
| **14:00 - 16:30** | **PLENARY SESSION 5: PARTNERING FOR PROGRESS AND INNOVATION** |
| Shahjehan | Co-Chairs/Facilitators: Ole Olesen, European & Developing Countries Clinical Trials Partnership (Netherlands) \| Renu Swarup, Biotechnology Industry Research Assistance Council (India) and Department of Biotechnology (India)<br>**Roundtable discussion featuring:**<br>• Fareed Abdullah, South African Medical Research Council (South Africa)<br>• Shelly Batra, Operation AHSA (India)<br>• Willem Hanekom, Bill & Melinda Gates Foundation (USA)<br>• Michel Kazatchkine, Global Health Centre, Graduate Institute for International and Development Studies (Switzerland)<br>• Rajiv I. Modi, Chairman of the Confederation of Indian Industry National Council on Pharmaceuticals (India) and Cadila Pharmaceuticals (India)<br>• Jacqueline Shea, Aeras (USA) |
| | **CLOSING SESSION** |
| | Co-Chairs: Danilo Casimiro, former Aeras (USA) \| Sanjay Mehandele, Acting Director-General, Indian Council on Medical Research (India) \| David Lewinsohn, Stop TB Partnership Working Group on New Vaccines (USA) \| Nick Drager, TuBerculosis Vaccine Initiative (Netherlands)<br>**Closing Address**<br>Lucica Ditiu, Stop TB Partnership (Switzerland) |

## Friday
## 23 February 2018

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| | **SITE VISITS (Pre-registration Required)** |
| 09:00 - 11:30 | International Centre for Genetic Engineering and Biotechnology (ICGEB) |
| 09:30 - 13:00 | National Institute for Tuberculosis and Respiratory Diseases (NITRD) |
| 08:30 - 12:30 | Operation ASHA |
| 08:30 - 14:00 | Translational Health Science and Technology Institute (THSTI) |

# POSTER PROGRAM

## Tuesday
## 20 February 2018

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|---|---|
| 16:15 - 17:45 | **POSTER DISCUSSION 1: BASIC VACCINE CONCEPTS AND CORRELATES OF PROTECTIVE IMMUNITY** |
| Roshanara | Facilitators: David Lewinsohn, Oregon Health & Science University (USA) \| Vinay Kumar Nandicoori, National Institute of Immunology (India) |
| PD-01 | **Treatment with non-steroidal anti-inflammatory drugs (NSAIDs) exacerbates TB infection after aerosol challenge in mice - implications for host-directed therapy**<br>Rasmus Mortensen, Statens Serum Institute (Denmark) |
| PD-02 | **Deciphering the role of VapBC TA modules in virulence and pathogenesis of Mycobacterium tuberculosis**<br>Sakshi Agarwal, Translational Health Science and Technology Institute (India) |
| PD-03 | **Mycobacterium tuberculosis hbhA and mtp deletion elicits unique canonical pathways during early infection in THP-1 differentiated macrophages**<br>Suventha Moodley, University of KwaZula-Natal (South Africa) |
| PD-04 | **Targeting ClpB abrogates stress tolerance in Mycobacterium tuberculosis and hence its growth and infectivity**<br>Prajna Tripathi, National Institute of Immunology (India) |
| PD-05 | **Circulating HLA-DR+IFNγhiIL-17hiCD4+T effectors resistant to CCR5 and PD-L1 mediated suppression compromise regulatory T cell function in tuberculosis**<br>Asma Ahmed, Indian Institute of Science (India) |
| PD-06 | **PPM, a novel Mycobacterium tuberculosis (Mtb) antigen: a candidate for vaccine development to prevent progression to tuberculosis**<br>Chaouki Benabdessalem, Institut Pasteur de Tunis (Tunisia) |
| PD-07 | **Evaluation of the immunogenicity of a promising vaccine regime to identify immune correlates of protection**<br>Nawamin Pinpathomrat, University of Oxford (UK) |
| PD-08 | **Demonstration of a correlation between the in vitro direct mycobacterial growth inhibition assay (MGIA) and protection from in vivo mycobacterial challenge**<br>Rachel Tanner, University of Oxford (UK) |
| PD-09 | **Altered systemic levels of neutrophil and mast cell granular proteins in tuberculosis-diabetes co-morbidity and changes following treatment**<br>Kadar Abbas Moideen, National Institute of Health-NIRT-International Center for Excellence in Research (India) |
| | **POSTER DISCUSSION 2: DIAGNOSTICS AND EPIDEMIOLOGY** |
| Sheesh Mahal | Facilitators: Johan Vekemans, Initiative for Vaccine Research, World Health Organization (Switzerland) \| Jaya Tyagi, Department of Biotechnology, All India Institute of Medical Sciences (India) |
| PD-22 | **BCG vaccine as proof-of-concept**<br>Marcel Behr, McGill University (Canada) |
| PD-23 | **Effect of anti-tuberculosis treatment on the systemic levels of matrix metalloproteinases and tissue inhibitors of MMP in tuberculosis - diabetes co-morbidity**<br>Nathella Pavan Kumar, NIH-ICER-NIRT (India) |
| PD-24 | **The ESAT-6 free IGRA, a companion diagnostic for ESAT-6 based TB vaccines**<br>Morten Ruhwald, Statens Serum Institut (Denmark) |
| PD-25 | **Circulating Mycobacterium tuberculosis DosR latency antigen-specific, polyfunctional, regulatory IL10+ Th17 CD4 T-cells differentiate latent from active tuberculosis**<br>Srabanti Rakshit, Indian Institute of Science (India) |
| PD-26 | **Proliferative T cell (CD3+Ki67+) response to PPD and M. tuberculosis cell membrane complements the tuberculin skin test for detection of latent TB infection in healthy North Indian hospital contacts**<br>Sudhir Sinha, Sanjay Gandhi Post-Graduate Institute of Medical Sciences (India) |
| PD-27 | **CD14+ CD16+ cells as immunological marker for protection in house hold contacts with latent tuberculosis infection**<br>Venkata Sanjeev Kumar Neela, Bhagwan Mahavir Medical Research Centre (India) |

PD-28 **Optimization and interpretation of serial QuantiFERON testing to measure acquisition of M. tuberculosis infection**
Elisa Nemes, South African Tuberculosis Vaccine Initiative, University of Cape Town (South Africa)

PD-29 **Updating the recommended age of BCG vaccination? Modelling the potential impact on global paediatric TB mortality**
Partho Roy, London School of Hygiene and Tropical Medicine (UK)
*Presented by Rebecca Harris, London School of Hygiene and Tropical Medicine (UK)*

PD-30 **Do we have identified target groups and a population based strategy for vaccination against tuberculosis to cut down transmission?**
U.D. Gupta, National JALMA Institute for Leprosy and Other Mycobacterial Diseases (India)

PD-31 **TB Infection among household contacts: Preventive therapy for all?**
Chandra Kumar Dolla, Byramjee Jeejeebhoy Government Medical College and Sassoon General Hospital (India)

PD-32 **Infection free "resistors" among household contacts of culture-confirmed adult pulmonary TB cases**
Vidya Mave, Byramjee Jeejeebhoy Government Medical College - Johns Hopkins University Clinical Research Site (India)

PD-33 **Incidence of Mycobacterium tuberculosis infection among household contacts of adult pulmonary tuberculosis cases in India**
Mandar Paradkar, Byramjee Jeejeebhoy Government Medical College Clinical Research Site (India)

## Mumtaz Mahal — POSTER VIEWING: NOVEL VACCINE CONCEPTS; CHEMISTRY, MANUFACTURING AND CONTROLS

### NOVEL VACCINE CONCEPTS

PA-01 **The impact of previous BCG vaccination in enhancing the effectiveness of tuberculosis drugs to control mycobacterial growth ex-vivo**
Satria Arief Prabowo, London School of Hygiene and Tropical Medicine (UK)

PA-02 **The role of DPP4 and antagonist CXCL10 in the pathogenesis of TB, an opportunity for vaccines and HDT?**
Morten Ruhwald, Statens Serum Institut (Denmark)

PA-03 **Mycobacterium tuberculosis H37Rv cell wall isolated poly L-glutamines as novel Th1-biased adjuvant**
Manish Gupta, Jawaharlal Nehru University (India)

PA-04 **De novo arginine biosynthesis pathway of Mycobacterium tuberculosis: A novel drug target and potential vaccine candidate**
Sangeeta Tiwari, Albert Einstein College of Medicine (USA)

PA-05 **Epitope-based vaccine design for Mycobacterium tuberculosis strains through pan-genomic reverse vaccinology**
Ravina Madhulitha Nalamolu, Sri Venkateswara Institute of Medical Sciences University (India)

PA-06 **Development of a recombinant BCG vaccine expressing a monomeric form of ESAT-6**
Makram Essafi, Institut Pasteur de Tunis (Tunisia)

PA-07 **Insights into mycobacterial membrane vesicles: a potential subunit vaccine candidate**
Praapti Jayaswal, Translational Health Science and Technology Institute (India)

PA-08 **Assessment of the protective effect, against tuberculosis, of a new vaccine composition**
Rania Bouzeyen, Insitut Pasteur de Tunis (Tunisia)

PA-09 **Immunological activity of the fusion protein consisted of the major secretory protein of Mycobacterium tuberculosis**
Hyun Shik Bae, Chungnam National University (South Korea)

PA-10 **Synthetic polysaccharide conjugate vaccines expressing Mycobacterium tuberculosis antigens induce high-titer antibody responses in mice, guinea pigs, and rabbits**
Dominick Laddy, Aeras (USA)

PA-11 **Rv2882c-Rv20xxc, a novel immunostimulatory antigen of Mycobacterium tuberculosis, activates bone-marrow derived dendritic cell**
Ki-Won Shin, College of Medicine, Chungnam National University (South Korea)

PA-12 **Mycobacterium tuberculosis protein Rv2299c fused-ESAT-6 subunit vaccine confers improved protection against the hypervirulent strain HN878 in mice**
Seunga Choi, College of Medicine, Chungnam National University (South Korea)

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| PA-13 | **Evaluation of attenuated strains as auxotrophic vaccines against Mycobacterium tuberculosis**<br>Tannu Priya Gosain, Translational Health Science and Technology Institute (India) |
| | **CHEMISTRY, MANUFACTURING AND CONTROLS** |
| PA-14 | **Miniaturized fluorescence adapter for fluorescence sputum smear microscopy using bright-field microscope**<br>Mamta Rani, IIT Delhi (India)<br>*Presented by Pooja Singh, IIT Delhi (India)* |
| PA-15 | **Development of an innovative, rapid, affordable and automated system for selective enrichment, isolation and detection of MTB in sputum sample**<br>Saumya Singh, IIT Delhi (India) |
| PA-16 | **Comparison of pellicle and liquid grown BCG reference strains in standard BCG batch release assays and protection studies**<br>Megan Fitzpatrick, Aeras (USA) |

## Wednesday
## 21 February 2018

| 16:30 - 18:00 | **POSTER DISCUSSION 3: PRECLINICAL RESEARCH** |
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| Roshanara | Facilitators: Danilo Casimiro, former Aeras (USA) \| Sarala Balachandran, Council of Scientific and Industrial Research (India) |
| PD-10 | **Early and local immune mechanisms of TB disease progression and control upon ultra-low dose infection in rhesus versus cynomolgus macaques**<br>Karin Djikman, Biomedical Primate Research Centre (Netherlands) |
| PD-11 | **Experimental evaluation of a novel microneedle device for BCG vaccination**<br>Jungho Kim, International Tuberculosis Research Center (South Korea)<br>*Presented by Jake Whang, International Tuberculosis Research Center (South Korea)* |
| PD-12 | **Role of BCG encapsulated alginate particles in activation of bone marrow derived dendritic cells for providing better immune response against TB**<br>Ashwani Kesarwani, National Institute of Immunology; Jamia Handard (India) |
| PD-13 | **bioA mutant of Mycobacterium tuberculosis shows severe growth defect and imparts protection against tuberculosis in guinea pigs**<br>Ritika Kar Bahal, University of Delhi South Campus (India) |
| PD-14 | **Animal dose response curve predicts lower optimal tuberculosis vaccine dose in humans: The use of vaccine Immunostimulation/Immunodynamic modelling methods to inform vaccine dose decision-making**<br>Sophie Rhodes, London School of Hygiene and Tropical Medicine (UK)<br>*Presented by Richard White, London School of Hygiene and Tropical Medicine (UK)* |
| PD-15 | **T cell immunity in the lung and protection following aerosol, intravenous, or intradermal administration of BCG in nonhuman primates**<br>Patricia Darrah, National Institute of Immunology and Infectious Diseases, National Institutes of Health (USA) |
| PD-16 | **A recombinant BCG-LTAK63 strain induces increased innate and long-term immunity correlating with enhanced protection against tuberculosis**<br>Luciana Leite, Instituto Butantan (Brazil) |
| PD-17 | **Recombinant BCG-LTAK63 strain induces lower immunopathological effects and superior protection against tuberculosis in BALB/c and C57BL/6 mice**<br>Carina Santos, Instituto Butantan (Brazil) |
| PD-18 | **Intransal vaccination with Mycobacterium indicus pranii leads to infiltration of protective memory T-cells in lung airway lumen**<br>Ananya Gupta, National Institute of Immunology (India) |

# POSTER PROGRAM

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| PD-19 | **Boosting with recombinant MVA expressing α-crystallin antigen of M. tuberculosis augments the protection imparted by BCG against tuberculosis in guinea pigs**<br>Prachi Nangpal, University of Delhi South Campus (India) |
| PD-20 | **A single dose nanoparticulate vaccine approach against tuberculosis**<br>Manish Gupta, Jawaharlal Nehru University (India) |
| PD-21 | **Passive vaccination with human IgA protects against MDR-TB infection in mice**<br>Andy Tran, St. George's University of London (UK) |
| | **POSTER DISCUSSION 4: CLINICAL RESEARCH AND COMMUNITY ENGAGEMENT** |
| Sheesh Mahal | Facilitators: Souleymane Mboup, Institut de Recherche en Santé, de Surveillance Epidemiologique et de Formations (Senegal) \| Lorraine Misquith, Lawyers Collective and Global Coalition of TB Activists (India) |
| PD-34 | **Immunogenicity of AERAS-404 or BCG revaccination in a prevention of established M. tuberculosis infection efficacy trial**<br>Virginie Rozot, South African Tuberculosis Vaccine Initiative, University of Cape Town (South Africa) |
| PD-35 | **Phase 1 clinical trial to evaluate the safety and immunogenicity of an adenovirus-based tuberculosis vaccine (Ad5Ag85A) administered by aerosol to healthy volunteers**<br>Fiona Mary Smaill, McMaster University (Canada) |
| PD-36 | **Dose definition of the novel TB vaccine ID93 + GLA-SE for TB endemic countries**<br>Adam Penn-Nicholson, South African Tuberculosis Vaccine Initiative, University of Cape Town (South Africa) |
| PD-37 | **The Toll-like receptor 4 agonist adjuvant, GLA-SE, improves magnitude and quality of immune responses elicited by the ID93 tuberculosis vaccine**<br>Tracey Ann Day, Infectious Disease Research Institute (USA) |
| PD-38 | **Safety and immunogenicity of H56:IC31 in HIV negative adults with and without latent tuberculosis (TB) infection**<br>Angelique Kani Kani Luabeya, South African Tuberculosis Vaccine Initiative, University of Cape Town (South Africa) |
| PD-39 | **Impact of implementing an effective community engagement strategy on retention rates in a Phase 2b TB disease prevention vaccine trial in South Africa, Zambia, and Kenya**<br>Anja van der Westhuizen, Aeras Africa (South Africa) |
| PD-40 | **Building a portfolio of community engagement projects to enhance TB**<br>Michele Tameris, South African Tuberculosis Vaccine Initiative, University of Cape Town (South Africa) |
| PD-41 | **Drama as a community engagement tool to raise TB awareness**<br>Kelvin Vollenhoven, South African Tuberculosis Vaccine Initiative, University of Cape Town (South Africa) |
| PD-42 | **Leveraging libraries to raise awareness about TB on World TB Day**<br>Kelvin Vollenhoven, South African Tuberculosis Vaccine Initiative, University of Cape Town (South Africa) |
| PD-43 | **Using eCompliance for tracking patients and ensuring accuracy of data in vaccine trials**<br>Shelly Batra, Operation ASHA (India) |
| Mumtaz Mahal | **POSTER VIEWING: BASIC SCIENCE RESEARCH, BIOMARKERS AND CORRELATES, EPIDEMIOLOGY** |
| | **BASIC SCIENCE RESEARCH; BIOMARKERS OF CORRELATES OF IMMUNITY AND PROTECTION** |
| PA-17 | **Functional, antigen-specific stem cell-like memory (Tscm) CD4+ T cells are induced by human Mycobacterium tuberculosis infection**<br>Cheleka Anne-Marie Mpande, South African Tuberculosis Vaccine Initiative, University of Cape Town (South Africa) |
| PA-18 | **Activation of L-type voltage gated calcium channel in macrophages suppresses protective responses during Mycobacterium tuberculosis infection**<br>Deepika Sharma, University of Delhi (India) |
| PA-19 | **Role of phosphorylation on secretion in Mycobacterium tuberculosis and its impact on its survival**<br>Basanti Malakar, National Institute of Immunology (India) |
| PA-20 | **Challenges in detecting TB drug resistance in a field setting in Southwestern Uganda**<br>Patrick Orikiriza, Mbarara University of Science and Technology (Uganda) |
| PA-21 | **Calcimycin induced autophagy decreases mycobacterial growth in THP-1 cells through P2RX7 dependent pathway mediated by intracellular calcium**<br>Shradha Mawatwal, National Institute of Technology, Rourkela (India) |

PA-22 **Phenotypic adaptation to drug treatment in Mycobacterium tuberculosis is mediated by DNA gyrase**
Eira Choudhary, Translational Health and Science Technology Institute (India)

PA-23 **Assessment of anti-mycobacterial activity of some selected Congolese medicinal plants**
Gedeon Ngiala Bongo, University of Kinshasa (Democratic Republic of Congo)

PA-24 **Various aspects of GTPases towards its essentiality in survival and pathogenesis of Mycobacterium tuberculosis H37Rv**
Shivangi, CSIR-Institute of Genomics and Integrative Biology (India)

PA-25 **Cytokines, matrix metalloproteinases, angiogenic factors and acute phase proteins as biomarkers in tuberculous lymphadenitis**
Gokul Raj Kathamuthu, National Institute for Research in Tuberculosis (NIRT)-NIH-ICER (India)

PA-26 **Urine IP-10 as a biomarker of therapeutic response in patients with active pulmonary tuberculosis**
Hyejon Lee, Yonsei University College of Medicine (South Korea)
*Presented by Bora Sim, Yonsei University College of Medicine (South Korea)*

**EPIDEMIOLOGY**

PA-27 **Sputum sample collection for diagnosis of pediatric pulmonary tuberculosis, does method and site of sample collection matter?**
Willy Ssengooba, Makerere University (Uganda)

PA-28 **Tuberculosis massive active case discovery in East Jakarta 2016-2017: the role of Ketuk Pintu Layani Dengan Hati (KPLDH) and Juru Pemantau Batuk (Jumantuk) cadre programs**
Ngabila Salama, East Jakarta Health Office (Indonesia)

PA-29 **Clinical profile of tuberculous meningitis in a tertiary care center in India**
Anita Basavaraj, Byramjee Jeejeebhoy Government Medical College and Sassoon General Hospital (India)

## PS-01

### The potential public health impact of new TB vaccines

**Richard White**[1,2], Rebecca Harris[2]

*[1]TB Modelling and Analysis Consortium, UK; [2]London School of Hygiene and Tropical Medicine, UK*

New and effective, tools, such as vaccines will be essential in reaching our shared goal of eliminating TB. This presentation will summarise the global modelling evidence on the potential public health impact of new TB vaccines. It will highlight the likely influence of new vaccine characteristics, and implementation decisions. It will discuss the implications of this evidence for TB vaccine clinical triallists, development strategists, and country-level decision makers, for low and middle income countries in general, and for India.

**Funding Sources and Conflicts of Interest:** Funded by Medical Research Council, Aeras, and the Bill & Melinda Gates Foundation

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## PS-02

### Decision-making in TB vaccine development: the stage-gate process

**Georges Thiry**

*Joint Aeras/TBVI Working Group on Stage Gates, France*

Vaccine development is a complex and long endeavour that requires multiple expertise, management of activities running in parallel and decision points. The Stage Gate Criteria (SGC) is a project management methodology that assists in the management of such large, long and complex projects. SGC organizes a project in two elements: the Stages, which describe packages of activities that occur in parallel and generate material and data, and the Gates that follow each stage and in which a review of data occurs using Criteria. These defined stages and gate criteria help management to follow progress and make a decision to advance a project to a next stage, to stop, hold or recycle it. In the methodology, criteria are either 'required' or 'supportive'. The SGC methodology is often associated with Portfolio Management as it introduces standards, aligns projects according to stages and gates, and evaluates them using similar criteria. Although the SGC methodology is not used to prioritise between projects, it could be one part of a broader prioritisation process.

A SGC has been used by AERAS and TBVI since 2010. Recently, a Working Group composed of experts from TBVI and AERAS revised these SGC for the development of a generic TB vaccine, from discovery to licensing. Next, the Working Group identified what is specific for TB vaccine indications (e.g., prevention of disease, of recurrence, therapeutic) and populations (e.g., infant, adolescents & adults, patients under treatment). The Working Group is currently working on a Guidance Document with explanation on how to use the SGC, examples and references (guidelines, publications…), a web tool and a publication. In parrallel, we have started consultation with external experts to further validate our methodology.

This SGC methodology will be presented.

**Funding Sources and Conflicts of Interest:** This project is supported by the BMGF to TBVI.

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## PS-03

### Can biomarkers advance the development of new TB vaccines?

**Hazel M. Dockrell**

*London School of Hygiene & Tropical Medicine, UK*

New and more effective vaccines against tuberculosis (TB) are urgently needed. Biomarker signatures that could identify whether a candidate TB vaccine was likely to induce protection could be used as part of a stage-gating process in order to select vaccine candidates for development, and to help identify the optimal vaccine dose, route and formulation. Identifying protective biomarkers is the focus of one of the work packages within the TBVAC2020 consortium (see www.tbvi.eu ).

Although T cells and production of interferon-g are required for protection, to date they have not provided correlates of protection. Using mycobacterial growth inhibition assays (MGIA) may therefore be more relevant. The protocols for MGIA assays as well as for a number of immunological assays have been optimised through multi-centre studies in European Consortia such as TRANSVAC and EURIPRED. Assessing global gene expression profiles may also be informative.

Studies using both immunological assays and host gene expression analysis have demonstrated geographical variation in responses, the underlying causes of which have not been identified to date. Coinfections such as with helminths and comorbidities may also modulate biomarker signatures, as demonstrated in recent findings in patients with both TB and type 2 diabetes in the TANDEM Consortium (www.tandem-fp7.eu). It is therefore important that biomarker studies are performed in different settings and in those with different coinfections and comorbidities.

**Funding Sources and Conflicts of Interest:** Funded by the European Community programmes Horizon 2020 and FP7 (TBVAC2020 grant no 643381 and TANDEM grant no 305279).

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## PS-04

### Human TB Challenge - you can do that?

**Eric J. Rubin[1],** Jeffrey C. Wagner[1], Flavio A. Franchina[2], Jacob Fohtung[1], Theodore Mellors[2], Aniek Lotterman[1], Matthew Zimmerman[3], Chidibiere Akusobi[1], Dirk Schnappinger[4], Véronique Dartois[4], Lennart K. Lundblad[5], Jane E. Hill[2], Sarah M. Fortune[1],

*[1]Harvard TH Chan School of Public Health, USA; [2]Dartmouth College, USA; [3]Public Health Research Institute, Rutgers University, USA; [4]Weill-Cornell Medical School, USA; [5]University of Vermont, USA*

**Background**: Testing vaccines for their ability to protect against TB requires a large number of patients and a considerable amount of time. It would be far more efficient if the attack rate were higher. One way to accomplish this would be to develop a human challenge model. To do this we would need to both produce an Mtb strain that was safe, i.e,, could be reproducibly cleared and not transmitted, and one that could be detected and quantified.

**Methods:** We are using genetic methods to produce strains that can be easily killed and that produce reporter molecules.

**Results:** In work that is currently underway we are using three different approaches to attenuating bacterial strains and two different volatile molecule reporters. We can combine attenuation systems to lower the rate of escape to full virulence and plan to detect and quantitate reporters using gas chromatography/mass spectrometry.

**Conclusion:** Our current research suggests that we can produce Mtb strains that could likely be used safely for human challenge. We are continuing to study whether these strains can be detected sensitively during human infection.

**Funding Sources and Conflicts of Interest:** Aeras, Bill & Melinda Gates Foundation

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# PS-05

## Enriching cohorts for smaller, quicker, more efficient TB vaccine studies

**Dereck Tait**[1]; A Ginsberg[2]; K Rutkowski[2]; E Lau[2]; A Kasmar[3]; W Hanekom[3]

*[1]Aeras, South Africa, [2]Aeras USA; [3]Bill & Melinda Gates Foundation, USA*

**Introduction:** There are no TB disease correlates of risk to support the selection of participants at particularly high risk of TB disease for TB vaccine studies. Consequently, even in those countries with high incidences of TB disease Phase 3 TB vaccine efficacy trials require large numbers of participants and lengthy follow up to accrue sufficient endpoints to demonstrate efficacy. Identification and evaluation of potential populations at high risk of TB infection and/or disease are important for smaller, more rapid, and less expensive proof of concept studies to identify candidates for Phase 2b/3 studies.

**Methods:** Populations identified as having high risk of *Mtb* infection and/or progression to disease include (1) prisoners, (2) miners, (3) individuals infected with the human immunodeficiency virus (HIV+), (4) diabetics, (5) household contacts of patients with active pulmonary TB (HHCs), (6) healthcare workers (HCWs), (7) individuals with latent TB infection (LTBI+) who have a "signature of risk" (SOR) for progression to disease, (8) vaccination after cure of drug-sensitive or resistant pulmonary TB disease (PTB) to prevent recurrence (POR). Potential populations were evaluated by literature reviews and personal communications with key experts. Practicality, sample size, potential study design, duration of study, and budget estimates were established for these populations.

**Results:** Data will be presented supporting the identification of the two most promising populations, i.e. HCWs and HHCs and why the others were less optimal.

**Discussion and Conclusion:** With the number of vaccines in clinical development it is important to identify populations for smaller and quicker proof of concept studies to select candidate TB vaccines for further clinical development.

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# PS-06

## A critical juncture in tuberculosis vaccine clinical development: overview of progress

**Ann M. Ginsberg**

*Aeras, USA*

Worldwide, there are at least thirteen tuberculosis (TB) vaccine candidates in clinical development, including adjuvanted recombinant proteins, viral vectored candidates and mycobacterial whole cell candidates and lysates, including the first live, attenuated M.tuberculosis vaccine. These candidates are being evaluated in a variety of populations – differing by age (infants, adolescents and/or adults), infection status (uninfected or already M.tuberculosis-infected), and disease status (healthy individuals or TB patients at the end of treatment). Candidates are also being developed for varied indications – to prevent TB by replacing infant BCG or by boosting BCG, and to improve LTBI or TB therapy by preventing progression to active TB, decreasing relapse rates, improving cure rates or shortening treatment duration. The last several decades have seen a dearth of human efficacy trials of novel TB vaccine candidates and consequently, limited knowledge of the protective human immune response. In the next few months to years (including in at least one instance at this conference), developers are due to announce results of five human efficacy trials – representing an unprecedented opportunity to determine not only the potential of five vaccine candidates but to advance knowledge of human protective immunity, evaluate the predictive ability of animal models used in these candidates' preclinical development, assess the value of novel trial designs, and potentially discover correlates of risk and protection from M.tuberculosis infection and disease. Key challenges and progress in the field will be discussed.

**Funding Sources and Conflicts of Interest:** Aeras is currently funded by the Bill and Melinda Gates Foundation, UK DFID, US Department of Defense (CDMRP) and the US NIAID, NIH. It receives co-funding for joint trials from Sanofi Pasteur and GSK.

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## PS-07

## Community engagement and Good Participatory Practice Guidelines for TB vaccine research and development

**Moses Zimba**

*Center for Infectious Disease Research in Zambia (CIDRZ), Zambia*

**Background:** Community engagement is an important part of research which requires appropriate planning and execution. The Good Participatory Practice Guidelines for TB Vaccine Research (GPP-TB VACC) provides systematic guidance on how to effectively engage various stakeholders throughout the entire life cycle of tuberculosis (TB) vaccine research, from trial design and conduct to results dissemination.

**Methods:** In a TB vaccine trial in Zambia, 136 healthy participants were enrolled in a trial that requires a 3-year follow-up period after vaccination via contact or clinic visits. The following challenges specific to TB vaccine research were anticipated:

- Possible stigmatization of participants
- Missed visits, adverse events, and serious adverse events due to the long follow-up period and infrequent (annual) clinic visits
- Participants lost to follow-up
- To mitigate these risks and to enhance participant retention and community engagement, the site research team developed Stakeholder Engagement and Issues Management Plans to:
- Anticipate questions and opinions about TB vaccine research as discussed with the Community Advisory Board (CAB).
- Appropriately organize retention events and home visits to maintain relationships with participants
- Address instances of stigmatization and misconceptions immediately

These plans included the development and dissemination of TB vaccine research information and literacy material

**Results:** A retention rate of 95% at year 2 was achieved with only 1 participant lost to follow up to date. Six participants relocated to other towns but were not lost to follow-up due to site staff quarterly visits.

**Conclusion:** Implementation of community engagement strategies is important to maintain high retention rates in TB vaccine trials. Effectively engaging community throughout the research process increases awareness and support for TB vaccine research amongst affected communities and may drive local advocacy for future trials and resource mobilization.

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## PS-08

## Evaluating potential of vaccine (s) in preventing disease in healthy household contacts of TB patients

**Kavita Singh**[1], Manjula Singh[2], Sanjay Mehendale[2]

[1]*Mutivaccine Development Program; India;* [2]*Indian Council of Medical Research, India*

**Background:** India has world's highest burden of TB accounting for one-fifth of global TB incidence. As per 2017 WHO report approximately 2.79 million new cases of TB are from India out of the global incidence of 10.4 million. The risk of transmission of TB bacilli to healthy household contacts (HHCs) is greatest when index case is sputum smear positive. Currently no intervention exists to prevent TB in adult HHCs. Therefore this trial aims to evaluate the efficacy, safety & tolerability of VPM1002 (novel recombinant Mycobacterium bovis Bacillus Calmette-Guérin (BCG) and Mw (heat killed, Mycobacterium indicus pranii) vaccines in prevention of TB among HHCs.

**Methods:** This is planned as a phase III, randomized, double-blind, placebo-controlled trial in India across multiple sites. Based on the anticipated incidence during 36 months in the control arm of 1.5% the calculated sample size would be 18,600. About 18,600 HHCs of newly diagnosed sputum positive pulmonary TB patients will be randomised to receive either VPM1002/Mw/Placebo

intradermally. At regular intervals subject will be followed for estimating incidence of disease by testing sputum for AFB and chest X-ray. Tuberculin skin test and immunological tests will also be done for response evaluation in vaccine/placebo groups.

**Results:** Efficacy evaluation: Bacteriologically confirmed and clinically diagnosed Pulmonary TB or clinically diagnosed Extra-Pulmonary Tuberculosis from 2 months after first dose of vaccine till 38 months follow-up period. Safety evaluation: Evaluation will be done within 60 min and 2 months post-vaccination for reactogenicity. All unsolicited Grade 3 adverse events and serious adverse events following immunization will also be captured till 3 years of follow-up period.

**Conclusion:** Vaccine exhibiting > 50% efficacy will be recommended for prevention of TB among HHCs.

**Funding Sources and Conflicts of Interest:** ICMR

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# PS-09

## A new TB vaccine on the horizon

**Umesh Shaligram**[1], Prasad Kulkani[1], Leander Grode[2], Mark Cotton[3], Stefan H. E.Kaufmann[4], Bernd Eisele[2] [1]*Serum Institute of India Ltd Pvt, India;* [2]*Vakzine Projekt Management GmbH, Germany;* [3]*Stellenbosch University, South Africa;* [4]*Max Planck Institute for Infection Biology, Germany*

VPM1002 is a live vaccine against tuberculosis (TB). As BCG is not sufficiently effective to stop the spread of TB, two modifications have been implemented in VPM1002 to improve its immunogenicity. Two Phase I studies and two Phase II in humans using multiparameter flow cytometry characterized the quality of the T cell response following immunization with our VPM1002 tuberculosis vaccine candidate or BCG. We completed a Phase II clinical trial in neonates in South Africa and first safety is available. The Phases II was a double blinded, randomized, controlled studies which evaluated safety and immunogenicity of VPM1002 in comparison with BCG. Safety and tolerability results from all clinical trials showed no serious adverse reactions after VPM1002 vaccination. VPM1002 is currently in Phase II/III double-blinded clinical trial post-exposure in India. Currently a phase III clinical trial is in preparation for Africa and the same product is being evaluated in Phase I/II for bladder cancer in Europe.

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# PS-10

## Prevention of infection with Mycobacterium tuberculosis by H4:IC31 vaccination or BCG revaccination in healthy adolescents: results of a randomized controlled trial

**Mark Hatherill,** on behalf of the C-040-404 Study Team
*South African Tuberculosis Vaccine Initiative (SATVI), University of Cape Town, South Africa*

**Background:** Recent Mycobacterium tuberculosis (M.tb) infection predisposes to tuberculosis disease, the leading global infectious disease killer. Demonstration of efficacy in a Prevention of M.tb Infection (POI) trial would provide impetus for candidate vaccines to enter larger trials to test efficacy against tuberculosis disease; allow identification of immune correlates of vaccine-mediated protection; and confirm the utility of the POI trial design as a tool for clinical vaccine development. We tested safety and efficacy of H4:IC31® vaccination or Bacille Calmette-Guerin (BCG) revaccination for prevention of M.tb infection (NCT02075203).

**Methods:** Healthy, QuantiFERON-TB Gold In-tube (QFT) negative, HIV-uninfected, remotely BCG-vaccinated, South African adolescents were randomized in the ratio 1:1:1 to receive placebo or H4:IC31® vaccine (15□g H4 polyprotein, Sanofi Pasteur, and 500nmol IC31®, Statens Serum Institut) on Days 0 and 56, or intradermal BCG revaccination (2-8x105 CFU, Statens Serum Institut) on Day 0. Primary outcomes were safety and acquisition of M.tb infection, defined by initial QFT conversion tested 6-monthly over 2 years. Secondary outcomes were immunogenicity and sustained M.tb infection, defined by sustained QFT conversion without reversion 3 and 6 months post-conversion. Immunogenicity was evaluated by PBMC intracellular cytokine staining (ICS) and whole blood ICS assays. This proof of concept trial for vaccine "up- vs. down-selection" was designed to distinguish 50% QFT conversion rate reduction compared to placebo for H4:IC31® or BCG, with 80% power and 10% one-sided Type-1 error rate. Results are currently under embargo but will be presented.

**Funding Sources and Conflicts of Interest:** Aeras

## PS-11

### The route of BCG vaccination determines immunity and protection against Mycobacterium tuberculosis infection in non-human primates

**Robert Seder[1],** Patricia A Darrah[1], Joshua A Hackney[1], Dominick J Laddy[3], Charles Scanga[2], Supriya Pokkali[1], Aurelio Bonavia[3], JoAnne L Flynn[2], and Mario Roederer[1]

*[1]Vaccine Research Center, NIAID, NIH, USA; [2]University of Pittsburgh School of Medicine, USA; [3]Aeras, USA.*

The magnitude, quality, breadth, and location of cellular immune responses are critical determinants of protection against Mycobacterium tuberculosis (TB). BCG, the only licensed vaccine given intradermally at birth prevents systemic TB infection during infancy/early childhood but has varying efficacy against pulmonary infection (the most common and transmissible form of TB in adolescents/adults). A potential explanation for these findings is that BCG given by the ID route does not induce a sufficient frequency of sustained T cells in the lung. Here, to assess the role of vaccine route on immunity and protection, rhesus macaques were immunized with BCG by the intravenous (IV), aerosol (AE), intradermal (ID), or ID/AE routes. NHPs immunized with BCG IV generated higher frequencies of PPD-specific CD4 (~35-45%) and CD8 (8-10%) T cells in bronchoalveolar lavage (BAL) that were maintained for at least 4months compared to ID or AE routes. IV BCG immunization increasing the absolute number of PPD-specific CD4 and CD8 T cells in the BAL by >10-fold compared to the other vaccination routes. PPD specific cytokine responses in all vaccine groups were comprised of multi-functional cells secreting IFNg, TNF and IL-2. IL-17 producing CD4 T cells were also induced in animals receiving BCG by AE or IV routes. Finally, BCG given IV resulted in a profound change in the normal ratio of macrophages and T cells in BAL. Collectively, these data highlight that varying the route and dose of immunization has a striking effect on the magnitude and composition of tissue resident T cell immunity in the lung. Six months after BCG immunization, animals were then challenged with a low dose (~15 CFU) of virulent Mycobacterium tuberculosis (MTb) Erdman and protection was assessed using PET/CT scanning, survival to endpoint, gross pathology, and bacterial burdens.

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## PS-12

### Vaccination following mycobacterial exposure

**Thomas J. Scriba**

*South African Tuberculosis Vaccine Initiative (SATVI), University of Cape Town, South Africa*

Preventing pulmonary TB in adolescents and young adults by vaccination would have major impact on control of drug-sensitive and multidrug-resistant TB, by interrupting transmission of Mycobacterium tuberculosis. Development of novel TB vaccine candidates targeted at adolescents and adults is therefore a research priority. However, large proportions of people living in settings where TB is endemic are already immunologically sensitized to mycobacteria, either because of BCG vaccination in early childhood and/or by exposure to environmental mycobacteria or infection with Mycobacterium tuberculosis. Such pre-sensitization has profound effects on the immune response and likely impacts protective efficacy of vaccination with BCG. This talk will review the effects of immunological sensitization on vaccination with whole cell mycobacterial vaccines as well as subunit vaccine candidates. The implications of these findings for preclinical vaccine development in animal models and clinical development in different human populations will be discussed.

Finally, novel insights from the first prevention of Mycobacterium tuberculosis infection trial, recently completed in adolescents from the Western Cape of South Africa, will be discussed. This Phase II randomized, controlled, partially blinded trial was designed to assess prevention of Quantiferon conversion by H4:IC31 vaccination or BCG revaccination in Quantiferon-negative adolescents in a setting highly endemic for TB. These trial participants received primary BCG vaccination at birth, thus presenting an ideal opportunity to understand how immunological pre-sensitization may impact vaccine immunogenicity and prevention of Mycobacterium tuberculosis infection.

# PS-13

## Cytomegalovirus (CMV)-based TB vaccines

**Aurelio Bonavia**
*Vir Biotechnology, USA*

CMV-VIR2-TB-001 is a novel, first-in-class, prophylactic vaccine for tuberculosis. The vaccine is to be administered to adolescents and young adults remotely vaccinated with bacillus Calmette-Guérin (BCG). The vaccine is composed of a genetically attenuated human cytomegalovirus containing six TB antigens derived from different stages of Mtb life cycle (active disease, latency and reactivation).

Attenuated forms of rhesus cytomegalovirus (rhCMV)were demonstrated to have the unique ability to serve as both an antigen-delivery and immune programming vector was first shown to be efficacious against SIV (Hansen et al., 2013). The rhCMV vector platform technology has also been applied to rhesus monkeys challenged with Mtb, resulting in a breakthrough: the first demonstration of the prevention of any microbiological evidence of TB in 10 of the 34 vaccinated rhesus monkeys with Mtb Erdman and no radiologic or pathologic evidence of pulmonary or extra-pulmonary TB in 14 of the 34 vaccinated animals (Hansen et al., 2017). Overall the vaccine imparts nearly a 70% reduction in pathology in vaccinated animals, as compared to controls.

Vir will present a summary of the program encompassing the generation of CMV-VIR2-TB-001, the advances achieved in manufacturing and the current status of the clinical development.

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# PS-14

## Nucleic acid-based vaccines for tuberculosis

**Jeffrey B. Ulmer**
*GSK Vaccines, USA*

Over the past two decades, vaccination with nucleic acid-based vaccines (e.g., viral vectors, plasmid DNA, mRNA) has become a promising alternative to conventional vaccines based on whole organisms and recombinant subunit proteins. This approach appears particularly well suited for tuberculosis, due to potent induction of broad-based immunity (including CD4+ and CD8+ T cells of the Th1 phenotype) and proof of principle has been established in animal models. Recent advancements have demonstrated that vaccines based on mRNA have the potential to combine the positive attributes of other types of nucleic acid-based vaccines. The broad utility of this novel vaccine technology has been demonstrated in various animal models, including non-human primates, suggesting that the technology has potential to be effective for tuberculosis. If mRNA vaccines prove safe, potent, well-tolerated, and effective in humans, this novel nucleic acid vaccine technology will enable a new generation of vaccines able to address the health challenges of the 21st century.

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# PS-15

## Protective potential of Mycobacterium indicus pranii (MIP) and the underlying mechanisms in animal models of tuberculosis

**Sangeeta Bhaskar,** Mohd. Saqib
*National Institute of Immunology, India*

MIP a nonpathogenic, soil-borne bacteria possesses strong immunomodulatory properties and conferred protection against experimental TB as well as in clinical trials. Protective efficacy of MIP given by aerosol route as well as by subcutaneous route was evaluated in guinea pig model of tuberculosis. Protection given by MIP aerosol vaccinated group was significantly higher than BCG vaccinated group. Reduction in bacterial load also reflected in total body weight and lung pathology.

Immunotherapy is a valuable adjunct to chemotherapy for tuberculosis. MIP-therapy as an adjunct to the chemotherapy was found to be effective in accelerating bacterial killing and improving organ pathology. Early increase in protective Th1 immune response was observed in the immunotherapy group. Following subsequent doses of MIP decrease in the inflammatory response was observed, which resulted in the improvement of lung pathology. Aerosol route of immunotherapy play a crucial role for inducing immediate local immune response in the lung which could act synergistically with chemotherapy for effective elimination of bacteria.

BCG, the only approved vaccine protects against severe form of childhood tuberculosis and has reduced the incidence of infant TB considerably in endemic areas; therefore prime-boost strategy is the most realistic measure for control of tuberculosis in near future. MIP shares significant antigenic repertoire with Mtb and BCG and thus evaluated for its efficacy as a booster to BCG. Study in our lab demonstrated for the first time, potential application of MIP as a booster to BCG vaccine, for efficient protection against tuberculosis. MIP booster by aerosol route induced Th1 and Th17 immune response in the lungs of infected animals along with poly-functional T cells. MIP, being a non-pathogenic whole bacterial vaccine with unique immunomodulatory properties, has major advantage for the practical implementation of this vaccine to masses and could be very cost effective strategy for effective control of tuberculosis.

**Funding Sources and Conflicts of Interest:** Project was funded by Department of Biotecnology, Govt.of India.

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## PS-16

## Predictive biosignatures to improve tuberculosis vaccine development

**Stefan H.E. Kaufmann**

*Max Planck Institute for Infection Biology, Germany*

Correlates of protection would be extremely valuable for rational design of novel tuberculosis (TB) vaccines. However, these are not available yet. Neither do correlates of natural protective immunity against TB disease exist, nor correlates of vaccine induced protection. However, biosignatures based on transcripts or metabolites, which predict risk of disease, have been designed. More precisely, these biosignatures likely diagnose incipient subclinical TB and a large proportion develops active TB within 6 to 12 months. Stratifying individuals with subclinical TB for vaccine trials can markedly reduce numbers of study participants and duration of trials. Obviously, this will cause profound reduction of trial cost. Similarly, vaccine trials assessing prevention of recurrence in individuals who had been cured from TB by chemotherapy can reduce numbers of study participants and trial duration. In both cases the issue arises whether progression to TB can be interrupted by vaccination. At this stage, proof of concept has been provided that observational studies on progression to active TB in household contacts can provide valuable signatures for vaccine trial design. These should be complemented by biosignatures derived from clinical vaccine trials to provide complementary information on vaccine induced effects (safety and protection). Supported by sophisticated computational analysis such a dual strategy will allow formulating guidelines for improvement of the vaccine undergoing clinical testing as well as for the design of a next generation vaccine against TB. To achieve this goal, clinical trial design of TB vaccines needs to integrate real-time monitoring by state-of-the-art technologies and bio-repositories of trial samples for future analysis with newly developed technologies.

**Funding Sources and Conflicts of Interest:** SHEK is co-inventor and patent holder of VPM1002.

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# PS-17

## Harnessing the power of innate immunity in vaccines against TB

**Maziar Divangahi**
*McGill University, Canada*

The dogma that adaptive immunity is the only arm of the immune response with memory capacity has been recently challenged by several studies demonstrating evidence for memory-like innate immune training. However, the underlying mechanisms and location for generating such innate memory responses in vivo remains unknown. Here we show that access of Bacillus Calmette-Guérin (BCG) to the bone marrow (BM) following intravenous immunization induced local hematopoietic stem cell (HSC) expansion and enhanced myelopoiesis at the expense of lymphopoiesis. Importantly, HSC reprogramming led to the generation of epigenetically-modified macrophages that provided significantly better protection against virulent M. tuberculosis infection than naïve macrophages. Finally, we demonstrate that training of the monocyte/macrophage lineage via BCG-induced HSC reprogramming is sustainable in vivo. Our results indicate that targeting the HSC compartment provides a novel approach for TB vaccine development.

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# PS-18

## Donor unrestricted T-cells (DURTS)

**David Lewinsohn**
*Oregon Health & Science University, USA*

As Mtb is an intracellular microbe, eliciting T cells that can recognize those cells harboring the bacterium is likely a critical component. Classical CD4 and CD8 T cells sample the proteome by presenting small peptides to T cells via MHC1 and MHC 2 molecules. These T cells use the T cell receptor to discern these peptides. The tremendous diversity in both MCH1 and MHC2 and the TCR reflects the need to discern peptides derived from the host from those derived from Mycobacterium tuberculosis (Mtb). For vaccine design, this diversity is also a vulnerability in that each host may have inherent limitations in their ability to recognize some peptides, and Mtb could have the capacity to change these protein to avoid immune recognition. Recently, attention has focused on the potential benefits of assessing immune responses generated via "non-classical" presentation of non-protein antigens. The advantage to these responses is that they use presentation molecules that have limited polymorphism, providing an attractive platform for vaccine development. Additionally, these responses often reflect the presentation of molecules that are unique to Mtb. Examples include HLA-E, which can present peptide and glycopeptide antigens; group 1 (CD1a-c) restricted T cell which recognize CD1 glycolipid and lipid antigens found within the outer mycobacterial membrane; mucosal associated invariant T cell (MAIT) cells which are enriched in the lungs and can recognize microbial metabolites such as those derived from riboflavin biosynthesis presented by the highly conserved molecule MR1; natural killer (NK) T-cells, which recognize glycolipids in the context of CD1d; and gamma-delta T-cells which can recognize mycobacterial lipids (ref). Together, these subsets are called "unconventional" or "donor unrestricted T-cells" (DURT) as they have the potential for vaccine development that can use substances unique to Mtb. Developing vaccines capable of stimulating these and other "unconventional" T-cell responses, along with conventional CD4+ and CD8+ T-cell responses, represents an important new frontier in TB vaccine research.

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## PS-19

### Tissue-resident memory T-cells in infection and inflammation

**Chang Ook Park**

*Department of Dermatology, Yonsei University College of Medicine, South Korea*

Recently, tissue-resident memory T cells (TRM), an important subset of memory T cells that indefinitely resides in tissues, have been widely studied. There is an emerging understanding that TRM cells have a role in tissue-specific immune responses in infection and inflammatory diseases. While TRM cells are located in barrier tissues at interfaces with the environment including skin, gut, vagina, and lung, these cells have also been found in brain, kidney, joint and other non-barrier tissues in humans and mice. Given the biology and behavior of these cells in tissues, it is likely that they have a frontier protective immunity against infection including Tuberculosis (TB). Recent insights into the biology of TRM cells could give us a more attractive TB vaccine strategy to generate lung TRM.

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## PS-20

### Targeting checkpoint inhibitor-PD-1 for enhancing efficacy of therapeutic vaccines in tuberculosis

**Dipendra K. Mitra**

*All India Institute of Medical Sciences, India*

**Introduction:** Therapy associated toxicity, poor compliance, immune-suppression and emergence of drug resistance necessitates therapeutic vaccination in tuberculosis. However, pre-existing immune-suppression in tuberculosis patients makes it essential to target the checkpoint inhibitors like PD-1 to enhance vaccine efficacy as vaccine itself might be subjected to such immune-suppression. We demonstrated that inhibiting PD-1 restores protective poly-functional T cells (PFTs) response. IFN-γ alone is essential but not sufficient for protective immunity against M. tuberculosis as TNF-α is critical for granuloma formation. Therefore, the role of PFTs is emerging as critical for protective immunity in tuberculosis. Here we investigated the impact of PD-1 inhibition in facilitating protective PFTs, bacillary-clearance and disease resolution in tuberculosis.

**Materials and methods:** PBMCs from tuberculosis patients were stimulated with M. tuberculosis antigen in presence or absence of PD-1 blockade and detected PFTs (IFN-γ+ and TNF-α+) by flow-cytometry. Mice study involved administration of anti-PD-1 in H37Rv infected mice followed by enumeration of PFT response and colony forming unit (CFU) in the lung and spleen. **Results:** We observed reduced number of PFT in TB patients and their preferential rescue by blocking PD-1. Further, we observed that poly-functional cytokine milieu favored the apoptotic death of infected MDM and showed reduced bacillary growth. Blocking PD-1 in vivo in infected mice demonstrated restoration of PFTs with significant reduction of bacillary load in the lung & spleen relative to chemotherapy alone.

**Funding Sources and Conflicts of Interest:** DBT

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# OA-01

## How EsxH controls host cellular responses to Mycobacterium tuberculosis?

**Ekansh Mittal**[1], Cynthia Portal Celhay[2], Alka Mehra[2], Fong-Fu Hsu[1], Jennifer A. Philips[1]

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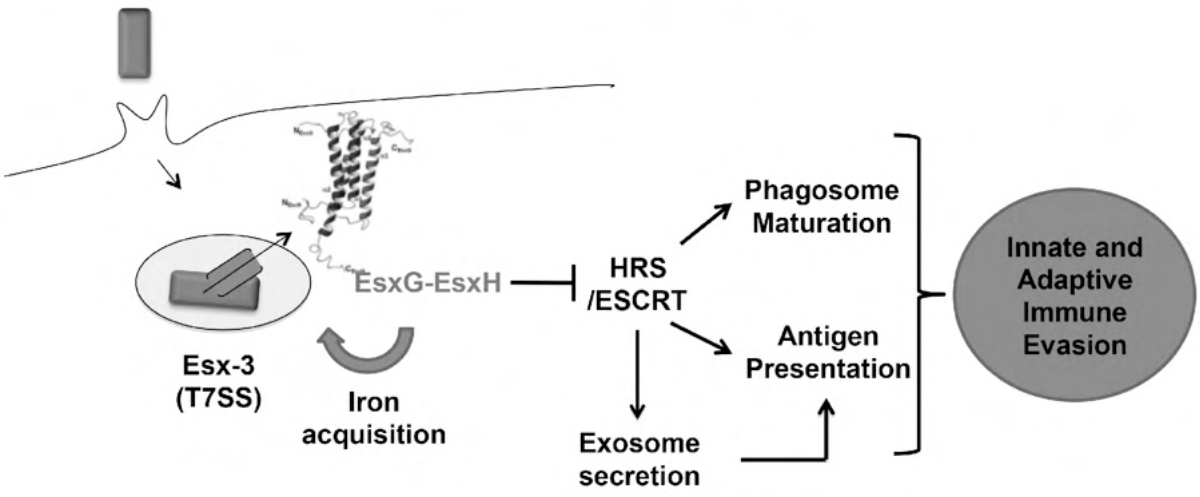
Mycobacterium tuberculosis (Mtb) is able to evade innate and adaptive immune responses to survive within the human host. Understanding Mtb's immune evasion strategies is critical to designing an effective vaccine. We showed previously that the Mtb secreted effector EsxH (also known as TB10.4) is required for virulence, and it contributes to Mtb's ability to impair phagosome maturation and inhibit MHC II antigen presentation. EsxH impairs the ability of CD4+ T cells to recognize infected macrophages and clear Mtb. Thus, EsxH may underlie the failure of vaccine efforts focused on augmenting CD4+ T cell responses. EsxH inhibits host hepatocyte growth factor-regulated tyrosine kinase substrate (HGS/HRS), a component of the endosomal-sorting complex required for transport (ESCRT). In addition to its role in lysosomal trafficking, ESCRT is also important in exosome production. Consistent with our finding that EsxH inhibits ESCRT, our data demonstrate that exosome production is enhanced in macrophages and dendritic cells infected with ΔesxH mutant as compared to wt Mtb. This suggests that in addition to inhibiting antigen presentation in infected cells, EsxH also impedes antigen transfer to bystander cells by altering exosomes. Given the importance of EsxH in immune evasion, we sought to gain mechanistic insight into how EsxH inhibits HRS. Comparing infection of wt Mtb with an ΔesxH mutant by immunofluorescence and immuno-electron microscopy, we found that HRS redistributes from endosomal membranes to the cytosol during infection, which depends upon EsxH. Downstream ESCRT components are also redistributed during infection in an EsxH-dependent manner. Ongoing work involves defining how EsxH causes the cellular redistribution of HRS/ESCRT. By understanding the mechanism of action of EsxH and the immune evasion strategies of Mtb, we might identify ways to interfere both therapeutically and within the context of a vaccine, thereby promoting immune-mediated clearance of Mtb.

**Funding Sources and Conflicts of Interest:** This research was supported by Washington University in St. Louis through NIH grant (R01 AI087682) to Dr. Jennifer Philips.

**Graphical representation of abstract**




The Esx-3 T7SS secretes EsxG and EsxH as a heterodimer which is required for iron acquisition by Mtb. EsxG-EsxH inhibit ESCRT, thereby impairing phagosome maturation, exosome secretion, and MHC-II antigen presentation.

## OA-02

### Elevated cyclic AMP inhibits Mycobacterium tuberculosis-stimulated T cell IFN-γ secretion through type I protein kinase A

**Buka Samten**[1], Yoon-tae Chung[1], Virginia Pasquinelli[2], Xisheng Wang[1], Na Yi[1], Garcia[3,4], Ramakrishna Vankayalapati[1], *[1]Department of Pulmonary Immunology, University of Texas Health Science Center, Texas, [2]Centro de Investigaciones y Transferencia del Noroeste de la Provincia de Buenos Aires, Universidad Nacional del Noroeste de la Provincia de Buenos Aires, Argentina [3]Departamento de Química Biológica. Facultad de Ciencias Exactas y Naturales. UBA, Ciudad Universitaria, Argentina [4]Universidad de Buenos Aires. Consejo Nacional de Investigaciones Científicas y Técnicas. Instituto de Química Biológica de la Facultad de Ciencias Exactas y Naturales. Facultad de Ciencias Exactas y Naturales. Ciudad Universitaria, Argentina*

Cyclic AMP (cAMP) is critical in immune regulation, and Mycobacterium tuberculosis (Mtb) intoxicates macrophages by its cAMP secretion. To examine the role of cAMP in immune response to Mtb infection, we determined cAMP levels in peripheral blood mononuclear cells (PBMC) from tuberculosis patients and the mechanisms for its suppression of T cell IFN-γ production. PBMC from tuberculosis patients contained significantly higher cAMP levels than their latent tuberculosis infected controls (LTBI), with an inverse correlation with Mtb-stimulated IFN-γ production. The expression of cAMP response element binding protein (CREB), activating transcription factor (ATF)-2 and c-Jun were reduced in tuberculosis patients compared with LTBI. cAMP analogs inhibited Mtb-induced IFN-γ production by PBMC in a PKA type I, but not PKA type II or EPAC (early exchange protein directly activated by cAMP) dependent manner. PKA type I specific cAMP analogs markedly suppressed Mtb-induced IFN-γ promoter binding activities and expression of CREB, ATF-2, and c-Jun as determined by gel shift assay and western blotting, respectively. Consistent with this, miR155, the target miRNA of these transcription factors was reduced by cAMP. Neutralizing both IL-10 and TGF-β1 or supplementation of IL-12 restored cAMP-suppressed IFN-γ production. We conclude that increased cAMP inhibits T-cell IFN-γ production through PKA type I pathway.

**Funding Sources and Conflicts of Interest:** This study was supported by the funds from the NIH grant (1R56AI116864) and the University of Texas Health Science Center at Tyler, Texas USA

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## OA-03

### A TOLLIP deficiency allele, rs5743854, is associated with decreased lncRNA TOLLIP-AS1 expression, BCG-specific T-cell memory phenotypes, and increased TB susceptibility

**Javeed Ali Shah**[1], Munya Musvosvi[3], Muki Shey[3], Robyn Emery[1], Glenna J. Peterson[1], Willem A. Hanekom[3], Thomas J. Scriba[3], Mark Hatherill[3], Thomas R. Hawn[1]

*[1]University of Washington School of Medicine, USA; [2]Puget Sound VA Health Care System, USA; [3]South African Tuberculosis Vaccine Initiative and Division of Immunology, Department of Pathology, University of Cape Town, South Africa*

**Background:** The molecular mechanisms that regulate tuberculosis (TB) susceptibility and BCG-induced immunity are mostly unknown. TOLLIP is a ubiquitin-binding protein that directly regulates host immune responses, but how it influences TB immunity is unknown. The TOLLIP SNP rs5743854 G/G genotype is associated with TOLLIP deficiency, hyperinflammation, and increased TB susceptibility. However, how this genotype influences TOLLIP expression and BCG-specific adaptive immune responses is uncertain. We hypothesized that rs5743854 influences the expression of TOLLIP-AS1, a long noncoding antisense RNA upstream of TOLLIP, and this RNA acts as an enhancer for TOLLIP promoter activity to influence BCG immune responses in infants

**Methods**: Vaccine responses from 174 South African infants was measured. shRNA knockdown was conducted on THP-1 cells. Gene expression was measured using rtPCR.

**Results:** Rs5743854 G/G genotype was associated with decreased TOLLIP-AS1 expression in monocytes of South African infants ($p = 0.04$, recessive genetic model), and TOLLIP and TOLLIP-AS1 expression were strongly correlated with each other ($R2 = 0.87$ in

adults, 0.39 in South African infants). Knockdown of TOLLIP-AS1 also significantly diminished TOLLIP expression ($p < 0.001$, Students' t-test). rs5743854 G/G genotype was associated with decreased frequency of BCG-specific IL-2+ cells 10 weeks after vaccination ($p = 0.022$, recessive genetic model) and fewer BCG-specific central memory T cells in the peripheral blood among BCG-specific IL-2+ and TNF+ CD4+T cells, ($p = 0.01$, partial permutation test).

**Conclusions:** TOLLIP-AS1 influences expression of TOLLIP, and rs5743854 G/G genotype is associated with decreased expression of both TOLLIP and TOLLIP-AS1. Rs5743854 G/G was associated with decreased BCG-specific T cell memory subsets and increased susceptibility to TB. This work is the first description of long noncoding RNA associated with vaccine responses and TB susceptibility.

**Funding Sources and Conflicts of Interest:** Funding Sources: NIH, Wellcome Trust. Conflicts of Interest: none

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# OA-04

## Pulmonary mucosal BCG vaccination shows protection of infection in a novel repeated ultra-low dose challenge model in rhesus macaques

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We have previously demonstrated that pulmonary mucosal administration of BCG provides protection of disease in a cohort of rhesus macaques in which standard intradermal BCG vaccination fails. In that study, infectious challenge comprised a single, high-dose inoculum of 500 CFU of M.tuberculosis strain Erdman.

Here we report on an alternative study design comprising repeated ultra-low dose (RULD) infection in highly susceptible rhesus such that infection becomes a stochastic event over time. Using the same fixed number of challenges for all animals, three groups in a proof-of-concept study received either a standard human dose of BCG by intradermal injection or by pulmonary instillation using a bronchoscope, or were left untreated prior to infection.

IGRA conversion post-infection by IFNg ELISPOT upon M.tuberculosis specific stimulation of PBMC in vitro, was significantly delayed by pulmonary over intradermal BCG, which did not significantly delay IGRA conversion compared to unvaccinated controls. Concordantly, post-mortem evaluation at fixed endpoint showed that pulmonary BCG vaccination significantly reduces lung pathology and draining hilar lymph node involvement in comparison to intradermal BCG, which in this study also showed a significant signal of protection of disease relative to unvaccinated controls. Further findings from clinical, pathological, bacteriological, PET/CT and immunological analyses will be discussed.

Our data demonstrate that (stochastic) RULD infection in rhesus for the evaluation of new vaccine regimes by readout for protection of infection - complementary to protection of disease - is feasible. Importantly, this vaccination-infection experiment in non-humane primates further corroborates our previous finding in a high-dose challenge study and strengthens the case for pursuing improved TB vaccination by developing local (pulmonary) mucosal administration strategies.

**Funding Sources and Conflicts of Interest:** Work supported through the TuBerculosis Vaccine Initiative (TBVI) under the TBVAC2020 Project, grant agreement No. 643381 from the European Commission, and in part under a 2017 grant from the Norwegian Agency for Development Coordination (NORAD); for PET/CT analysis through an infrastructure grant O

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## OA-05

### Memory, activation and functional profiles of Mycobacterium tuberculosis-specific CD4 T cells in recent QFT converters

**Cheleka Anne-Marie Mpande,** Virginie Rozot, Hassan Mahomed, Willem Hanekom, Mark Hatherill, Elisa Nemes, Thomas J. Scriba
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**Background:** An improved understanding of primary T cell responses during the early stages of Mycobacterium tuberculosis (M.tb) infection in humans is critical to inform vaccine strategies. We aimed to determine the kinetics of memory, activation and functional features of M.tb-specific CD4 T cells during and after acquisition of M.tb infection.

**Methods:** We studied immune responses to natural M.tb infection in PBMCs from a longitudinal adolescent cohort of recent QuantiFERON (QFT) converters with no evidence of M.tb-sensitisation at baseline (n=41). M.tb-specific CD4 T cells were detected by flow cytometry using MHC-class II tetramers bearing Ag85, CFP-10 and ESAT-6 peptides, or by intracellular cytokine staining after PBMC stimulation with M.tb antigens. Expression of memory markers, HLA-DR, CXCR3, KLRG1 and functional markers (IFN-γ, IL-2, TNF-α, CD40L and CD107a) was measured on M.tb-specific CD4+ T cells.

**Results:** M.tb-specific tetramer+ (Mtb-tet+) CD4 T cells were not detected before M.tb infection. Acute M.tb infection (within 6 months of QFT conversion) was marked by higher expression of the activation marker HLA-DR on M.tb-tet+ CD4 T cells, compared to established infection (12-18 months post-conversion). HLA-DR+ M.tb-tet+ CD4 T cells were predominantly effector memory. However, HLA-DR- M.tb-tet+ CD4 T cells, predominantly central memory (TCM), were present during acute infection and significantly increased during established infection. Analysis of the functional profiles, and CXCR3 and KLRG1 expression of M.tb-specific CD4 T cells in recent QFT converters is currently on-going.

**Discussion and Conclusion:** Highly activated M.tb-specific CD4 T cells during acute M.tb infection suggest high levels of bacterial replication. This is followed by an increase in resting M.tb-specific TCM CD4 T cells during established infection, suggestive of lower levels of antigenic stimulation, consistent with persistent but more contained bacterial replication.

**Funding Sources and Conflicts of Interest:** Funding: South African Medical Research Council and US National Institutes of Health

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## OA-06

### Protein kinase G confers survival advantage to Mycobacterium tuberculosis during latency like conditions

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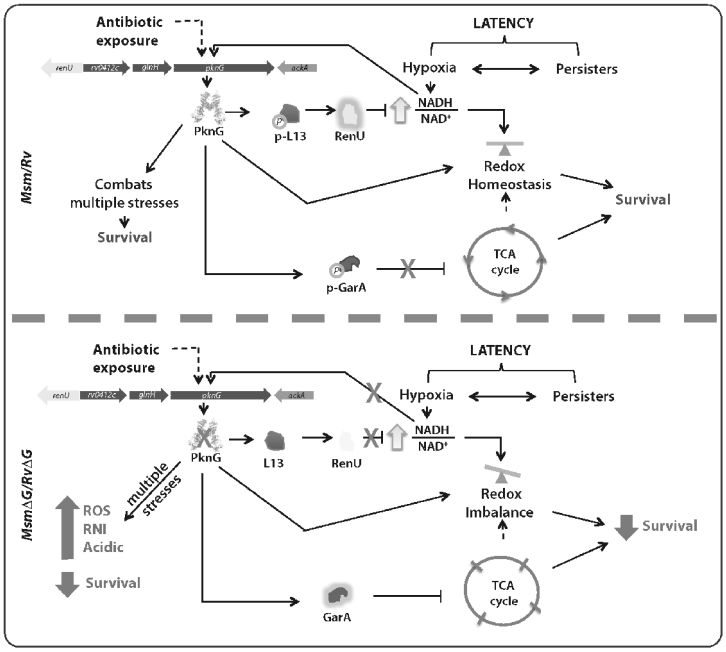
Tuberculosis (TB), though curable, is the leading cause of death from bacterial diseases. Eradication of TB, caused by Mycobacterium tuberculosis (Mtb), has been a challenge due to its uncanny ability to survive latently inside the host granulomas for decades. Mtb rewires its metabolic and redox regulatory circuits to survive in hostile hypoxic and nutrient limited environment, and become drug tolerant to resist clearance. Protein Kinase G (PknG), a thioredoxin-fold containing serine/threonine protein kinase in Mtb, is required for inhibition of phago-lysosomal fusion. Recently, we unravelled novel functional facets of PknG during latency like conditions. We find that PknG mediates persistence under stressful conditions like hypoxia and abets drug tolerance. PknG mutant displayed minimal growth in nutrient limiting conditions suggesting its role in modulating cellular metabolism. Intracellular metabolic profiling revealed that PknG is necessary for efficient metabolic adaptation during hypoxia. Notably, PknG mutant exhibited reductive shift in mycothiol redox potential (EMSH) and compromised stress response. Exposure to antibiotics and hypoxic environment resulted in higher oxidative shift in EMSH of

PknG mutant compared with the wild type. Persistence during latency like conditions required kinase activity and thioredoxin motifs of PknG and is mediated through phosphorylation of a central metabolic regulator GarA. Finally, using guinea pig model of infection, we assessed the in-vivo role of PknG in disease pathology and established a role for PknG in stable granuloma formation, hallmark structures of latent tuberculosis. Taken together, PknG mediated GarA phosphorylation is important for maintenance of mycobacterial physiology and redox poise, an axis which is dispensable for survival under normoxic conditions but is critical for non-replicating persistence of mycobacteria. In conclusion, we propose that PknG likely acts as modulator of latency-associated signals.

**Funding Sources and Conflicts of Interest:** This work was supported by the funding provided by Department of Biotechnology (DBT), Government of India (BT/PR5557/Med/29/526/2012) to VKN.

Figure 6




# OA-07

## DAR-901: an inactivated whole cell NTM booster vaccine

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**Background:** The DAR-901 booster represents inactivated Mycobacterium obuense (MO), an environmental non-tuberculous mycobacterium, and is designed to simulate the protection afforded by polyantigenic exposure to organisms in the mycobacterial genus. As an inactivated vaccine it does not require replication to boost BCG.

**Methods:** The original agar-grown MO, SRL-172, demonstrated efficacy in a randomized, controlled Ph3 trial among 2000 HIV-positive subjects in Tanzania. A scalable, agar-grown manufacturing method was developed for MO DAR-901.

**Results:** Pre-clinical studies established the safety of DAR-901 and an animal challenge study demonstrated that a DAR-901 booster provided superior protection to a BCG booster. A US Ph1 trial in 59 adults with prior BCG resulted in the selection of a 1 mg dose for further clinical trials. The trial demonstrated safety and tolerability in HIV-negative, HIV-positive, IGRA-negative and IGRA-positive subjects. IFN responses to the vaccine antigen and to LAM antibody were demonstrated. A Ph2b Prevention of Infection randomized, controlled trial is underway among 650 BCG-positive, IGRA-negative adolescents age 13-15 in Tanzania. All subjects have received 3 doses of vaccine or placebo with acceptable tolerability and safety. The primary endpoint is conversion to a positive IGRA and the secondary endpoint is conversion to a persistently positive IGRA. Repeat IGRAs have been obtained at 2 months (3% conversion) and at 12 months (1.5% conversion) and will be obtained again at 24 months. Post-dose 3 samples have been obtained for RNA expression assays.

**Discussion:** A 3-dose intradermal series of the polyantigenic whole cell DAR-901 booster is safe and well tolerated in adolescents and adults. Cellular and humoral immune responses have been comparable to those observed with SRL172 in the prior Ph3 trial. DAR-901 will advance to a Ph3 Prevention of Disease trial with a target start date in Q1 2020.

**Funding Sources and Conflicts of Interest:** Funding: The Global Health Innovative Technology Fund Conflict of Interest: None

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## OA-08

## A randomized, double-blind, dose-escalation clinical trial of MTBVAC compared to BCG Vaccine SSI, in newborns living in a tuberculosis endemic region

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**Background:** MTBVAC, a live-attenuated derivative of Mycobacterium tuberculosis, has been developed to replace newborn BCG vaccination.

**Objectives:** Evaluation of safety and immunogenicity of 3 doses of MTBVAC vs BCG in newborns in a TB endemic region.

**Methods:** Eighteen HIV-, QuantiFERON (QFT) -, previously BCG vaccinated healthy adults were randomized 1:1 to receive MTBVAC (5 x 105 CFU) or BCG SSI. Thereafter, 36 HIV-unexposed, BCG-naïve healthy newborns were randomized 1:3 to receive BCG SSI or MTBVAC at 2.5x 103, 2.5x104 , or 2.5x105 CFU within 96 h of birth. QFT was performed at D180 and D360 and QFT+ infants were referred for isoniazid preventive therapy.

**Results:** All adults experienced local injection site reactions with swelling in 18(100%), redness in 16(88.9%) and ulceration in 10 (55.5%). Nine reactions were reported as moderate and a single swelling event was severe(35mm). No SAEs were reported at D28.

Unavailability of BCG Vaccine SSI resulted in open-label dosing of 6 infants with MTBVAC at the highest dose. Sixteen (44.4%) infants across all 3 cohorts had local reactions 2[16.6%], 3[25%] and 11[91.6%]), all rated mild with swelling in 14 (38.9%), erythema in 5 (13.9%) and scarring in 9(25.0%). No ulceration was seen. Systemic AEs were similar across cohorts (n=32/42/40) with 9 graded moderate (n=3/4/2) and 8 severe (n=4/2/2). Six infants experienced 7 unrelated SAEs including an unrelated death due to viral pneumonia, confirmed by autopsy.

Dose-related QFT conversion was noted at D180 in MTBVAC recipients in Cohort 1:(n=3, 37.5%), Cohort 2(n=6, 75%) and Cohort 3 (n=7, 77.8%), but in zero of 7 BCG recipients. A positive QFT at D360 was seen in 0 Cohort 1 MTBVAC recipients (0.0%), 2 in Cohort 2 (25.0%) and 4 in Cohort 3(44.4%).

**Conclusion:** MTBVAC appeared safe at 3 dose levels in South African newborns; and appeared to result in transient dose-dependent QFT conversion, which may be an encouraging indicator of immunogenicity in TB endemic regions.

**Funding Sources and Conflicts of Interest:** Biofabri, SL funded the trial IM, JD, EP are employees of Biofabri CM is co-inventor in a patent application on MTBVAC filed by the University of Zaragoza

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# OA-09

## Clinical development of ID93+GLA-SE as a prophylactic or therapeutic vaccine for tuberculosis

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**Background:** IDRI has developed the candidate tuberculosis (TB) vaccine, ID93+GLA-SE, a tetravalent fusion protein combined with the Toll-like Receptor 4 agonist adjuvant GLA-SE. Preclinical studies show that prophylactic vaccination with ID93+GLA-SE induces long-lived protection against TB and post-exposure vaccination in combination with antibiotics promotes more rapid bacterial clearance than antibiotics alone.

**Methods:** A series of Phase 1/2 clinical trials have been conducted to evaluate safety and immunogenicity for immunization with ID93+GLA-SE in a variety of populations including BCG naïve, BCG-vaccinated, QFT-, QFT+, and in TB patients upon completion of treatment.

**Results:** A first-in-human Phase 1 trial that administered ID93 alone or in combination with GLA-SE in BCG-naïve, unexposed US adults demonstrated an acceptable safety profile and a Th1 cellular and humoral response. A Phase 1b trial evaluated enrolled BCG-vaccinated adults in South Africa with or without latent TB infection. ID93+GLA-SE was safe in this endemic population and induced durable CD4+ T-cell and humoral responses. The vaccine induced CD4 T cells with a diverse spectrum of phenotypes and robust levels of IgG1 and IgG3. These results led to a Phase 2a trial in TB patients at the end of antibiotic treatment. This trial is completed; no safety concerns have arisen and immunogenicity was confirmed in an interim analysis.

**Conclusions and Discussion:** Based on demonstrated safety and immunogenicity, ID93+GLA-SE is being advanced to efficacy testing. Phase 2 trials in BCG vaccinated QFT- healthcare workers are also planned in Seoul, South Korea. Phase 1 and 2 studies in India are planned in which the vaccine will be evaluated in individuals with latent TB infection, drug-susceptible pulmonary TB patients, and multidrug-resistant TB patients.

**Funding Sources and Conflicts of Interest:** These studies were funded by Aeras, the Paul G Allen Family Foundation, and the Wellcome Trust.

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# OA-10

## Use of oral inactivated Mycobacterium manresensis to reduce the risk of TB

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Oral administration of heat-killed Mycobacterium manresensis bacilli (hkMm) triggers a beneficial response in the intestinal epithelium characterized by its anti-oxidant and anti-inflammatory activities, demonstrated in experimental models in Caenorhabditis elegans and Drosophila melanogaster. It is also able to promote the induction of a diverse, protective microbiota in the C3HeB/FeJ mice, were it has proven its capacity to stop the progression towards active TB. Oral administration of 10^5 hkMm daily for 14 days allows the induction of a balanced immune response related to the increase of Tuberculin Purified Protein Derivative (PPD) memory-specific Tregs (CD4+CD25+CD39+ cells), IL-10 and IFN-g in the spleen. It reduces de IL-17 and IL-6 levels in the lungs, together with the bacillary load, and the pathology (granulomatous and neutrophilic infiltration.

A double-blind placebo-controlled clinical trial (CTs) has been done in adults administering 10^5 hkMm daily for 14 days. The NYADATREG study (Clinicaltrials.gov identifier NCT02076139; 2013-2014) has demonstrated an excellent safety record and detected a significant increase in PPD-specific memory Tregs. The NYADAPETRICS study (Clinicaltrials.gov identifier NCT02581579) is also running in the pediatric population looking for the same parameters.

An efficacy study is running since March 2017 in Tbilisi, Georgia. The NYADAGEORG (randomized, double-blinded, placebo-controlled, n=3300) recruits close contacts of active TB cases with positive sputum not tributaries of chemoprophylaxis (<5-year-old children and HIV-positive individuals). A 40% reduction in active TB incidence is expected (Clinicaltrials.gov identifier NCT02897180).

Oral administration of hkMm appears to be a new, easy, safe, and reliable method for reducing the risk of developing active TB.

Currently is being registered as supplement food in several countries.

**Funding Sources and Conflicts of Interest:** PJC is a funder of Manremyc, a spin-off of the IGTP to develop hk-M.manresensis

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# OA-11

## Phase III, placebo-controlled, 2:1 randomized, double-blinded trial of tableted immunotherapeutic TB vaccine (V7) containing 10 microgram of heat-killed M. vaccae

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*Immunitor LLC, Mongolia*

**Introduction:** Heat-killed Mycobacterium vaccae TB vaccine has shown promising results in multiple clinical trials, but due to inconvenience of parenteral delivery it has not been adopted commercially, except in China. Orally delivered vaccine (V7) has been demonstrated in prior Phase II trials to be safe and fast-acting immune adjunct when given with TB drugs [1,2].

**Materials and Methods:** Interim results of Phase III trial of tableted therapeutic TB vaccine containing 10 µg of hydrolyzed M. vaccae (NCTC 11659) were analyzed in 152 patients randomized at 2:1 ratio: V7 (N=100): placebo (N=52). Both arms received conventional 1st or 2nd line anti-TB chemotherapy co-administered with daily pill of V7 or placebo. Patients had four categories of TB: (1) drug-sensitive (DS); (2) multi-drug-resistant (MDR); (3) TB/HIV, and (4) extensively drug-resistant (XDR) distributed in V7 and placebo at 45:45:9:1 and 22:20:9:1 ratios.

**Results:** After one month mycobacterial clearance in sputum smears was observed in 68% (P<0.0001) and 23.1% (P=0.04) of patients on V7 and placebo. Stratified conversion rates in V7 recipients with DS and MDR were 86.7% and 55.6% vs. 27.2% and 15% in placebo. Sputum conversion correlated with weight gain in V7 recipients: 2.4 kg (P<0.0001) vs. 0.3 kg (P=0.18) in placebo. Improvement in hemoglobin levels, erythrocyte sedimentation rate and leukocyte counts was significantly better than in placebo - indicative of anti-inflammatory activity of V7. Liver function tests revealed that V7 prevented chemotherapy-induced hepatic damage.

**Conclusion**: Oral M. vaccae is safe and can overcome TB-associated weight loss and inflammation; reduce hepatotoxicity of TB drugs; improve three-fold sputum conversion rate; and shorten treatment duration by at least six-fold.

**References:** 1 Efremenko et al. Hum Vaccin Immunother 2013;9:1852-6; 2 Butov et al. Immunotherapy 2013;5:1047-54

**Funding Sources and Conflicts of Interest:** Grant #0532 Grand Challenges Canada

Table 1. The interim results of Phase III one-month trial of daily oral *M. vaccae* as an immune adjunct in TB therapy

| Arm | N | Gender F/M | Age | Height (cm) | Diagnosis | Sputum conversion (%) | Weight (kg) | | Hg (g/L) | | ESR (mm/h) | | WBC (x10⁹L) | | Lymphocytes (%) | | ALT (mM/h/ml) | | AST (mM/h/ml) | | Bilirubin (µM/L) | | Protein (g/L) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Before | after | before | after | before | after | before | after | Before | after | before | after | before | after | before | after | before | after |
| V7 | 100 | 26/74 | 39.3 ±11 | 172.1 ±6.6 | DS=45 MDR=45 XDR=1 TB/HIV=9 | DS=86.7 MDR=55.6 XDR=0 TB/HIV=44.4 | 64.2 ±8.3 | 66.6 ±8.2 | 132 ±17.8 | 136.9 ±14.7 | 18.2 ±11.9 | 12.4 ±9 | 8.95 ±3.8 | 7.45 ±2.3 | 26.4 ±7.0 | 26.8 ±5.6 | 0.34 ±0.15 | 0.33 ±0.21 | 0.16 ±0.09 | 0.17 ±0.07 | 11.4 ±2.4 | 13.7 ±3.4 | 73.8 ±5.1 | 74.6 ±5.6 |
| | | | | | | | P<0.0001 | | P=0.001 | | P<0.0001 | | P<0.0001 | | P=0.54 | | P=0.65 | | P=0.41 | | P<0.0001 | | P=0.048 | |
| Placebo | 52 | 7/45 | 39.6 ±9.9 | 172.9 ±7.0 | DS=22 MDR=20 XDR=1 TB/HIV=9 | DS=27.2 MDR=15 XDR=0 TB/HIV=33.3 | 61.5 ±10.7 | 61.8 ±10.5 | 129.2 ±14.9 | 127.2 ±16.9 | 16.9 ±11.7 | 17.4 ±13.4 | 8.1 ±2.4 | 7.9 ±2.8 | 27.8 ±5.7 | 29.3 ±5.3 | 0.44 ±0.49 | 0.61 ±0.68 | 0.14 ±0.05 | 0.18 ±0.07 | 11.4 ±2.6 | 14.4 ±3.5 | 74.6 ±6.3 | 75.0 ±5.7 |
| | | | | | | | P=0.18 | | P=0.39 | | P=0.77 | | P=0.49 | | P=0.02 | | P=0.03 | | P=0.009 | | P=0.003 | | P=0.93 | |

# OA-12

## Randomized open phase 1 trial of TB/FLU-01L vaccine administrated intranasally or sublingually for immunotherapy of pulmonary tuberculosis

**Marina Stukova**[1], Berik Khairullin[2], Maira Zhaparkulova[3], Maria Pisareva[1], Janna Buzitskaya[1], Anna-Polina Shurygina[1], Marhabat Kassenov[2], Nurlan Sandybaev[2], Ainur Nurpeisova[2], Gulbanu Sarsenbaeva[2], Nikolay Bogdanov[2], Eugeny Volgin[2], Timur Isagulov[2], Tleuhan Abildaev[3], Sansyzbay Abylai[2]

[1]*Research Institute of Influenza, Russia,* [2]*Research Institute for Biological Safety Problems, Republic of Kazakhstan,* [3]*National Center of Tuberculosis Problems, Republic of Kaakhstan*

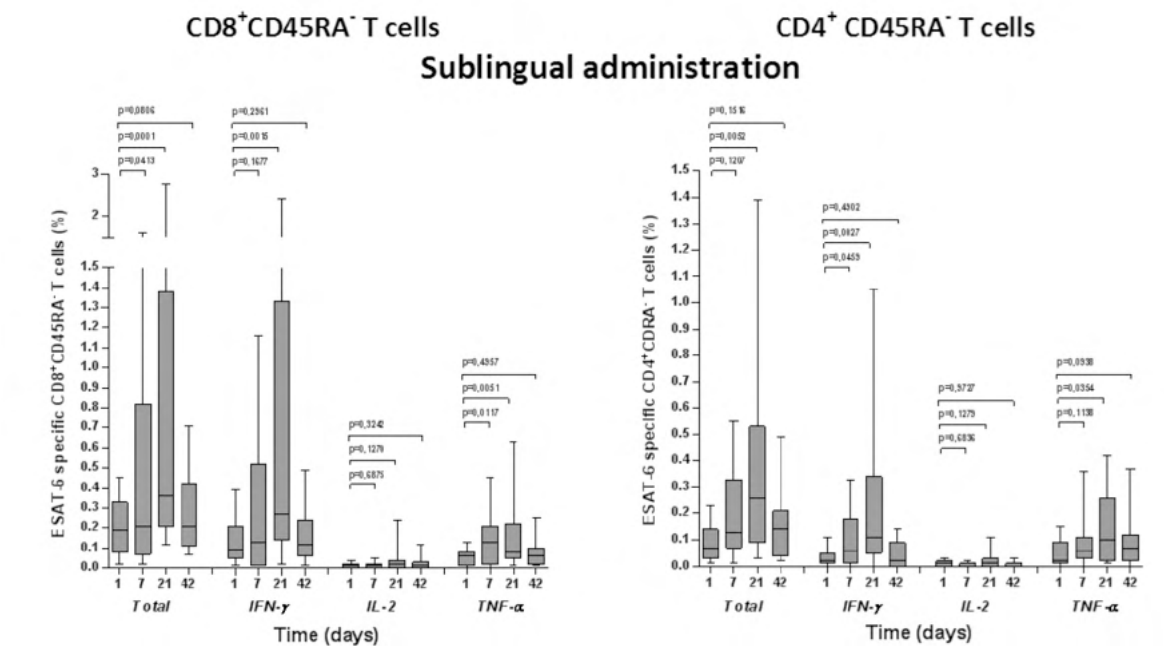
**Background:** This study was undertaken to evaluate safety and immunogenicity of TB/FLU-01L influenza vector based tuberculosis vaccine expressing mycobacterium antigen ESAT-6. In our vaccine construct we used optimal influenza virus vector backbone providing a replicating-deficient phenotype and containing partial NS1 deletion followed by tuberculosis antigen sequence. The obtained vector induced a substantial immunotherapeutic effect in animals with pre-established tuberculosis infection and had a strong synergistic effect with TB chemotherapy treatment.

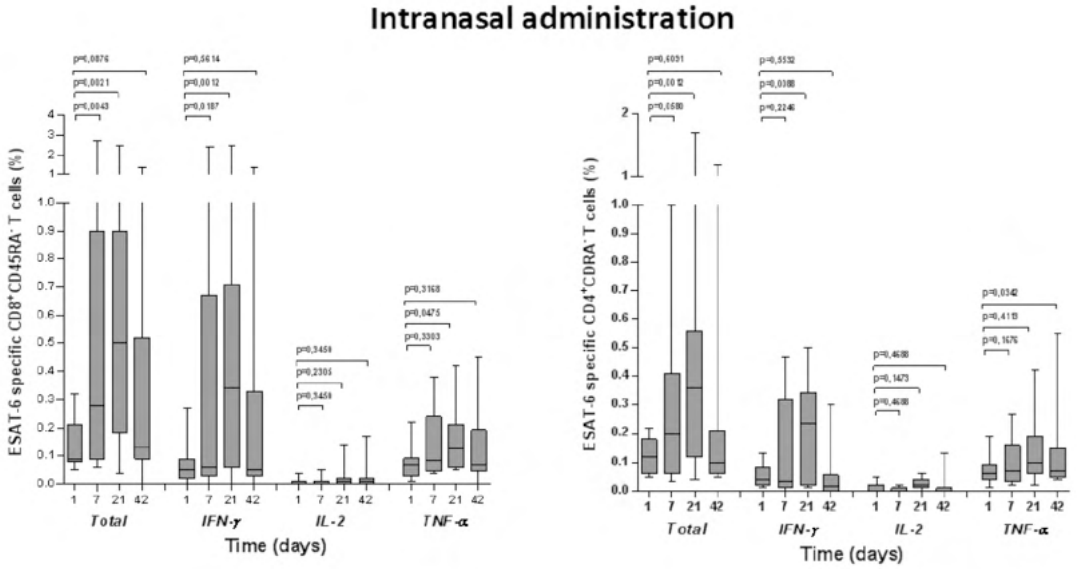
**Methods:** 36 healthy adults from 18 to 50 years old previously immunized with BCG were vaccinated twice 21 days apart through intranasal or sublingual route at 1:1 ratio. Subjects were closely monitored 7 days after each vaccination for follow-up of reactogenicity, adverse events and viral shedding. Ag-specific CD4 and CD8 T-cell memory response was measured by intracellular cytokine staining in whole blood collected at Days 1, 7, 21 and 42.

**Results:** Influenza vector vaccine administered intranasally or sublingually had an acceptable safety profile and was well tolerated. Vaccination induced statistically significant CD4+ and CD8+ memory T-cell response in both groups by increasing the number of IFN-γ and TNF-α producing cells. IL-2 response was relatively low showing no significant elevation in both groups. Overall, 72.2% of subjects from sublingual group and 77.8% of subjects from intranasal group were considered as "responders" (defined as any cytokine response at any time point). ESAT-6 specific IFN-γ producing CD8+ T cells response was higher in intranasal group, while TNF-α production by this cell population was higher in sublingual group. In both groups CD8+ memory (CD45RA-) T cell response predominated.

**Conclusion:** Two doses of TB/FLU-01L vaccine were well tolerated in healthy BCG-vaccinated adults. Potential of sublingual vaccine delivery as an alternative to the intranasal route was demonstrated.

**Funding Sources and Conflicts of Interest:** None






## OA-13

## Stress-response deficient attenuated Mycobacterium tuberculosis as next-gen TB vaccines

**Deepak Kaushal**[1], Smriti Mehra[2], Taylor W. Foreman[1,3], Allison N. Bucsan[1,3], Shabaana A. Khader[4], Jyothi Rengarajan[5], William R. Jacobs[6]

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**Background:** Novel anti-tuberculosis (TB) vaccines are urgently needed. Failure to replace BCG with efficacious anti-TB vaccines has prompted out-of-the-box thinking, including pulmonary vaccination to elicit local immunity. It has also been argued that attenuated Mtb may afford protection against TB due to their ability to elicit responses to the virtually entire array of bacterial antigens. Furthermore, strains deficient in bacterial counter-immune strategies could elicit even stronger (and wider) immune responses.

**Methods:** We assessed the efficacy of a Mtb stress-response deficient mutant attenuated in the nonhuman primate model of TB, as a potential vaccine. While live mycobacterial vaccines show promising efficacy, HIV co-infection and the resulting immunodeficiency prompts safety concerns about their use. We therefore also assessed the persistence and safety of ΔsigH, delivered directly to the lungs, in the setting of HIV coinfection.

**Results:** Aerosol immunization of macaques with a Mtb mutant in sigH (ΔsigH), that is unable to scavenge oxidative stress resulted in enhanced recruitment of lymphoid follicles as well as activated and proliferating CD4+s and CD8+s to the lungs. Vaccination with ΔsigH significantly protected against a lethal TB challenge, evidenced by ~3-logs reduction in bacterial burdens, significantly diminished clinical manifestations and granulomatous pathology. When vaccinated animals were subsequently co-infected with SIVmac239, all macaques remained asymptomatic of pulmonary TB. Thus, non-pathological infection of macaque lungs by ΔsigH was not reactivated by SIV, despite high viral titers and massive ablation of pulmonary CD4+s. Protective pulmonary responses were retained, including CD8+ effector memory cells and lymphoid follicles.

**Discussion:** These findings highlight the efficacy and safety following mucosal vaccination with ΔsigH and pave the way for its further development as a vaccine to potentially combat TB in HIV endemic areas.

**Funding Sources and Conflicts of Interest:** R01AI134240; R01AI111914; R01AI111943;

# OA-14

## Mechanisms of attenuation and protection of MTBVAC, a live attenuated tuberculosis vaccine moving to efficacy clinical trials

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**Background**: The only vaccine against TB today in use, BCG (a live-attenuated strain of Mycobacterium bovis) offers variable protection against the respiratory forms of TB. MTBVAC is a new TB vaccine candidate, based on a rational attenuation of an M. tuberculosis clinical isolate by inactivation of transcriptional factor phoP and fadD26 genes, both essential for M. tuberculosis virulence. MTBVAC conserves all the genomic regions absent in BCG, and therefore it expresses the whole repertoire of T cell epitopes described for TB, including the major immunodominant antigens of the RD1 region: ESAT6 and CFP10, absent in BCG.

**Objective:** After almost 20 years of discovery and preclinical development, MTBVAC is the only live attenuated vaccine based on the human pathogen that has successfully entered clinical trials as a preventive vaccine. Our studies are focused to decipher the molecular mechanisms of attenuation and protection of MTBVAC in order to support the acceleration of efficacy clinical trials.

**Methods:** Construction of MTBVAC-derived mutants. Global proteomic and genomic analysis. Immunology studies in animal models.

**Results:** Preclinical studies have demonstrated that MTBVAC-induced immunity to ESAT6 and CFP10 correlate with improved efficacy relative to BCG. This finding encourages exploration of inmune responses against these antigens as potential biomarkers and possible correlates of vaccine-induced protection in human clinical trials.

**Conclusions:** We have identified possible correlates of vaccine-induced protection. Such data would be extremely valuable as they would greatly accelerate clinical development to efficacy trials.

**Funding Sources and Conflicts of Interest:** Funding: Spanish Ministry of Economy and Competitiveness (BIO2014-5258P) and the European Commission H2020 program (TBVAC2020 643381). Conflict of Interest: CM and JGA are co-inventors of the patent 'tuberculosis vaccine' owned by the University of Zarag

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# OA-15

## Increased efficacy of chemotherapy against Mycobacterium tuberculosis by additive immunotherapy using a multistage MVA vaccine

**Stéphane Leung-Theung-Long**[1], Marie Gouanvic[1], Charles-Antoine Coupet[1], Doris Schmitt[1], Aurélie Ray[1], Chantal Hoffmann[1], Huguette Schultz[1], Paul J. Converse[2], Lilibeth Arias[3], Benoît Sansas[1], Cris Villaplana[3], Pere-Joan Cardona[3], Khisimuzi Mdluli[4], Eric Nuermberger[2], Jean-Baptiste Marchand[1], Nathalie Silvestre[1], Geneviève Inchauspé[1]

*[1]Transgene SA, France, [2]Johns Hopkins University, USA, [3]Fundació Institut Germans Trias i Pujol, Universitat Autònoma de Barcelona, Spain; [4]Global Alliance for Tuberculosis Drug Development, USA*

Despite the existence of the prophylactic Bacille Calmette-Guérin (BCG) vaccine, infection by Mycobacterium tuberculosis (Mtb) remains a major public health issue causing up to 1.8 million yearly deaths worldwide. Increasing cases of Mtb strains resistant to antibiotics represent a threat for global health that has resulted in the search for alternative treatment regimens not subject to development of resistance. Immunotherapy constitutes a promising approach to improving current antibiotic-based treatments through enrollment/re-education of the host's immune system.

We have designed a multi-antigenic and multiphasic vaccine, based on the Modified Vaccinia Ankara (MVA) virus, denoted MVATG18598, which expresses ten antigens representative of each of the three phases of Mtb infection (active, latent and resuscitation). In vitro analysis coupled with multiple-passage evaluation have demonstrated that this vaccine is genetically

stable i.e. fit for manufacturing. Using different mouse strains, we show that MVATG18598 vaccination results in both Th1-associated T-cell responses and cytolytic activity, targeting all 10 vaccine-expressed Mtb antigens. In chronic post-exposure mouse models, MVATG18598 vaccination in combination with an antibiotic regimen decreases significantly the bacterial burden in lungs of infected mice, compared with chemotherapy alone, and is associated with a long-lasting antigen-specific Th1-type T cell response. In one model, co-treatment with MVATG18598 was shown to prevent rebound of the disease, an important clinical goal.

These results demonstrate the capacity of the therapeutic MVATG18598 vaccine to significantly improve efficacy of chemotherapy against TB. These data support further development of this novel immunotherapeutic in the treatment of resistant infections.

**Funding Sources and Conflicts of Interest:** Funding sources: NIAID and EU H2020 / Conflicts of interest: None

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# OA-16

## Immunogenicity and efficacy evaluation of multiple ChAd3-5Ag ± MVA-5Ag prime-boost vaccine regimens in rhesus macaques

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**Background:** Aerosol (AE) delivery of a TB vaccine that directly targets the organ of infection, the lung, may potentially maximize the protective immune response locally. Here, we evaluate the immunogenicity and efficacy of different Chimpanzee adenovirus serotype 3/modified vaccinia Ankara (ChAd3/MVA) prime-boost regimens administered via parenteral [intradermal (ID), intramuscular (IM)] and aerosol routes in rhesus macaques (NHP).

**Methods:** Four groups of 10 NHPs were subjected to 2 consecutive ChAd3 primary vaccinations ± an MVA boost: a) "IM/ID", ChAd3-IM/MVA-ID; b) "IM/AE", ChAd3-IM/MVA-AE; C) "AE/AE", ChAd3-AE/MVA-AE; d) "AE", ChAd3-AE; with (e) 10 "non-v", naive controls. Both vectors express Ag85B, ESAT-6, Rv2626, Rv1733, and RpfD antigens. Immunogenicity was assessed by ICS (IFNγ, IL2 and TNFα) on PBMC and bronchoalveolar lavage (BAL) T-cells, 4 weeks post-ChAd and 2 weeks post-MVA. An IFNγ ELISpot assay was performed on PBMC. All animals were challenged with Mtb Erdman strain 12 weeks after the final vaccination. Endpoint measures include PET/CT scans every 4 weeks and gross pathology scores and lung CFU counts 12 weeks post-Mtb challenge.

**Results:** Longitudinal evaluation of TB-specific T cell responses by IFNγ ELISpot confirmed vaccine take in all groups. ICS analyses of the lung T cell response demonstrated a sustained TB-specific increase in total cytokine production only when ChAd3 is administered AE; the specific T cell responses were dominated by Ag85B-specific CD4 and RpfD-specific CD8 T-cells. Boosting with MVA AE ("ID/AE", "AE/AE") induced the highest levels of TB-specific T cell responses with improved antigenic breadth in the BALs (>20% of T cells). In contrast, the MVA ID boost "IM/ID" elicited the highest responses in PBMC samples.

**Conclusion:** Aerosol delivery of MVA boost after ChAd3 priming (AE or IM) resulted in a more robust T-cell response in the lung compared to parenteral routes. Outcomes of the Mtb challenge will be presented.

**Funding Sources and Conflicts of Interest:** None

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# OA-17

## Recombinant BCG expressing ESX-1 of Mycobacterium marinum combines low virulence with cytosolic immune signaling and improved tuberculosis protection

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**Background:** Recent insights into the mechanisms by which Mycobacterium tuberculosis is recognized by cytosolic nucleotide sensors have opened new avenues for rational vaccine design. The only licensed anti-tuberculosis vaccine, M. bovis BCG, provides limited protection. A feature of BCG is the partial deletion of the ESX-1 type VII secretion system, which governs phagosomal rupture and cytosolic pattern recognition, key intracellular phenotypes linked to increased immune signaling. Our objective was to improve protective efficacy by equipping BCG with the ESX-1 dependent phenotype of cytosolic access.

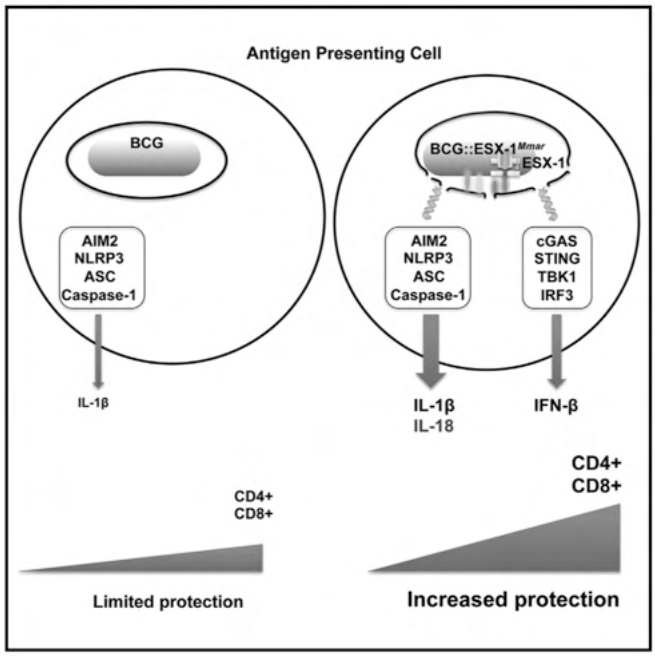
**Methods:** BCG was transformed with a vector containing the esx-1 region of Mycobacterium marinum. BCG::ESX1Mmar functionality was assessed by ESX-1 specific T-cell hybridomas. THP-1 wild-type and cGas/STING K.O. cells were used to study phagosomal access and activation of cytosolic nucleotide sensors. Mice were vaccinated to characterize cellular immunity and virulence. Independent mouse vaccination models were employed to study virulence and efficacy.

**Results:** This new ESX-1 proficient BCG can access the host cytosol and activates the cGas/STING/TBK1/IRF-3/type I interferon axis and AIM2-mediated NLRP3 inflammasome activity while maintaining low virulence. This results in both higher proportions of CD8+ T cell effectors against mycobacterial antigens shared with BCG and polyfunctional CD4+ Th1 cells specific to ESX-1 antigens. Importantly, independent mouse vaccination models show BCG::ESX-1Mmar confers superior protection relative to parental BCG against challenges with highly virulent M. tuberculosis.

**Conclusions:** We describe the virulence-neutral expression of the ESX-1 type VII secretion system of Mycobacterium marinum in BCG. The functioning ESX-1 system enables this novel vaccine candidate to rupture the phagosome and to induce cytosolic pattern recognition and dedicated immune signaling in mice, resulting in increased protection against tuberculosis.

**Funding Sources and Conflicts of Interest:** European Union's Horizon 2020 Research and Innovation Program (grant 643381 TBVAC2020), the Agence National de Recherche (grants ANR-14-JAMR- 001-02, ANR-14-CE-08-0017-04, ANR-10-LABX-62-IBEID), the Fondation pour la Recherche Me dicale FRM (DEQ20130326

Graphical Abstract



## OA-18

### Novel mucosal TB vaccine candidates generated by EMI-TB consortium

**Rajko Reljic[1],** Peter Hart[1], Alastair Copland[1], Gil Diogo[1], Andy Tran[1], Shane Harris[1], Mahavir Singh[2], Matthew Paul[1]
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Tuberculosis (TB) is the most deadly infectious disease in existence, and the only available vaccine, Bacillus Calmette-Geurin (BCG), is almost a century old and poorly protective. The immunological complexity of TB, coupled with rising resistance to antimicrobial therapies, necessitates a pipeline of diverse novel vaccines. Here, we show that B. subtilis spores can be coated with a fusion protein ('FP1') consisting of M. tuberculosis (Mtb) antigens Ag85B, ACR and HBHA. Tuberculosis (TB) is the most deadly infectious disease in existence, and the only available vaccine, Bacillus Calmette-Geurin (BCG), is almost a century old and poorly protective. The immunological complexity of TB, coupled with rising resistance to antimicrobial therapies, necessitates a pipeline of diverse novel vaccines. Here, we show that B. subtilis spores and Yc-NaMA nanoparticles can be coated with a fusion protein ('FP1') consisting of M. tuberculosis (Mtb) antigens Ag85B, Acr and HBHA. The resultant vaccines, Spore-FP1 and Nano-FP1, were tested in a murine low-dose Mtb aerosol challenge model. Mice were primed with subcutaneous BCG, followed by mucosal booster immunisations with Spore-FP1 or Nano-FP1. We show that these novel vaccine candidates enhanced pulmonary and extra-pulmonary control of Mtb, as evidenced by reduced bacterial burdens in the lungs and spleen. This was associated with elevated antigen-specific IgG and IgA titres in the serum and lung mucosal surface, respectively. Spore-FP1 and Nano-FP1 immunisations generated superior antigen-specific memory T-cell proliferation in both CD4+ and CD8+ compartments, alongside bolstered Th1-, Th17- and Treg-type cytokine production, compared to BCG immunisation alone. CD69+CD103+ tissue resident memory T-cells (Trm) were found within the lung parenchyma after mucosal immunisation, confirming the advantages of mucosal delivery. Our data show that Spore-FP1 and Nano-FP1 are promising new TB vaccine candidates that can successfully augment p (exceeded character count)

**Funding Sources and Conflicts of Interest:** European Union. No conflict of interest

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## OA-19

### NK cells and memory-like NK cells as immunological markers of protection against latent TB conversion in house hold contacts of TB patients

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House hold contacts (HHCs) of TB patients are at an increased risk of developing LTBI (Latent TB Infection) because of their continuous exposure to the bacteria. With new candidate vaccines aimed at either prevention of infection (POI) or prevention of disease (POD), there is a need for biomarkers and correlates of protection. Identification of immune biomarkers and correlates of protection would allow focused immunoprophylaxis to persons with increased risk. We determined if biomarkers can predict development of LTBI in these individuals. Subjects: Individuals living with TB cases for at least 6 months from the date of diagnosis were enrolled as HHCs. Study was approved by institutional ethical committee. HHCs were screened for HIV and an in-house QuantiFERON test was performed to determine latent TB. Subjects were evaluated after every 4 months for 2 years. Results: These observations were made regarding IL-17 levels in stimulated culture supernatants (a) The baseline levels in LTBI- HHCs who converted to LTBI+ during follow-up were significantly high compared to those who did not (p=0.02, n=25). (b) The levels were high in LTBI+ HHCs who did not develop active tuberculosis when compared to those who did (p=0.01, n=6). Baseline CD16+CD56+ and CD3-CD56+CD27+CCR7+ cell numbers were significantly high in LTBI- individuals who never converted to LTBI+ compared to those did (p=0.002, n=15).Conclusion: High IL-17 production at baseline by T-cells from HHCs who convert to latent or active TB indicates an ongoing inflammation and can be used as an early marker of conversion to latent/ active TB. We also could demonstrate differences in memory like NK cell percentages as potential markers of protection and might serve as a

tool to identify individuals at risk for conversion and in need for immuno-prophylaxis. Future studies include determining the mechanisms involved in expansion of the above identified cell population using microarray, multiplex and siRNA technologies.

**Funding Sources and Conflicts of Interest:** This project is supported by DBT, CRDF and NIH as a part of RePORT India consortium (BT/PR9622/MED/15/109/2013. Conflict of Interest: None

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# OA-20

## Gene expression profiles of pediatric tuberculosis patients and exposed controls from India

**Jeffrey A Tornheim[1],** Mandar Paradkar[2], Chhaya Valvi[3], Nikhil Gupte[2], Anil Madugundu[4,5] Vandana Kulkarni[2], Sreelakshmi Sreenivasamurthy[4,5], Remya Raja[4], Neeta Pradhan[2], Shri Vijay Bala Yogendra Shivakumar[6], Rewa Kohli[2], Akshay Gupte[1], Padmapriyadarsini Chandrasekaran[7], Vidya Mave[2], Akhilesh Pandey,[4,5] Amita Gupta[1]

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**Background and rationale:** Despite advances in TB diagnosis among adults, diagnostic tools for pediatric TB are limited. Previous attempts to diagnose TB using host gene transcription signatures have included few children, Indian patients, and microbiologically confirmed patients.

**Methods:** Samples from CTRIUMPH RePORT India, a prospective cohort of Indian adults and children with TB and their household contacts. Children <15 years with confirmed TB ("cases") from Pune, India were age- and sex-matched to 2 non-related children ("controls"). Controls were ruled out for TB by symptoms, and had negative TST and IGRAs. Whole blood was collected at enrollment, 1 mo, and 6 mo of treatment (cases), and at enrollment, 4 mo, and 12 mo (controls). TST and IGRAs were repeated during followup of controls. RNA-seq was performed by Illumina HiSeq 2500 to generate ☒170 million 100 basepair paired-end reads/sample. Differential expression analysis was conducted in R using DESeq2 with a false discovery rate of <0.05. After controlling for age, sex, site of disease (cases), and TST conversion (controls), genes exhibiting >2-fold change were considered differentially expressed.

**Results:** 16 TB cases and 32 controls were assessed. Comparison of cases to controls identified 135 upregulated genes and 29 downregulated genes, 8 had > 2-fold change (APOL4, AZU1, CTSG, DEFA3, GBP6, METTL7B, MPO, and PRTN3). Successful treatment was associated with 6 upregulated genes and 336 downregulated genes, 10 of which had ≥2-fold change in the first month (C1QC, CD177, CLRN1, ELANE, GLDN, GPR4, MMP1, MPO, PRTN3, ZG16). Comparison of results with previously published gene signatures found little overlap.

**Conclusions:** Transcriptomic analysis of confirmed pediatric TB cases and matched controls from India identified different gene signatures from those published outside of India. Further evaluation of children and distinct global populations is necessary before universal signatures can be developed.

**Funding Sources and Conflicts of Interest:** CTRIUMPH is part of the RePORT consortium funded with Federal funds from the Government of India's (GOI) Department of Biotechnology (DBT), the Indian Council of Medical Research (ICMR), USA, National Institutes of Health (NIH), USA

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## OA-21

### Evaluating immune correlates of risk of Mycobacteria tuberculosis infection in humans

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**Background:** The identification of immune correlates of risk of tuberculosis (TB) disease and Mycobacterium tuberculosis (M.tb) infection is crucial for TB vaccine development. We have previously identified an association between activated HLA-DR+ CD4+ T cells and increased risk of TB disease, whereas there was a negative association between BCG-specific T cells secreting IFN-γ and serum Ag85A-specific IgG and risk of disease (Fletcher et al, Nature Commun 2016).

In the current study we are investigating correlates of risk of M.tb infection; i.e those who developed a positive QuantiFERON test during the study but did not develop TB disease.

**Methods:** This is a case-control (1 case : 3 controls ratio) study analysing potential immune correlates of risk of M.tb infection.

Samples are from 43 South African infants from the infant MVA85A efficacy study (Tameris et al, Lancet 2013,) and 75 HIV infected adults from the MVA85A study from South Africa (39 cases) and Senegal (36 cases) (Ndiaye et al, Lancet Respir Med 2015,).

**Assays:** We will use flow cytometry to characterise T cells, monocytes, regulatory cells and activation and inhibitory markers (e.g. HLA-DR, CD38 and PD1). Enzyme-Linked ImmunoSpot (ELISpot) will be conducted to assess IFN-γ responses to a range of antigens (BCG, CMV, EBV and Flu). Ag85A-specific antibody responses will be evaluated by Enzyme-Linked Immunosorbent Assay (ELISA).

**Results, Discussion and Conclusions:** Data on cell phenotyping and antigen-specific IFN-γ and antibody responses will be presented and discussed. Findings of this study will allow the comparison of parameters associated with risk of M.tb infection to those associated with TB disease.

**Funding Sources and Conflicts of Interest:** This work is funded by: Aeras, Wellcome Trust and TuBerculosis Vaccine Initiative (TBVI). Conflict of interest: None

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## OA-22

### Maximising impact of the TB vaccine pipeline – mathematical modelling to inform target product profiles

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Target Product Profiles (TPPs) guide strategic development of new TB vaccines to maximise future epidemiological impact. Insufficient evidence exists to guide such decisions, so to inform TPP development by BMGF, WHO and others, we estimated the influence of new TB vaccine characteristics on impact in China, India and South Africa.

An M.tb transmission model was calibrated to country-level age-stratified estimates of population, TB prevalence, notification, incidence and mortality rates. Vaccine efficacy for prevention of infection (VE-POI) and disease (VE-POD) (0-100%), duration of

protection (2yrs-life), and efficacy pre- and post-infection were explored. Vaccine was introduced in 2025, with 80% routine coverage at age 9, and 70% coverage of ≥10 year olds in 10-yearly campaigns. Primary outcome was incidence rate reduction in 2050 compared to no new vaccine. China results are provided; India and South Africa will follow by the Forum.

In China, to achieve a 20-29% reduction with 10-yearly campaigns, at least 5 years protection was needed, with a median VE-POD of 40% (range:0-60%) and VE-POI of 60% (range:0-100%). This was also achievable with a 90-100% VE-POI-only vaccine or 40-60% VE-POD-only vaccine. For greater impact, increased VE-POD or duration of efficacy was essential, as outcomes were insensitive to VE-POI. Post-infection or pre- and post-infection POD vaccines would maximise impact. Greatest rate reduction was 79% (UR:77-81%), reaching 7/100,000pop/yr (UR:6-8) and averting 11million cases (UR:10-12) 2025-50. Fig.1 shows cases averted by different vaccines.

TPPs to inform vaccine development in China and similar epidemics should recommend candidates with anticipated efficacy against disease and post-infection. Trials should assess disease endpoints, include M.tb-infected populations, and extend beyond the usual 2-3 years. Results will be available for India and South Africa. This research is imperative for data-driven TPPs to maximise future impact.

**Funding Sources and Conflicts of Interest:** The Bill and Melinda Gates Foundation.

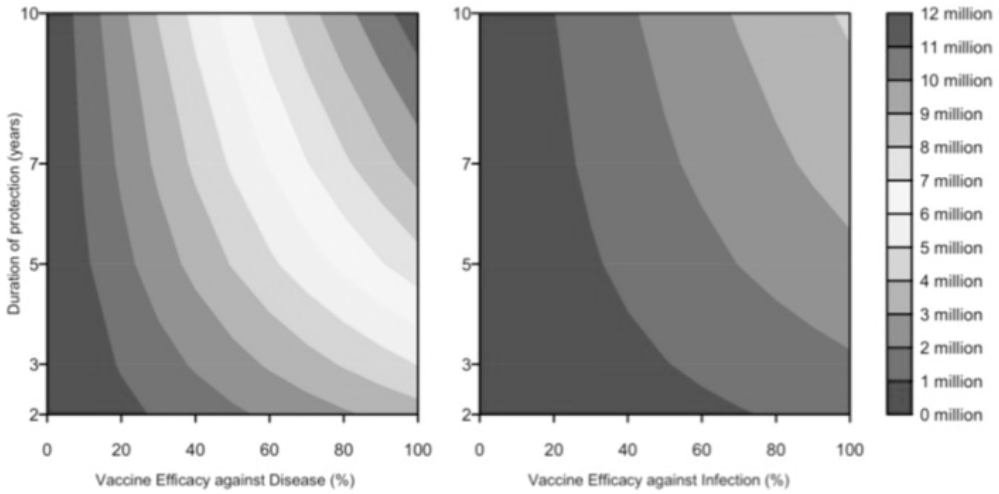


Fig. 1: Median cumulative number of cases averted for the period 2025-2050 for a pre- and post-infection vaccine compared to no new vaccine baseline, by percentage efficacy against disease or infection (x-axes), and duration of protection (y-axis).

# OA-23

## Incidence of tuberculosis disease among household contacts of adult pulmonary tuberculosis patients in India- a multi centric cohort study

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**Background:** Understanding the time and rate of development of Tuberculosis (TB) disease among the Household Contacts (HHC) of newly diagnosed Pulmonary TB (PTB) patients would help in designing effective vaccines and chemoprophylaxis regimens.

**Methods:** Cohort of HHCs of newly diagnosed adult PTB patients started on treatment in India were enrolled and evaluated for TB infection and disease at 0,4,6,12,18 and 24 months. TB infection was defined positive if tuberculin skin test (TST) was ≥5mm and/or Quantiferon GoldIn Tube test (QGIT) ≥0.35IU/mL. TB disease was confirmed using smear, culture, chest X ray and/or clinical symptoms. We analyzed co-prevalent TB cases at baseline and incident TB cases from 1-24 months using cumulative incidence, incidence density and Kaplan-Meier curves. Poisson regression adjusted for the household clustering and factors significant at 10% level by univariate analysis were used to estimate adjusted relative risk (aRR) for factors associated with the TB incidence.

**Results:** Of 1050 HHCs enrolled 18 (1.7%) had co-prevalent TB and 1032 HHCs were eligible for follow up. 740/1032 HHCs(<14 years=199,>14years=541) who had completed 12 to 24 months follow-up, 11 developed TB disease: 9/11 were diagnosed by clinical symptoms;10/11 had PTB and 10/11 were diagnosed within 4 to 6 months of enrollment (Figure1).7/11 were male,9/11 were <14 years,8/11 had no BCG scar,5/11 had BMI<16 and 6 /11 had baseline TST and QGIT positivity.9/11 had index PTB culture positivity at baseline. Cumulative Incidence of TB was 1.5%[95% CI:0.8% to2.8%] and TB Incidence Density was 8.93/1000 person-years follow-up[95%CI:4.95–16.13].Age <14 years[aRR-12.7(95%CI:4.4 -36.9)] and absence of BCG scar[aRR-4.3(95%CI:1.04-17.86)] were significantly associated with TB incidence.

**Conclusion:** The risk of TB disease among the HHCs is high during the first 6 months of follow-up from the time of diagnosing index TB case and is associated with younger age group and absence of BCG scar.

**Funding Sources and Conflicts of Interest:** The authors declare that they have no conflict of interest.

Figure 1a:Time of detection of Co-prevalent and incident TB among HHCs of PTB patients in India

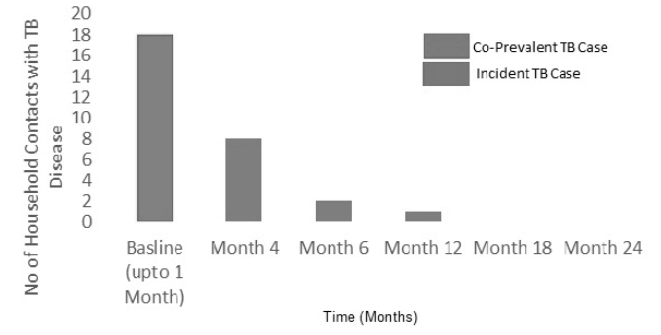
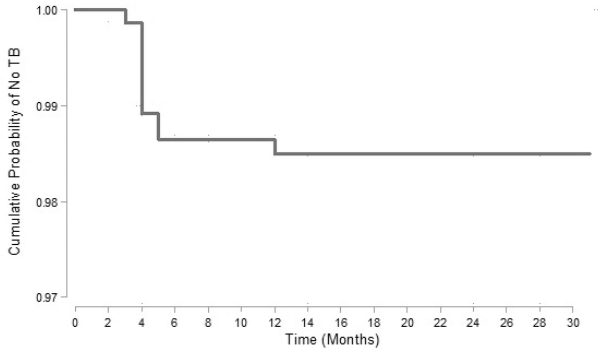



Figure 1b: Risk of incident TB among HHCs of PTB patients in India




# OA-24

## High risk for tuberculosis infections among medical and nursing trainees in India

**Aarti Avinash Kinikar[1],** Ajay Chandanwale[1], Dileep Kadam[1], Samir Joshi[1], Anita Basavaraj[1], Geeta Pardeshi[1], Sunita Girish[1], Sangeeta Shelke[1], Andrea Deluca[2], Gauri Dhumal[3], Jonathan Golub[2],Neelima Lokhande[3], Nikhil Gupte[3], Amita Gupta[2], Robert Bollinger[2], Vidya Mave[3]

*[1]Byramjee Jeejeebhoy Government Medical College and Sassoon General Hospital, India, [2]Johns Hopkins University, USA, [3]Byramjee Jeejeebhoy Government Medical College Clinical Research Site, India*

**Background:** Health care workers (HCWs), specifically medical and nursing trainees, are at particularly high risk for acquiring tuberculosis (TB), including multi-drug resistant TB (MDRTB) and are potential sources of TB transmission in their hospital, homes and communities. India has the world's largest TB burden, yet in-country data on TB infection (TBI) risk among trainees are limited.

**Methods:** A prospective longitudinal cohort study of medical and nursing trainees in a public tertiary care teaching hospital in Pune, India was conducted between May 2016 and August 2017. They underwent tuberculin skin test (TST) and QuantiFERON® TB Gold Test-in-tube (QGIT, Cellestis) at study entry. QGIT was repeated at 1 month, and every 3 months thereafter for a year, TST was repeated at one year. Primary outcomes were estimates of TBI (>10mm TST induration and/ or >0.35IU/mL QGIT) prevalence and incidence; secondary outcomes was risk factors for incident TBI using Poison regression.

**Results:** Of 200 trainees enrolled, median age was 25 years (IQR, 19 - 27) and 90 (45%) were nursing students; 112 (56%) were females. Prevalent TBI was 26% (95% CI: 20% - 33%). Median follow up was 8.7 months (IQR, 1-9) and incidence TBI was 413 (95% CI), 296 - 560) per 1000 person-years. 19 (37%) of those with prevalent TB infections and 15 (37%) of those with incident TB

infections reported TB exposure in the hospital. Medical residents (relative risk (RR), 2.0; 95% CI,1.05 – 3.82) had increased risk for incident TBI while trainees who were unsure of their smear positive TB exposure had lower risk of incident TBI (RR, 0.47; 95% CI,0.11 – 2.11).

**Conclusion:** Our study demonstrates that trainees in India are at high risk for TBI with highest risk among medical residents. Since HCWs are continuously exposed to known and unknown cases of TB in workplace, a TB vaccine that could prevent TBI as well as implementation of infection control guidelines are urgently needed.

**Funding Sources and Conflicts of Interest:** Funding Sources: This study was supported by the BJGMC JHU HIV TB Program funded by the Fogarty International Center, National Institutes of Health (NIH) (grant # D43TW009574) and Byramjee-Jeejeebhoy Medical College HIV Clinical trials Unit [U01 Ai069497]

## PD-01

### Treatment with non-steroidal anti-inflammatory drugs (NSAIDs) exacerbates TB infection after aerosol challenge in mice – implications for host-directed therapy

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Adjunctive host-directed therapy has gained increased interest as a means of shortening TB treatment duration and improving regimens for drug resistant Mtb strains. Clinical trials are investigating NSAIDs, including cyclooxygenase inhibitors (Coxi), as potential therapeutic targets. In an experimental intravenous infection model in mice, we could confirm the results of others; that the bacterial burden can be reduced by Coxi administration during Mtb infection. The lower bacterial load in lungs of ibuprofen-treated mice, was associated with a decrease in neutrophils and proinflammatory cytokines. We extended the study to high-dose aerosol infection and were surprised to find the opposite effect; that ibuprofen treatment increased mortality. The same results were obtained with low-dose aerosol infection, where treated mice had significantly higher bacterial burden in both lungs and spleens, which was consistent across independent experiments with both ibuprofen and celecoxib. Importantly, in Coxi-treated animals, pulmonary CD4 T cell counts were decreased, which correlated with lower IL-12p70 levels and lower T cell expression of T-bet and Th1 cytokines (IFNγ, TNFα and IL-2). In contrast, neutrophils were unaffected by Coxi-treatment in this model. Finally, we explored the long-term effect of Cox inhibition by clearing Coxi-treated mice with a 12-week antibiotic regimen followed by a resting period before secondary infection. Interestingly, we observed that mice that were Coxi-treated during primary infection were also significantly more susceptible to reinfection than untreated controls. Based on these findings, we speculate that therapy with Cox inhibitors, and potentially other NSAIDs, could alleviate excessive inflammation during acute TB disease, but might risk to impair immune control of the infection by manipulating adaptive immune responses. This is the subject of current research activities in animal models as well as an ongoing human clinical trial.

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## PD-02

### Deciphering the role of VapBC TA modules in virulence and pathogenesis of Mycobacterium tuberculosis

**Sakshi Agarwal,** Prabhakar Tiwari, Saquib Kidwai, Ramandeep Sign *Vaccine and Infectious Disease Research Centre, Translational Health Science and Technology Institute, India*

**Background:** TA (Toxin-Antitoxin) modules are bicistronic genetic elements that are ubiquitously present in the genome of prokaryotes. TA module encode toxin that inhibit various essential cellular process curbing the growth of bacteria where it turns into metabolically inactive persistent state and labile antitoxin which in native condition inhibit their toxin counterpart. Virulence associated protein (VapBC) is most abundant type II category in the genome of M. tuberculosis. Despite of their abundance, their role in physiology and virulence of pathogen is still elusive.

**Methods:** We have done a comprehensive analysis and functionally characterize 47 VapC toxins in slow growing M.bovis (BCG) using anhydrotetracycline (Atc) inducible vector. We used qRTPCR to measure the level of toxins that are induced under stress conditions. We have also generated deletion mutants of these VapC toxins by phage based method to elucidate their role in stress conditions and measure bacterial loads in animal model.

**Results:** Overexpression of these VapC toxins were deterimental for the growth of bacteria. These toxins were differentially induced under different stress conditions. Despite these VapC toxins were found redundant in invitro stress conditions we found that VapBC were essential for survival of M.tuberculosis invivo in host tissues. Guinea pigs infected with VapBC single mutant exhibit significant reduction in bacillary load in infected tissues as compared to their parental strain.This is the first study which highlighted the role of TA systems in the virulence and pathogenesis of M.tuberculosis.

**Conclusion:** VapC toxins inhibit the growth of bacteria and contributes towards the virulence and pathogenesis of M.tuberculosis. They can be used as vaccine candidate in future to combat tuberculosis.

**Funding Sources and Conflicts of Interest:** This work has been supported by Department of Biotechnology (BT/COE/34/15219/2015).

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# PD-03

## Mycobacterium tuberculosis hbhA and mtp deletion elicits unique canonical pathways during early infection in THP-1 differentiated macrophages.

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**Introduction:** M. tuberculosis was responsible for an estimated 10.4 million new cases and 1.4 million deaths in 2015 (WHO, 2016). Understanding host gene regulation provides vital information about pathogenesis that possibly translates into novel therapeutic targets. This study utilised THP-1 human macrophages infected with a hbhA-mtp knockout mutant of Mycobacterium tuberculosis to assess the effect of hbhA gene deletion in the Δmtp mutant on the host transcriptome.

**Methods:** In order to compare the transcriptome changes elicited by wild type (WT) and ΔhbhA-mtp infection at 4 hr post-infection, RNA was extracted from THP-1 differentiated macrophage monolayers and sequenced using Hiseq 2500 platform (Illumina). Reads were trimmed using Trimmomatic and mapped to the Homo sapiens reference genome Hg19 (UCSC) using TopHat (2.1.0) and Bowtie2. Differential gene expression patterns were identified using cuffdiff. Changes in canonical pathways were analysed by Ingenuity Pathway Analysis.

**Results:** WT infection enriched the TREM1 signalling pathway to a greater degree than ΔhbhA-mtp infection in macrophages. ΔhbhA-mtp infection enriched the dendritic cell maturation pathways to a greater degree than WT infection. ΔhbhA-mtp infection, but not WT, enriched Th1 and Th2 Activation, Th1, Th2, Melatonin degradation, Sumoylation, Methylglyoxal degradation III, Granzyme A signalling, PCP pathways.

**Conclusions:** The absence of HBHA and MTP proteins resulted in activation of host immune responses that are detrimental to the survival of M. tuberculosis, suggesting that these adhesins may assist the pathogen to evade the host immune responses during early infection.

**Funding Sources and Conflicts of Interest:** None

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# PD-04

## Targeting ClpB abrogates stress tolerance in Mycobacterium tuberculosis and hence its growth and infectivity

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Mycobacterium tuberculosis (M. tb) is known to persist in extremely hostile environment within the host macrophages. The ability to withstand such proteotoxic stresses and rapidly adapt to them comes from its highly conserved molecular chaperone machinery which mediates the stress tolerance. ClpB, a member of the HSP100 family of chaperones, is known to be involved in conferring thermo-tolerance to various pathogens. M. tb has also been shown to deploy ClpB to reactivate aggregated proteins, in vitro, in concert with the DnaKJE chaperone machinery; however, there is no direct evidence of its involvement in stress tolerance in these bacilli. Our study addresses the same with the help of ClpB deficient and complemented strains of M. tb. We cultured these bacilli under conditions that mimicked various physiological stresses encountered by mycobacterium inside the host and observed that ClpB deficient bacilli had a marked defect in recovering from stressful conditions and had compromised infectivity. The cellular morphology of these bacilli and biofilm formation by them was also found to have altered as compared to the wildtype bacteria. Although an up-regulation of other molecular chaperones was observed in the ClpB deficient strain, it couldn't make up for the loss of ClpB. Further, our study also investigates the immunogenic potential of ClpB. Taken together, our

findings establish the involvement of ClpB in regulating some of the most important virulence determinants of the pathogen and could thus prove to be a potential vaccine candidate.

**Funding Sources and Conflicts of Interest:** None

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# PD-05

## Circulating HLA-DR+IFNγhiIL-17hiCD4+T effectors resistant to CCR5 and PD-L1 mediated suppression compromise regulatory T cell function in tuberculosis

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**Background:** Chronic T cell activation is a hallmark of tuberculosis (TB). The mechanisms underpinning this important phenomenon are however, poorly elucidated, though recognised as critically reliant on effective homeostatic control of T effectors (Teff) by regulatory T cells (Treg).

**Methods:** Latent TB (positive for an IFNγ Release Assay {IGRA}), sputum positive, treatment naïve, pulmonary TB and healthy control (IGRA negative) subjects were studied. Tregs were enumerated, and their function was assessed by suppression assays. Phenotypic characterisation in terms of expression of activation markers HLA-DR, CD38 and regulatory receptor PD-1 on Teff and Treg cells coupled with RNA sequencing and blocking/neutralisation studies were used to understand Treg mediated homeostasis in TB.

**Results:** We demonstrate that circulating CD25hiCD127lowTreg cells in adults with TB preserve their suppressive potential but Teff cells from such subjects are rendered resistant to Treg-mediated suppression specifically by expansion of an activated Teff subset identified by HLA-DR expression, with sensitivity to suppression restored to control levels by depletion of this subset. Comparative transcriptome analysis of Teff cells that contain HLA-DR+ cells versus the fraction depleted of this population identified putative resistance mechanisms linked to IFNγ, IL17A, IL22, PD-L1 and β-chemokines CCL3L3, CCL4 expression. Antibody blocking experiments confirmed HLA-DR+ Teff cells, but not the fraction depleted of HLA-DR+ effectors, to be resistant to Treg suppression mediated via the β-chemokine receptor, CCR5 and PDL-1 pathways. In addition, HLA-DR+ Teff cells expressed significantly higher levels of Th1/Th17 cytokines that limit Treg function through a reciprocal counter-balancing relationship.

**Conclusion:** Taken together, our study provides new mechanistic insight on how activated HLA-DR+CD4+ cells contribute to disease by compromising Treg-mediated homeostasis in TB.

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# PD-06

## PPM, a novel Mycobacterium tuberculosis (Mtb) antigen: a candidate for vaccine development to prevent progression to tuberculosis

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**Background/Introduction:** Mtb uses secreted antigens export to manipulate host adaptive immune responses. Most of TB vaccine candidates in the pipeline are based on secreted antigens of Mtb. Moreover, the huge heterogeneity promoted by the asymmetric growth and division of mycobacterial cells suggests that an ideal candidate antigen for vaccine development should be essential for mycobacterial cells survival and division. PPM is the extracellular domain of an essential protein that plays a critical role in modulation of cell shape and cell division. Herein, we aimed to better assess immune responses to this potential candidate vaccine.

**Materials and methods:** A total of 63 volunteers: 21TB; 26LTBI and 16controls were included. We measured by ELISA the production of IFN-g, TNFa and GrzB secreted by PBMCs after stimulation with recombinant (r) PPM, PPD, rESAT6 and PHA for 24h in the presence of IL7. We further characterized by intra cellular staining (ICS) the T cell subset producing GrzB. We also evaluated the in vitro growth of H37Rv under hypoxic and normoxic conditions in the presence of anti-rPPM polyclonal antibodies.

**Results:** Our results showed that PPM induces significantly higher IFNg amounts in LTBI group when compared to TB patients ($p<0.0025$). PPM induces high amount of GrzB in LTBI group. Interestingly, GrzB has been recently identified as a correlate of protection from TB reactivation in non human primates. Moreover, TB patients apparently loose this cytotoxic activity. Thus, the PPM-specific GrzB release assay allows important discriminative power between LTBI and Active TB ($p<0.0008$). ICS experiment showed that CD8 T cells are the source of PPM-specific GrzB. Using polyclonal antibodies we observed a log fold decrease in CFU of H37Rv under both normoxic and hypoxic conditions upon treatment with 10ug/ml of anti-rPPM.

**Conclusion:** Taken together, these findings argue in favor of PPM as a candidate for development of post-infection TB vaccine.

**Funding Sources and Conflicts of Interest:** None

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# PD-07

## Evaluation of the immunogenicity of a promising vaccine regime to identify immune correlates of protection

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A vaccine against tuberculosis (TB), a disease resulting after infection with Mycobacterium tuberculosis (M.tb), is urgently needed to prevent more than a million deaths per year. Bacillus Calmette–Guérin (BCG) is the only available vaccine against TB but its efficacy is variable throughout the world. Subunit vaccine candidates, based on recombinant viral vectors expressing mycobacterial antigens, is one of the strategies used to boost BCG primed host immune responses. A promising vaccination regimen composed of BCG prime, followed by vaccination with a chimpanzee adenoviral vector (ChAdOx1) and a modified vaccinia Ankara virus (MVA), both expressing Ag85A, was previously identified in our laboratory. This regimen significantly improved BCG efficacy in animal studies. Effector and memory immune responses induced by BCG-ChAdOx1.85A-MVA85A (B-C-M), were evaluated, to identify immune correlates of protection in mice. This regime induced strong Ag85A-specific cytokine responses in CD4+ and CD8+ T cells, both in the systemic and pulmonary system. To discriminate lymphocytes in the vasculature from lymphocytes in the lung parenchyma, a fluorochrome-conjugated antibody was injected intravascularly before harvesting the lungs. Lung parenchymal Ag85A-specific memory CD4+ T cells that were CXCR3+ KLRG1-, significantly increased in B-C-M immunised mice compared to BCG alone at 4, 8 and 20 weeks post vaccination but the cell number decreased at the latter time point. These memory cells correlated with protection against M.tb challenge, which was observed at 4 and 8 weeks but not when mice were challenged 20 weeks post vaccination. Adoptive transfer of lung parenchymal Ag85A-specific CD4+ T cells will be performed to investigate the protective function of these putative protective T cells.

**Funding Sources and Conflicts of Interest:** Wellcome Trust Senior Fellowship, TBVAC H2020

## PD-08

### Demonstration of a correlation between the in vitro direct mycobacterial growth inhibition assay (MGIA) and protection from in vivo mycobacterial challenge

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The BCG vaccine has variable efficacy, but development of an effective alternative is hindered by the lack of an immune correlate of protection. Functional in vitro mycobacterial growth inhibition assays (MGIAs) can detect a response to BCG vaccination and offer a tractable model for investigating immune mechanisms. However, their biological relevance can only be confirmed by demonstrating a correlation with protection from in vivo challenge.

We have previously developed and optimised a direct MGIA for use across species. Whole blood or peripheral blood mononuclear cells are cultured with mycobacteria prior to quantification of net inhibition using the BACTEC MGIT system. Here, we apply the assay to studies of mycobacterial challenge in non-human primates (NHPs) and humans.

We report a significant correlation between fold change in mycobacterial growth pre- and post-BCG vaccination ('vaccine response') in vitro and measures of protection from in vivo challenge with Mycobacterium tuberculosis (M.tb) in NHPs. Furthermore, we observed a significant association between in vitro mycobacterial growth at the peak of response and CFU recovered from the lymph nodes (LN) following in vivo challenge with BCG as a surrogate for pathogenic M.tb. There was a negative correlation between the vaccine response by MGIA and LN CFU. In two independent studies of BCG-vaccinated humans, a significant association was observed between in vitro mycobacterial growth and mycobacterial load recovered from a challenge site skin biopsy. BCG growth in the MGIA correlated inversely with BCG-specific IgG, CD4+ and CD8+ IFN-γ responses.

This is the first description of an MGIA correlating with in vivo protection on an individual basis, and suggests the assay may represent a promising correlate of protection for application in preclinical vaccine testing, reducing the need for animal challenge experiments and accelerating development of an effective vaccine.

**Funding Sources and Conflicts of Interest:** TBVAC2020, EURIPRED, Aeras, NC3Rs

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## PD-09

### Altered systemic levels of neutrophil and mast cell granular proteins in tuberculosis-diabetes co-morbidity and changes following treatment

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**Background:** Tuberculosis (TB) remains a serious global public health problem that results in up to 2 million deaths each year. Diabetes patients present with an overall threefold increased risk of developing active TB. Innate immune responses in tuberculosis – diabetes (TB-DM) co-morbidity are poorly explored where the granulocytes get activated during the Mycobacterium tuberculosis (Mtb) infection and act as immune effector cells.

**Methodology:** Granular proteins were assayed from peripheral blood plasma in individuals with pulmonary tuberculosis and diabetes (PTB-DM), pulmonary tuberculosis alone (PTB) or diabetes alone (DM). Plasma levels of neutrophil, eosinophil and mast cell granular proteins provide an indirect measure of degranulation. Assay includes the measurement of plasma levels of neutrophil elastase, myeloperoxidase (MPO) and proteinase-3; eosinophil cationic protein (ECP), eosinophil derived neurotoxin (EDN), eosinophil peroxidase (EPX) and major basic protein (MBP); mast cell tryptase (MCT), leukotriene C4 (LTC4) and mast cell

carboxypeptidase-A3 (CPA-3) in these individuals. Finally, we also measured the levels of all of these parameters in PTB-DM individuals following anti-tuberculosis treatment.

**Results:** The study showed that PTB-DM individuals exhibit significantly lower plasma levels of MPO, elastase, human proteinase 3 and LTC4 and significantly higher plasma levels of EDN, CPA-3 and MCT in comparison to PTB and/or DM individuals. And the treatment of TB resulted in alterations in plasma levels of most of these granular proteins, indicating that changes in these proteins are associated with TB disease.

**Conclusion:** Degranulation and the activation of granulocyte are the hallmarks of Mtb infection and TB-DM co-morbidity, the data suggest that neutrophil and mast cell granular proteins could play a potential role in the innate immune response of PTB-DM co-morbidity.

**Funding Sources and Conflicts of Interest:** No potential conflicts of interest

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# PD-10

## Early and local immune mechanisms of TB disease progression and control upon ultra-low dose infection in rhesus versus cynomolgus macaques

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Experimental M.tuberculosis infection of macaques is considered a high-end model for TB vaccine research. So far, reported studies comprised a single dose infectious challenge subsequent to vaccination, such that all non-vaccinated controls did get infected and developed TB. While under such conditions rhesus typically show progressive disease, with a relatively low dose inoculum (of about 25 colony forming units, CFU) cynomolgus macaques have been reported to develop a latent type of infection in about 50% of cases.

Here we set out in a randomised comparison study to identify the lowest infectious dose for rhesus and cynomolgus macaques. A dose escalation regime was applied, eventually requiring less than 10 CFU of M.tuberculosis strain Erdman to establish infection in all animals. Analyses of the peripheral and local pulmonary compartments for innate and adaptive immune parameters were executed along the infection time line.

Both macaque species appeared equally susceptible to infection, by extrapolation to as little as a single CFU. However, cynomolgus macaques developed significantly less lung pathology than rhesus, in the absence of any correlation to the evolving IFNg response. Peripheral and local immune profiling, however, showed that cynomolgus present a significantly more prominent pro-inflammatory innate cytokine signature including TNFa early after infection. Rhesus, on the other hand, exhibited a predominant anti-inflammatory monocyte phenotype in the periphery, associated with reduced cytokine production.

Together, the data indicate that early innate immune orchestration by pro-inflammatory cytokines and regulatory innate immune signals correlate with the differential outcome of experimental, ultra-low dose infection in rhesus versus cynomolgus macaques, reminiscent of what has been published for human TB susceptibility. These findings contribute to the refinement of study design for preclinical TB vaccine research in non-human primates.

**Funding Sources and Conflicts of Interest:** Work supported through the TuBerculosis Vaccine Initiative (TBVI) under the 'TBVAC2020' Consortium Grant from the European Commission (EC Horizon 2020 programme).

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# PD-11

## Experimental evaluation of a novel microneedle device for BCG vaccination

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**Introduction:** To complement any complexity of intradermal technique, a novel microneedle device has been introduced to deliver vaccines and biologics. In our previous study, Tuberculin Skin Test (TST) using the microneedle device found to be effective, safe and less painful in healthy adults. In this study, we plan to test several experimental conditions to observe BCG can be delivered by the microneedle device, MicronJet600TM and compared them with the conventional needle.

**Methods:** The number of viable Pasteur bacille Calmette-Guerin (BCG) bacilli was enumerated after injection through the microneedle and conventional needle. Counting of colony-forming units in solid media and confocal microscopic images were used to observe whether viable BCG bacilli could be passed through the device under different field conditions, such as, time delay of vaccination, vaccine storage and handling.

**Results:** We observed the Pasteur BCG bacilli could get through a novel microneedle with 0.6 mm in length, showing 96.4 % recovery rate in term of CFU counts.

**Conclusion:** The BCG vaccine can be delivered intradermally using a novel microneedle, MicronJet 600TM, expecting to be safer, easier, and simper to handle than conventional needle. Following experimental evaluation, we plan to conduct a clinical trial of BCG vaccination using MicronJet 600TM in healthy adults and infants.

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# PD-12

## Role of BCG encapsulated alginate particles in activation of bone marrow derived dendritic cells for providing better immune response against TB

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Tuberculosis (TB) is one of the deadliest infectious diseases caused by Mycobacterium tuberculosis. India accounts for one fourth of the global TB burden. Today there is an urgent need for the development of a suitable vaccine type that has better efficacy to provide enhanced immune response against tuberculosis.

In our present studies, we analysed the potential of the BCG encapsulated alginate particles (BEAP) to enhance immune responses in H37RV challenged mice. These particles were generated by encapsulating the BCG in Sodium Alginate and Trehalose mixture when passed through Calcium chloride solution in the aerosol form. The size of microparticle (3-5um) was achieved by passing it through high pressure jet mill and the size was determined by Scanning Electron Microscopy (SEM). The release profile of mycobacterium from BEAP was validated by plating on 7H11 agar medium. BEAP was found to be stable at room temperature for atleast 4 months.

We observed that delivery of BEAP in form of dry powder aerosol invoked superior immune response and provided higher protection in challenged mice than the liquid aerosol as suggested by higher CFU counts in immunized animals. BEAP significantly increased the surface expression of activation markers like CD80, CD86, MHC II and CCR7 on bone morrow dendritic cells (BMDCs) compared to their level of activation when treated with BCG. The BEAP were engulfed by BMDCs and co-localized with lysosomes and these activated BEAPs exhibited higher chemotaxis besides enhanced ability of antigen presentation to T cells. This indicates that BEAP acts to boost a dendritic cell driven immune response and protection against tuberculosis.

# PD-13

## bioA mutant of Mycobacterium tuberculosis shows severe growth defect and imparts protection against tuberculosis in guinea pigs

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**Introduction:** Studies in several microorganisms including mycobacteria have shown that genes involved in biotin biosynthesis are essential for growth and survival. In this study, we show that attenuated M. tuberculosis bioA mutant has vaccinogenic potential against tuberculosis.

**Methods:** A bioA gene mutant of M. tuberculosis was generated and phenotypically characterized. The effect of disruption of the bioA gene on the virulence of M. tuberculosis, was assessed by aerosol infection study in guinea pigs. The intradermal route of administration in guinea pigs was also employed to assess the attenuation and in vivo growth kinetics of MtbΔbioA strain. Next, we evaluated the MtbΔbioA strain for its ability to impart protection in guinea pigs aerogenically infected with virulent M. tuberculosis.

**Results:** The study demonstrates that disruption of bioA gene in M. tuberculosis renders the pathogen highly attenuated in vivo in guinea pigs when administered via aerosol as well as intradermal routes demonstrating limited survival of the strain in vivo. Following intradermal administration, the in vivo growth kinetics of MtbΔbioA differed from the kinetics of BCG. Intradermal immunization with MtbΔbioA provided significant protection against aerosol challenge with virulent M. tuberculosis in guinea pigs, when compared with unvaccinated control animals. Boosting with a second dose of MtbΔbioA conferred no additional advantage.

**Conclusion:** This work features the prospective of biotin auxotrophy as a favourable initiating point for generation of novel strains based on attenuated M. tuberculosis as vaccines against TB. In this short-term efficacy study the protection provided by MtbΔbioA and BCG were not significantly different, which encourages further evaluation by mucosal vaccination or modification of MtbΔbioA strain by overexpressing certain immunodominant antigens or combining biotin auxotrophy with immunomodulatory mutations.

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# PD-14

## Animal dose response curve predicts lower optimal tuberculosis vaccine dose in humans: The use of vaccine Immunostimulation/Immunodynamic modelling methods to inform vaccine dose decision-making

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**Introduction:** Unlike drug dose optimisation, mathematical modelling has not been applied to find vaccine dose. In tuberculosis(TB) vaccine development, current methods are selecting sub-optimal doses. We applied mathematical modelling to translate multi-dose TB vaccine immune responses from mice, to predict most immunogenic dose in humans.
**Methods:** Data were available on IFN-γ secreting CD4+ T cells over time for novel H-series TB vaccines (H-series: H56 and H56/H1) in mice (5 doses, 45 mice/dose) and humans (1 dose, 18 humans). A two-compartment mathematical model describing the dynamics of the post-vaccination IFN-γ T cell response was calibrated to mouse and human data, separately, using nonlinear mixed effects methods. We then used these calibrated models and a vaccine dose allometric scaling assumption, to predict the most immunogenic human dose.

**Results:** The mathematical models were successfully calibrated to the animal and human data. Lower dose was associated with a higher and more sustained IFN-γ response after revaccination in mice. At day 224, the predicted median number of IFN-γ secreting CD4+ T cells were 304, 179, and 97 for the low, middle and high (0.1-10μg, 50μg and 150μg H56/H1+IC31, respectively) dose groups, suggesting the lowest dose group may be most immunogenic in humans.

**Conclusion:** H-series TB vaccine doses used in clinical trials may be too high. Giving lower doses than previously tested, may increase immune response, and possibly protection, in humans. Mathematical modelling is a novel and potentially revolutionary tool to predict most immunogenic vaccine doses for use in clinical trials.

**Funding Sources and Conflicts of Interest:** Funding by Aeras

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# PD-15

## T cell immunity in the lung and protection following aerosol, intravenous, or intradermal administration of BCG in nonhuman primates

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**Background:** Critical determinants of T cell-mediated protection against infections such as HIV, malaria, and tuberculosis (TB) include the magnitude, quality, breadth, and location of cellular responses. For TB, the licensed vaccine (BCG) is given intradermally at birth and protects against disseminated TB though childhood. However, developing a vaccine that prevents pulmonary infection (the most common and transmissible form of TB in adolescents/adults) may require an immunization route that elicits a high frequency of durable tissue resident T cells in the lungs providing immediate control of TB following exposure.
**Methods:** Rhesus macaques were immunized with varying doses of BCG via the intravenous (IV), aerosol (AE), intradermal (ID), or simultaneous ID/AE routes and the immune responses were compared in blood and bronchoalveolar lavage (BAL). Six months after immunization, animals were challenged with a low dose (~15 CFU) of virulent Mycobacterium tuberculosis Erdman and vaccine efficacy was assessed for three months post-TB using PET/CT scanning as well as gross pathology and bacterial burden at necropsy.

**Results:** Compared to ID or AE, NHPs immunized with IV BCG generated higher frequencies of PPD-specific CD4 (~35-45%) and CD8 (8-10%) T cells in BAL that were maintained for at least 4 months. IV BCG immunization also resulted in a striking recruitment of CD4 and CD8 T cells into the lung, increasing the absolute number of PPD-specific CD4 and CD8 T cells by >10-fold compared to the other vaccination routes. Moreover, this recruitment resulted in a profound change in the ratio of T cells and macrophages in BAL.

**Summary:** These data show that varying the route and dose of immunization influences the magnitude, quality, and site of TB-specific T cell immunity. Full challenge results will be presented. Differences in protection will allow us to mine local and systemic immune responses for correlates of protection that will better inform vaccine development.

**Funding Sources and Conflicts of Interest:** Funding. This work was funded by the intramural research program of the Vaccine Research Center, NIAID, NIH and the Bill & Melinda Gates Foundation.

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# PD-16

## A recombinant BCG-LTAK63 strain induces increased innate and long-term immunity correlating with enhanced protection against tuberculosis

**Luciana Leite,** Carina C. Santos, Ivan P. Nascimento, Dunia Rodriguez *Instituto Butantan, Brazil*

Tuberculosis (TB) is responsible for over 9.6 million cases and 1.5 million deaths annually. The only currently available vaccine, Mycobacterium bovis Bacille Calmette-Guérin (BCG), fails to prevent pulmonary tuberculosis. The aim of this study was to characterize the innate and long-term immune response induced by a vaccine candidate against TB based on recombinant BCG

expressing the non-toxic mutant of E. coli heat labile enterotoxin (rBCG-LTAK63). The recruitment of cells to the peritoneum 24 h and 7 days after intraperitoneal administration of BCG or rBCG-LTAK63 showed early cellular infiltration with the presence of neutrophils in the peritoneum at 24 h and higher number of lymphocytes in rBCG-LTAK63 group as compared to the BCG group at 7 days. An increased nitric oxide production was observed after 24 h and higher hydrogen peroxide concentration after 7 days in the rBCG-LTAK63 group as compared to the BCG group. BALB/c mice were immunized subcutaneously to evaluate the long-term immune response. Lung cells were collected after 3 months and in vitro stimulated to analyze the Th1 / Th17 cytokine profile. Higher levels of inflammatory cytokines, IFN-γ, TNF-α and IL-6 and also IL-17 were induced in the rBCG-LTAK63 group as compared to BCG in the lungs of animals 85 days after immunization. Furthermore, increased level of the regulatory cytokine, IL-10 was also observed in the rBCG-LTAK63 group, correlating with the lower pathology observed in the lung of challenged animals. These results can be correlated with previous data showing superior protection induced by rBCG-LTAK63. Our results demonstrate that rBCG-LTAK63 induces early recruitment of cells with the presence of activated macrophages and lymphocytes. This may be important to develop a Th1 and Th17 immune response and increasing protection against TB.

**Funding Sources and Conflicts of Interest:** Funding sources/conflict of interest: FAPESP and Fundação Butantan/LCCL and IPN have a patent on the rBCG-LTKA63.

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# PD-17

## Recombinant BCG-LTAK63 strain induces lower immunopathological effects and superior protection against tuberculosis in BALB/c and C57BL/6 mice

**Carina Santos,** Ivan Nascimento, Dunia Rodriguez, Luciana Leite *Instituto Butantan, Brazil*

New strategies against Mycobacterium tuberculosis (Mtb) are urgently needed, since Mycobacterium bovis Bacille Calmette-Guérin (BCG) has shown controversial results on its protective efficacy and there is a rising frequency of multi-drug resistant (MDR) Mtb strains. A recombinant BCG expressing the adjuvant LTAK63 (rBCG-LTAK63) has been shown to be more protective than BCG against tuberculosis (TB) in an intratracheal challenge model. In an attempt to seek correlates of protection, we evaluated the immune response, protection and reduction of alveolar area in the lungs induced by rBCG-LTAK63 after the challenge. BALB/c and C57BL/6 mice were immunized subcutaneously with rBCG-LTAK63 or BCG. The CD4 T cells response, cytokine production, histopathology and CFU in the lungs were accessed 15 days after the intratracheal challenge to BALB/c mice; the protection and histopathology was accessed in C57BL/6 mice 30 days after the challenge. The results showed that rBCG-LTAK63 induced superior protection against TB in BALB/c and C57BL/6 mice and lower damage in lung tissues as compared to BCG. The BALB/c mice immunized with rBCG-LTAK63 presented increased CD4 T cells producing TNF-α at 15 days after challenge; we also observed a high production of IL-10 and low Th1 cytokine production in these animals. At this point, the animals presented lower reduction of alveolar area than BCG and a superior protection was observed 30 days after the challenge. The C57BL/6 mice immunized with rBCG-LTAK63 also presented lower reduction of alveolar area than BCG and a superior protection was observed 30 days after the challenge. Our results demonstrate that rBCG-LTAK63 is able to induce a modulatory immune response after the challenge with a balanced cytokine production and superior protection against TB. Since an important aspect in the development of new strategies against TB is to reduce the immunopathological effects, it will be critical to further investigate this mechanism.

**Funding Sources and Conflicts of Interest:** Supported by FAPESP and Fundação Butantan. Ivan Nascimento and Luciana Leite have a patent application involving the rBCG-LTKA63 use as Mtb vaccines.

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## PD-18

### Intransal vaccination with Mycobacterium indicus pranii leads to infiltration of protective memory T-cells in lung airway lumen.

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Mycobacterium indicus pranii (MIP), a saprophytic mycobacterium shares significant antigenic repertoire with M. tuberculosis. It has been investigated as a vaccine against tuberculosis in animal models. Immunization with MIP by aerosol route provides significantly higher protection as compared to immunization by subcutaneous (s.c.) route in animal models of tuberculosis. However, mechanism behind differential protection has not been studied. In this study, using mice model we have evaluated and compared the M.tb specific immune response in lung compartments (airway lumen / lung interstitium) as well as spleen following MIP immunization via nasal (i.n.) and s.c. route. MIP i.n. vaccination resulted in increased seeding of memory T cells (CD4+ and CD8+ T-cells) in the airway lumen. Frequency of CD4+ T cells expressing Th1 migratory marker and activation marker were also high in airway lumen of MIP i.n. group. Significantly high ex vivo secretion of cytokines- IFN-, IL-12, IL-17 and TNF- from cells of airway luminal spaces provides evidence of antigen-specific lung immune response, besides generating systemic immunity comparable to MIP s.c. group. Analysis of T cell response on per cell basis revealed that antigen specific T-cells of MIP i.n. group were functionally superior as higher percentage of these cells simultaneously secreted IFN-gamma, IL-2 and TNF-alpha cytokines as compared to MIP s.c. group. Adoptive transfer of airway luminal T-cells from MIP i.n. group into trachea of naive B6 mice revealed that MIP induced CD8 T-cells play crucial role in providing long term protection. Thus the study demonstrates that MIP intranasal vaccination induces M.tb specific memory T-cells in the airway lumen that results in an early and robust recall response against M.tb infection.

**Funding Sources and Conflicts of Interest:** The work is funded by Department of Biotechnology, Govt. of India, New Delhi.

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## PD-19

### Boosting with recombinant MVA expressing α-crystallin antigen of M. tuberculosis augments the protection imparted by BCG against tuberculosis in guinea pigs.

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**Background:** Tuberculosis (TB) is one of the major causes of mortality all over the globe that accounted for 1.4 million TB deaths in 2015 and an additional 0.4 million deaths resulting from TB disease among people living with HIV. BCG is the only vaccine available against this disease and has been successful in preventing the severe forms of childhood TB. However, the unsatisfactory performance of BCG in controlling the adult pulmonary tuberculosis has made the development of an effective vaccine against M. tuberculosis a prime objective of TB research.

**Methods:** This study is focused on the development and evaluation of heterologous prime boost approach based on α-crystallin (acr Rv2031c) by employing Modified Vaccinia Ankara (MVA) as a delivery vehicle. In this study, a marker-free, genetically stable recombinant MVA expressing α-crystallin antigen of M. tuberculosis (rMVA.acr) was generated. The recombinant virus was further evaluated for its ability to impart protection as a prophylactic booster vaccine against tuberculosis in a heterologous prime boost approach.

**Results:** Our results demonstrated that intradermal delivery of rMVA.acr was able to efficiently boost the BCG induced protection against M. tuberculosis infection in guinea pigs by significantly reducing the pulmonary bacillary load (1.27 log10 fewer bacilli) in comparison to BCG vaccination alone. In addition, boosting BCG vaccinated animals with intramuscular delivery of rMVA.acr resulted in significantly superior protective efficacy in both lungs and spleen with 0.83 log10 and 0.74 log10 CFU fewer bacilli, respectively, when compared to animals vaccinated with BCG alone.

**Conclusion:** This study highlights the importance of α-crystallin as an important vaccine antigen. The results clearly substantiate the potential use of MVA based vaccine expressing α-crystallin as a booster TB vaccine and establish the promise of this prime-boost strategy involving rMVA.acr in enhancing the efficacy of BCG.

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# PD-20

## A single dose nanoparticulate vaccine approach against tuberculosis

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Bacillus Calmette-Guérin (BCG), the attenuated strain of Mycobacterium bovis, remains the only currently available vaccine against TB since 1921, though BCG is ineffective in adults against pulmonary TB. Also, the protective efficacy of BCG varies from 0 to 85% in different models, prompting an urgent need for the development of an improved and efficient TB vaccine. In this milieu, the immune-modulating properties of Poly-(D, L-lactide-co-glycolide) (PLGA)-NPs encapsulating the H1 chimeric antigen (a fusion of Mtb Ag85B and ESAT-6 proteins) was investigated and their role in protection upon Mtb challenge, was assessed. The H1-PLGA nanoparticles were prepared by water/oil/water solvent evaporation method, with H1 encapsulation efficiency of 86.18±3.2%, size of 246.8±19.4 nm diameter and negatively charged surface (zeta potential = -4.2±0.6 mV). Under physiological conditions, PLGA-NPs degraded slowly and the encapsulated H1 antigen was released over a period of weeks. As a proof-of-concept vaccine candidate, H1-PLGA NPs were efficiently internalized by the THP-1 human macrophage cell line. Six weeks after a single vaccination, compared to H1 alone, mice vaccinated with H1-PLGA NPs showed significant increase in the productions of total serum IgG and its isotypes, with IgG2b being the predominant one, followed by IgG1. A single dose vaccination with H1-PLGA NPs induced a stronger Th1 cellular immune response with an exclusively higher IFN-γ profile than those of H1 alone or blank PLGA nanoparticles in a C57BL/6J mice model. Briefly, the H1-PLGA Nps vaccinated mice displayed 7 and 3 fold increase in the levels of Th1-type IFN-γ and TNF-α cytokines, compared to H1 alone. In protective efficacy studies, H1-PLGA vaccinated mice displayed significant reduction in lung bacillary load ($P < 0.05$), with a mean survival time (MST) of 177 days, compared to H1 antigen alone vaccinated mice (MST= 83 days).

**Funding Sources and Conflicts of Interest:** NONE

# PD-21

## Passive vaccination with human IgA protects against MDR-TB infection in mice

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Tuberculosis (TB) killed 1.5 million people in 2015. Failure of current treatments and preventative measures for TB have resulted in multi-drug resistant TB (MDR-TB), which is difficult and expensive to treat. Passive vaccination using the human 2E9-IgA antibody has the potential to improve current treatments by shortening treatment duration and improving cure rates, and at the same time provides the rationale for a potential protective role of vaccine induced mucosal antibodies.

We investigated the mechanism of action of 2E9-IgA, and tested its efficacy when combined with IFN-☒ which is associated with protective immunity in TB. We investigated this in genetically modified mice displaying human IgA antibody receptor by infecting them with aerosolised MDR-TB and treating them with IgA/IFN-gamma combined immunotherapy. We found that the 2E9-IgA antibody reduced bacterial infection of human monocytes, suggesting that blocking of uptake of bacteria is a potential mechanism of action. Treatment of MDR-TB infected mice with 2E9IgA and IFN-ɣ reduced MDR-TB infection by 10-50 fold. This therapeutic effect following passive IgA transfer was highly reproducible, indicating that this treatment has the potential to be developed into an effective MDR-TB therapy in humans and importantly, that Acr is a promising target antigen for vaccine induced mucosal antib

**Funding Sources and Conflicts of Interest:** European Community

## PD-22

### BCG vaccine as proof-of-concept

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BCG vaccination has been efficacious against TB in several randomized-controlled trials (RCTs). We hypothesize that this proof-of-concept could be leveraged via reductionist studies to explore a mechanism of protection. Given that BCG vaccines used in RCTs lack 5 prominent M. bovis antigens (ESAT-6, CFP-10, MPB64, MPB70, MPB83), we tested whether the presence/absence of these antigens affected protection in murine models of vaccination, followed by M. tuberculosis aerosol challenge. In published investigations, expression of mpt64 by BCG Pasteur led to a detectable T cell-mediated response to MPB64, but no change in protection (Kozak, Vaccine, 2011). In separate investigations, we introduced wild-type sigK into BCG Pasteur, restoring the high-level production of MPB70 and MPB83 (Charlet, Mol Micro, 2005). Again, we observed antigen-specific interferon-gamma production, but no change in protection (Charlet, Izzo, Behr; unpublished). To test whether the ESAT-6 and CFP-10 are critical for protection, we vaccinated with M. kansasii, which produces and secretes these proteins (Wang, GBE, 2015). Protection in the murine model was reduced, as compared to BCG Pasteur. In summary, the provision of these 5 antigenic proteins by live mycobacteria does not predict protection against M. tuberculosis, in a murine model. Given that BCG Pasteur reproducibly elicits a 1-log protection, despite the absence of ESAT-6, CFP-10, MPB64, MPB70, MPB83, we hypothesize that the mechanism of protection is independent of antigen-specific T cell responses.

**Funding Sources and Conflicts of Interest:** Canadian Institutes for Health Research

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## PD-23

### Effect of anti-tuberculosis treatment on the systemic levels of matrix metalloproteinases and tissue inhibitors of MMP in tuberculosis – diabetes co-morbidity

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**Background:** Matrix metalloproteinases (MMPs) are considered to be key mediators of tuberculosis (TB) pathology and tissue inhibitors of metalloproteinases (TIMPs) facilitate the remodeling and repair of tissue following destruction by MMPs but their role in tuberculosis – diabetes comorbidity (TB-DM) is not well understood.

**Methods:** To study the association of MMP and TIMP levels with TB-DM comorbidity at baseline and in response to anti-TB treatment, luminex multiplex ELISA was performed to examined the systemic levels of MMP1, 2, 3, 7, 8, 9, 10, 12, 13 and TIMP 1, 2, 3, 4 in individuals with either tuberculosis alone (TB) or tuberculosis – diabetes comorbidity (TB-DM) at baseline and at 6 months completion of anti-TB treatment.

**Results:** Circulating levels of MMP 1, 2, 3, 7, 10, 12 and TIMP 1, 3, 4 were significantly higher in TB-DM compared to TB at baseline and 6 months post treatment. Moreover, the levels of MMP 1, 2, 3, 9 and 12 and TIMP 1, 3, 4 were significantly higher in TB-DM individuals with bilateral and cavitary disease and also exhibited a significant positive relationship with bacterial burdens at baseline. In addition, MMP 1, 7, 10 and TIMP 3, 4 levels exhibited a positive relationship with HbA1c levels. Finally, hierarchical cluster analysis reveals the utility of MMP and TIMP family in discriminating TB patients with diabetes from TB patients without diabetes.

**Conclusion:** Therefore, our results imply that MMP inhibition might be useful in host directed therapy (HDT) in TB-DM patients. Our data also add to the growing list of evidence indicating heightened immune activation in this immune-metabolic nexus. Finally, our study reinforces the necessity of aggressively controlling the dysregulated glucose metabolism and inflammatory milieu that characterized TB-DM to minimize inflammatory pathology and possibly poor outcomes in TB-DM co-morbidity.

**Funding Sources and Conflicts of Interest:** All authors: No potential conflicts of interest

# PD-24

## The ESAT-6 free IGRA, a companion diagnostic for ESAT-6 based TB vaccines

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**Background:** There is a need for an improved vaccine for tuberculosis. ESAT-6 is a cardinal vaccine antigen with unique properties and is included in several vaccine candidates in development. ESAT-6 is also a core antigen in the IFN-γ release assays (IGRA) used to diagnose latent infection, rendering IGRA tests unspecific after vaccination with these candidates. This challenge has prompted the development of a companion diagnostic for ESAT-6 based vaccines, an ESAT-6 free IGRA (Ef-IGRA).

**Methods:** We screened a panel of seven potential new diagnostic M.tb antigens, not expressed by BCG, in LTBI and TB patients from Egypt, Denmark, South Africa and Greenland. Most promising antigens were combined with CFP10 in the Ef-IGRA peptide cocktail, lyophilized with heparin in field-friendly vacutainer tubes. The diagnostic performance was determined in cross-validation studies in Denmark, Tanzania and South Africa.

**Results:** Immunodominant epitopes from three highly recognized antigens EspC, EspF and Rv2348c were identified and included in the Ef-IGRA. Quantiferon-TB Gold (QFT) and the Ef-IGRA induced a comparable magnitude of both IFN-γ and IP-10 release.

The diagnostic performance of Ef-IGRA was on-par with QFT: sensitivity 84% vs 79% (active TB, n=68), specificity 99% vs 97%, (unexposed controls, n=100). Concordance in endemic controls was 97% (Tanzania (n=193), 21% QFT positive) and 92% (South Africa (n=200), 42% QFT positive).

**Discussion:** The comparable performance of the Ef-IGRA to QFT suggests potential as companion diagnostic for ESAT-6 containing vaccines and importantly as an endpoint assay in prevention of infection trials. Ef-IGRA antigens have potential for combination with ESAT-6 for more robust detection of LTBI in immunosuppressed individuals and children.

**Funding Sources and Conflicts of Interest:** SSI, Aeras, GLOBVAC (Research Counsil Norway)

## PD-25

### Circulating Mycobacterium tuberculosis DosR latency antigen-specific, polyfunctional, regulatory IL10+ Th17 CD4 T-cells differentiate latent from active tuberculosis

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The functional heterogeneity of T cell responses to diverse antigens expressed at different stages of Mycobacterium tuberculosis (Mtb) infection, in particular early secretory versus dormancy related latency antigens expressed later, that distinguish subjects with latent (LTBI), pulmonary (PTB) or extrapulmonary (EPTB) tuberculosis remains unclear. An effective antigen-specific CD4 T cell response is critical for TB control and maintaining a disease free state, as loss of CD4 T cells during HIV coinfection remains the single most important driver of global incidence of active TB.

The immune response to two functional classes of Mtb antigens (immunodominant and DosR latency) as well as two common recall antigens was studied in clinically well-defined LTBI, PTB and EPTB Indian subjects by intracellular cytokine staining assay using advanced 16-colour flow cytometry and analyzed by the advanced bioinformatics algorithm COMPASS (COMbinatorial Polyfunctionality Analysis of Antigen-Specific T cell Subsets).

Blood central memory CD4 T-cell responses specific to Mtb dormancy related (DosR) latency, but not classical immunodominant secretory antigens, clearly differentiate LTBI from EPTB and PTB. The polyfunctionality score integrating up to 31 DosR-specific CD4 T-cell functional profiles was significantly higher in LTBI than EPTB or PTB subjects. Further analysis of 256 DosR-specific T-cell functional profiles identified regulatory IL10+Th17 cells to be significantly enriched in LTBI; in contrast to pro-inflammatory Th17 cells (IFNγ+IL17A+) in the blood and lung of EPTB and PTB subjects respectively. Preliminary data also show that regulatory Th17 phenotype is restored in treated TB cases, whereas progressively lost in HIV+IGRA+ patients.

A blood polyfunctional, Mtb DosR latency antigen specific, regulatory, central memory response is therefore a novel functional component of T-cell immunity in latent TB and potential correlate of protection.

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## PD-26

### Proliferative T cell (CD3+Ki67+) response to PPD and M. tuberculosis cell membrane complements the tuberculin skin test for detection of latent TB infection in healthy North Indian hospital contacts

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**Background:** Estimates of latent TB infection (LTBI) can help in devising new TB control measures. Tuberculin skin test (TST) is widely used to detect LTBI, as evidences show that the test is reasonably specific. However, evidences also show that the test is

grossly insensitive and may underreport prevalence of LTBI to a large extent. Looking for an alternative, studies have shown that blood T cells from TST unresponsive persons can respond to PPD. It has also been shown that T cell response to M. tuberculosis (Mtb) membrane may discriminate between TB and LTBI. We therefore explored whether in vitro T cell responses to PPD and Mtb membrane, along with TST, can unravel the true prevalence of LTBI in a high disease burden setting.

**Methods:** 80 North Indian hospital workers were studied. Their demographic data and TST responses were recorded. To assess proliferative T cell (CD3+Ki67+) responses, diluted blood was incubated (5 days in CO2 incubator) with medium, PHA (as controls) or Mtb antigens. Cells were stained with fluorescent anti-CD3 antibody and, after lysing (RBCs), fixing and permeabilizing, with a fluorescent antibody to nuclear protein Ki67. Data was collected and analysed on flow cytometer.

**Results:** 48% subjects showed positivity for TST independently of their BCG status. 72% and 100% of TST positives, respectively, were positive for proliferative T cell responses to PPD and membrane. Importantly, 62% and 88% the TST negatives were also positive for the two in vitro assays. Positivity by either assay was 82% for PPD and 94% for membrane.

**Conclusion:** The in vitro T cell response to PPD partly complements in vivo (TST) response. However, T cell response to Mtb membrane turned out to be most sensitive biomarker for LTBI. These results can be reconciled with the fact that India is a TB hyperendemic country and, in a study from North India (PLoS ONE, 2017, e0169539) comparable number of new TB cases emerged from TST positive and negative contacts.

**Funding Sources and Conflicts of Interest:** Funding Sources: Indian Council of Medical Research (EMS project of SS) and SGPGIMS (intramural project of RM). Conflict of interest: None.

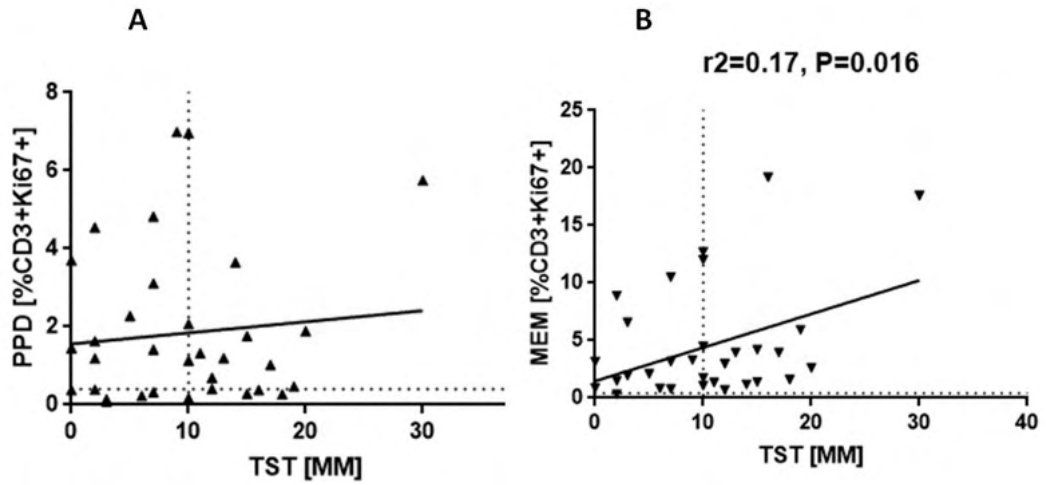


Figure: Scatter plots showing Tuberculin Skin Test indurations (mm, x axis) and proliferative T cell (CD3+Ki67+) responses (y axis) to PPD (A) and Mtb membrane (B) as % of total T cells (CD3+). Cutoff values for a positive response are indicated by dotted lines.

# PD-27

## CD14+ CD16+ cells as immunological marker for protection in household contacts with latent tuberculosis infection

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**Background:** One-third of the global population is estimated to have Latent TB Infection (LTBI). Biomarkers can be used to identify both; persons who are at great risk for development of active TB disease and those who are resistant to TB having

significant exposure. Monocytes play a pivotal role as cellular component of the innate immune response also influence the process of adaptive immunity due to their role in antigen presentation. The CD14+CD16+ cells were found to secrete pro-inflammatory cytokines for arresting bacterial growth and activation of T cells. Monitoring these cells with the cytokines levels in HHCs would be informative and indicative of either TB protection or progression. HIV negative household contacts (HHCs) of active pulmonary TB patients visiting clinics of Mahavir hospital and LEPRA were enrolled for the study after written and informed consent.

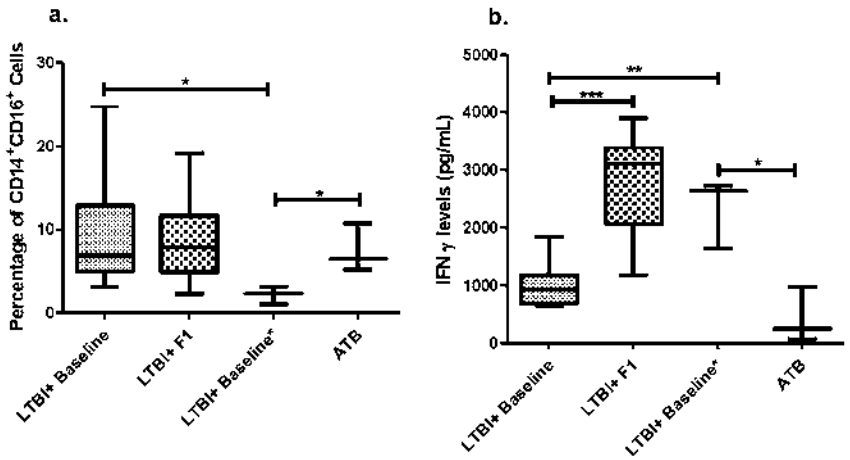
**Methods:** PBMCs from the venous blood (20ml) were isolated by density gradient centrifugation. Immunophenotyping of circulating CD14+CD16+ cells was performed by flow cytometry. PBMCs were cultured with CFP10+ESAT6 antigens for 96 hours. The IFN-γ levels in culture supernatants were assessed by ELISA and the levels were used to determining latency. Above experiments were repeated after every 4 months for 2 years.

**Results:** The baseline CD14+CD16+ cells were significantly high (p=0.03) in non-progressors (HHCs who remained LTBI+ on follow up) when compared to TB progressors (HHCs who progressed to active TB on follow up) (fig. 1a). PBMCs from non progressors expressed significantly lower levels of CFP+ESAT6 specific IFN-γ (p=0.003) when compared to TB progressors at baseline. The levels of IFN-γ significantly increased in non-progressors (p=0.0004) and decreased (p=0.01) in TB progressors on follow up (fig 1b).

**Conclusion:** High percentages of CD14+CD16+ cells in non progressors indicates robust innate immune system and can be used as an immune correlate of protection against TB in high risk HHCs.

**Funding Sources and Conflicts of Interest:** This project is supported by DBT, CRDF and NIH as a part of RePORT India consortium (BT/PR9622/MED/15/109/2013). Conflict of Interest: None

**Figure 1: a. Circulating percentage of CD14+CD16+ cells at baseline and follow up b. CFP+ESAT6 specific IFN-γ levels at baseline and follow up; in TB progressors and non-progressors.**




## PD-28

## Optimization and interpretation of serial QuantiFERON testing to measure acquisition of M. tuberculosis infection

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**Background:** Conversion from negative to positive QuantiFERON-TB test (QFT) is indicative of established Mycobacterium tuberculosis (Mtb) infection, which predisposes to tuberculosis (TB) disease. Interpretation of serial tests is confounded by immunological and technical variability. We aimed to improve consistency of serial QFT testing algorithms and to provide a data-driven definition of conversion, to evaluate vaccine efficacy in prevention of Mtb infection trials.
**Methods:** Sources of QFT variability were assessed and optimal procedures implemented. Distributions of IFNγ response levels were analysed in healthy adolescents, Mtb-unexposed controls, and pulmonary TB patients.

**Results:** Individuals with no known Mtb exposure had IFNγ values <0.2 IU/mL. Among individuals with IFNγ values <0.2, 0.2-0.34, 0.35-0.7, and >0.7 IU/mL, tuberculin skin test positivity was 15%, 53%, 66% and 91% (p<0.005), respectively. These findings suggest that values <0.2 IU/mL were true negatives. In short-term serial testing, "uncertain" conversions, with at least one value within the uncertainty zone (0.2-0.7 IU/mL), were partly explained by technical assay variability. Individuals who had a change in QFT IFNγ values from <0.2 to >0.7 IU/mL had 10-fold higher TB incidence rates than those who maintained values <0.2 IU/mL over 2 years (p=0.0003). By contrast, "uncertain" converters were not at higher risk than non-converters (p=0.229). Eighty-seven percent of active TB patients had IFNγ values >0.7IU/mL, suggesting that these values are consistent with established Mtb infection.

**Discussion:** Implementation of optimized procedures and a more rigorous QFT conversion definition, an increase from IFNγ <0.2 to >0.7 IU/mL, allow more definitive detection of recently established Mtb infection and should guide interpretation of serial QFT testing for clinical decision-making and for clinical trials in which acquisition of Mtb infection, measured by QFT assay conversion, is the endpoint

**Funding Sources and Conflicts of Interest:** Funding: Aeras, Sanofi Pasteur, Bill & Melinda Gates Foundation, NIH. No conflict of interest

**QFT conversion and prospective risk of TB disease**

| QFT Class | TB Cases | n | Observation Years | Incidence (cases/100 person years) | (95% Confidence interval) | P value | IRR* | (95% Confidence interval) |
|---|---|---|---|---|---|---|---|---|
| Stringent Non converters† | 2 | 648 | 1289.79 | 0.16 | (0.02-0.56) | ref | ref | ref |
| Stringent Persistent positives‡ | 19 | 989 | 1953.07 | 0.97 | (0.59-1.52) | 0.005 | 6.27 | (1.51-55.55) |
| Stringent Converters§ | 14 | 485 | 874.3 | 1.60 | (0.88-2.69) | 0.0003 | 10.33 | (2.37-93.62) |
| "Uncertain" converters‖ | 3 | 310 | 453.3 | 0.66 | (0.14-1.95) | 0.229 | 4.27 | (0.49-51.10) |

*IRR= incidence rate ratio
† IFNg (TB Ag – Nil) <0.2 IU/mL at day 0, 360 and 720
‡ IFNg (TB Ag – Nil) >0.7 IU/mL at day 0, 360 and 720
§ IFNg (TB Ag – Nil) <0.2 IU/mL at day 0 and IFNg >0.7 IU/mL at day 360
‖ IFNg (TB Ag – Nil) <0.35 IU/mL at day 0 and IFNg ≥0.35 IU/mL at day 360, with at least one result within 0.2-0.7 IU/mL

## PD-29

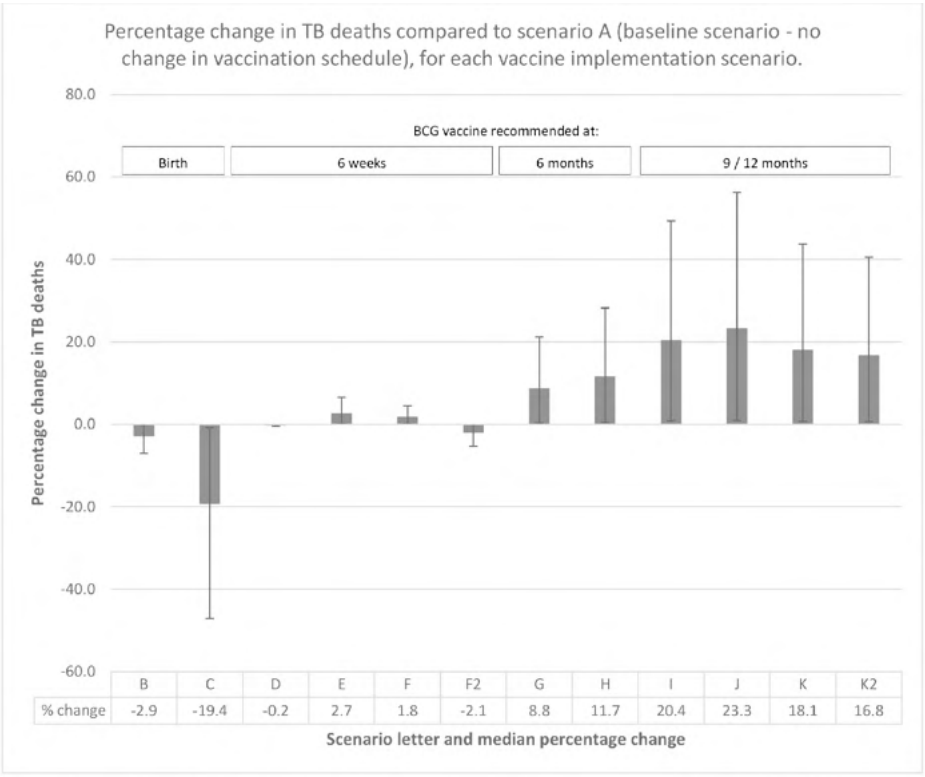
# Updating the recommended age of BCG vaccination? Modelling the potential impact on global paediatric TB mortality

**Partho Roy,** Rebecca C Harris, Richard G White

*TB Modelling Group, London School of Hygiene & Tropical Medicine, UK*

The World Health Organization (WHO) recommends HIV-negative infants in high burden tuberculosis (TB) countries should receive Bacillus Calmette–Guérin (BCG) as soon as possible after birth. However, globally, 50% BCG vaccination coverage is achieved at 3-4 weeks of age. WHO is considering updating the existing recommendations. We estimated the potential impact of changes to the age of BCG vaccination on global paediatric TB mortality. A static mathematical model, calibrated to the 2015 number of global childhood TB deaths and current age distribution for BCG vaccination, was developed. Number of TB deaths per global birth cohort over the first 15 years of life was estimated for 12 hypothetical scenarios for age of BCG vaccination. Scenarios included recommending BCG at birth, 6 weeks, 6 months or 1 year of age, with 2-4 implementation scenarios per recommendation, including BCG co-administration with the first dose of Diptheria-Tetanus-Pertussis vaccine (DTP1) or Measles containing vaccine (MCV). Achieving BCG final coverage (89.4%) at birth was estimated to reduce global TB deaths by 2.9% (95%UR: 0.1%-7.1%). Co-administration with DTP1 with no increase in final BCG coverage was estimated to increase TB deaths by 1.8% (95%UR: 0.1%-4.5%), or if BCG coverage reached DTP1 coverage (92.9%) decreased TB deaths by 2.1% (95%UR: 0.1%-5.3%). Co-administration with MCV, recommended at 9 or 12 months, was estimated to lead to 18.1% (95%UR: 0.7%-43.8%) additional TB deaths, assuming no increase in BCG coverage. Eliminating existing delays in BCG vaccination, would lead to the greatest reduction in global paediatric TB mortality. Delayed vaccination would likely increase global paediatric TB mortality; though BCG/DTP1 co-administration may result in a small reduction in TB mortality if BCG coverage increased to equal DTP1 coverage. When updating current BCG recommendations, WHO policy makers should consider the feasibility of achieving earlier vaccination or increased coverage.

**Funding Sources and Conflicts of Interest:** The TB Modelling Group at London School of Hygiene & Tropical Medicine received funding from the World Health Organisation to conduct this research.




| Scenario | Scenario Description |
|---|---|
| A | Baseline: No change in vaccination schedule. 2015 BCG vaccination coverage by age distribution (89.4% final coverage). |
| B | 89.4% immediate coverage at birth |
| C | 100% immediate coverage at birth |
| D | 0% coverage until six weeks of age, then 89.4% immediate coverage at six weeks. |
| E | 0% coverage until six weeks of age, then 89.4% final coverage delaying the baseline BCG coverage distribution by six weeks. |
| F | Co-administration with DTP1, using 2015 DTP1 coverage by age distribution (capped when coverage reached 89.4%). |
| F2 | Co-administration with DTP1, using 2015 DTP1 coverage by age distribution (final coverage of 92.9%). |
| G | 0% coverage until six months of age then 89.4% immediate coverage at six months. |
| H | 0% coverage until six months of age, then 89.4% final coverage delaying the baseline BCG coverage distribution by six months. |
| I | 0% coverage until 12 months of age, then 89.4% immediate coverage at 12 months. |
| J | 0% coverage until 12 months of age, then 89.4% final coverage delaying baseline BCG coverage distribution by 12 months. |
| K | Co-administration with MCV, using 2015 MCV coverage by age distribution (capped when coverage reached 89.4%). |
| K2 | Co-administration with MCV, using 2015 MCV coverage by age distribution (final coverage of 90.9%). |

Figure 1. Percentage change in TB deaths compared to scenario A (baseline scenario – no change in vaccination schedule) for each vaccine implementation scenario, together with scenario descriptions. 95% uncertainty ranges are represented by error bars.

# PD-30

## Do we have identified target groups and a population based strategy for vaccination against tuberculosis to cut down transmission?

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**Background:** Globally research is underway to develop vaccines for TB. However, the epidemiological strategy to deploy the vaccines on a population basis to effectively interrupt the transmission of TB is lacking. Lack of evidence on TB transmission and it's patterns complicates the situation. The probability of household contacts to get the disease is 7-10%. However, the importance of contacts in epidemiology of Tuberculosis is not delineated. This study reports interim findings of an effort to understand the role of contacts in TB epidemiology.

**Methodology:** Qualitative & quantitative methods study wherein data collected from TB patients under treatment in a high endemic area of a Central Province of India. Data was collected on whether the TB patients have had any other TB patient in contact prior to developing their disease along with parameters such as type of contact, duration of contact etc.(mix methods study)

**Results:** At the time of writing this report, interview of 103 TB patients had been completed. Of the 103 TB patients, 100 (97%) reported to have been in contact with a TB patient in their lifetime. 20% of these reported contacts being from their household; 51% from neighborhood; 3% social contacts; 4% working place contacts; 18% were relatives; and 4% others. 20% patients reported an average of 50 person-hours of contact with the TB patient spread over one month; 6% reported 720 person-hours of contact in 6 months; 69% reported 900 person-hours of contact for more than six months and 5% could not recollect.

**Conclusion:** above results indicate that in high endemic setting "contacts" is an extremely important method for transmission of TB in the community. However, this is not limited to household contacts and could be neighborhood, social, workplace and other settings. Targeting the contacts with an expansive definition inclusive of neighborhood, social, workplace contacts for vaccination could be a very useful strategy to interrupt transmission.

**Funding Sources and Conflicts of Interest:** Not applicable

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# PD-31

## TB Infection among household contacts: Preventive therapy for all?

**Chandra Kumar Dolla[3],** Mandar Paradkar[2], Akshay Gupte[4], Kannan Thiruvenkadam[3], Nikhil Gupte[2,4], Vandana Kukarni[2], Elizabeth Hannah[3], Kavitha Dhanasekaran[3], Renu Bharadwaj[1], Shri Vijay Bala Yogendra Shivakumar[2,3], Sanjay Gaikwad[1], Sushant Meshram[1], Rewa Kohli[2], Rahul Lokhande[1], Beena Thomas[3], Aarti Kinikar[1], Soumya Swaminathan[3], Vidya Mave[2,4], Amita Gupta[2], Padmapriyadarshini Chandrasekaran[3]

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**Background:** Tuberculosis (TB) is the biggest killer among infectious diseases worldwide and India has the highest burden of TB globally. Household contacts (HHCs) of TB patients are at high risk of acquiring TB infection (TBI) from their household index cases and develop TB disease. Many countries recommend TB preventive therapy only for children less than 6 years of age and for people living with HIV.

**Methods:** We assessed the age-specific prevalence of TBI among HHCs by both tuberculin skin test (TST) and QuantiFERON-Gold in tube test (QGIT) testing among household contacts of pulmonary TB patients in Chennai and Pune, India. We defined TBI positivity as either TST ≥5mm or QGIT ≥0.35 IU/ml as per manufacturer instructions. We stratified prevalence of TB Infection by TST and QGIT by age groups 0-5 years, 6-14 years, 15- 45 years, 46 years and above. Kappa agreement was calculated for TST and QGIT by age group.

**Results:** Of 850 HHCs of 369 adult pulmonary TB cases, 244 (28.7%) were children <15 years, 375 (44.1%) female, 17 (2.0%) HIV-infected, 55/618 (9%) with diabetes. We observed the age group TBI prevalence as follows: 41.2% age 0-5yrs; 55.7% age 6-14 yrs, 74.6% age 15- 45years and 86.1% age >45 years (Table 1). We also found 2.1% of culture positive TB disease in our cohort, TB disease by age groups are 4.5% in 0-14 years, 0.8% in 15-45 years and 2.5% in ≥46 years respectively. We noted that prevalence of TB infection increased with age by both TST and QGIT.

**Discussion and Conclusion:** We observed very high prevalence of TB infection that increased with age among our household contacts, who had recent exposure to infectious Pulmonary TB patients in their households. TB disease is very high among age groups 0-14 years and 45 and above. Preventive TB therapy should be recommended for all household contacts to help TB elimination goals of WHO. Prevention of infection and disease vaccines are urgently needed for this high risk population.

**Funding Sources and Conflicts of Interest:** Funding NIH,DBT, conflicts of interest none

Table 1: Age specific prevalence and agreement between TST and QGIT testing

| | | Age | | | | Total | p Value |
|---|---|---|---|---|---|---|---|
| | | < 6 | 6 - 15 | 15 - 45 | > 45 | | |
| TST, n | | 68 | 176 | 484 | 122 | 850 | |
| | Pos | 22 (32.4%) | 74 (42%) | 248 (51.2%) | 81 (66.4%) | 425 (50%) | < 0.001 |
| | Neg | 46 (67.6%) | 102 (58%) | 236 (48.8%) | 41 (33.6%) | 425 (50%) | |
| QGIT, n | | 55 | 162 | 443 | 109 | 769 | |
| | Pos | 16 (29.1%) | 69 (42.6%) | 257 (58%) | 79 (72.5%) | 421 (54.7%) | < 0.001 |
| | Neg | 39 (70.9%) | 93 (57.4%) | 186 (42%) | 30 (27.5%) | 348 (45.3%) | |
| TBI (T+/Q+), n | | 68 | 176 | 484 | 122 | 850 | |
| | Pos | 28 (41.2%) | 98 (55.7%) | 361 (74.6%) | 105 (86.1%) | 592 (69.6%) | < 0.001 |
| | Neg | 40 (58.8%) | 78 (44.3%) | 123 (25.4%) | 17 (13.9%) | 258 (30.4%) | |
| Only TST (T+&Q-), n | | 58 | 166 | 459 | 119 | 802 | |
| | Yes | 12 (20.7%) | 29 (17.5%) | 104 (22.7%) | 26 (21.8%) | 171 (21.3%) | 0.574 |
| | No | 46 (79.3%) | 137 (82.5%) | 355 (77.3%) | 93 (78.2%) | 631 (78.7%) | |
| Only QGIT (T-&Q+), n | | 55 | 162 | 443 | 119 | 779 | |
| | Yes | 6 (10.9%) | 24 (14.8%) | 113 (25.5%) | 24 (20.2%) | 167 (21.4%) | 0.007 |
| | No | 49 (89.1%) | 138 (85.2%) | 330 (74.5%) | 95 (79.8%) | 612 (78.6%) | |
| Both (T+&Q+), n | | 55 | 162 | 443 | 109 | 769 | |
| | Yes | 10 (18.2%) | 45 (27.8%) | 144 (32.5%) | 55 (50.5%) | 254 (33%) | < 0.001 |
| | No | 45 (81.8%) | 117 (72.2%) | 299 (67.5%) | 54 (49.5%) | 515 (67%) | |
| Agreement between TST & QGIT | | 73% | 70% | 55% | 63% | 60% | |
| | Kappa | 0.374 (0.132) Fair | 0.383 (0.073) Fair | 0.086 (0.047) Poor | 0.15 (0.097) Poor | 0.205 (0.035) Fair | |

# PD-32

## Infection free "resistors" among household contacts of culture-confirmed adult pulmonary TB cases

**Vidya Mave**[1,2], Padmapriyadarshini Chandrasekaran[3], Mandar Paradkar[1], Akshay Gupte[4], Neeta Pradhan[1], Gomathy Narayan Sivaramakrishnan[3], Kannan Thiruvengadam[3], Shri Vijay Bala Yogendra Shivakumar[5], Vandana Kulkarni[1], Kavitha Dhanasekaran[3], Balaji Subramanyam[3], Sriram Selvaraju[3], Lakshmi Murali[6], Renu Bharadwaj[7], Sanjay Gaikwad[7], Sushant Meshram[7], Aarti Kinikar[7], Luke Elizabeth Hannah[3], Soumya Swaminathan[8], Nikhil Gupte[1,2], Amita Gupta[2,4]

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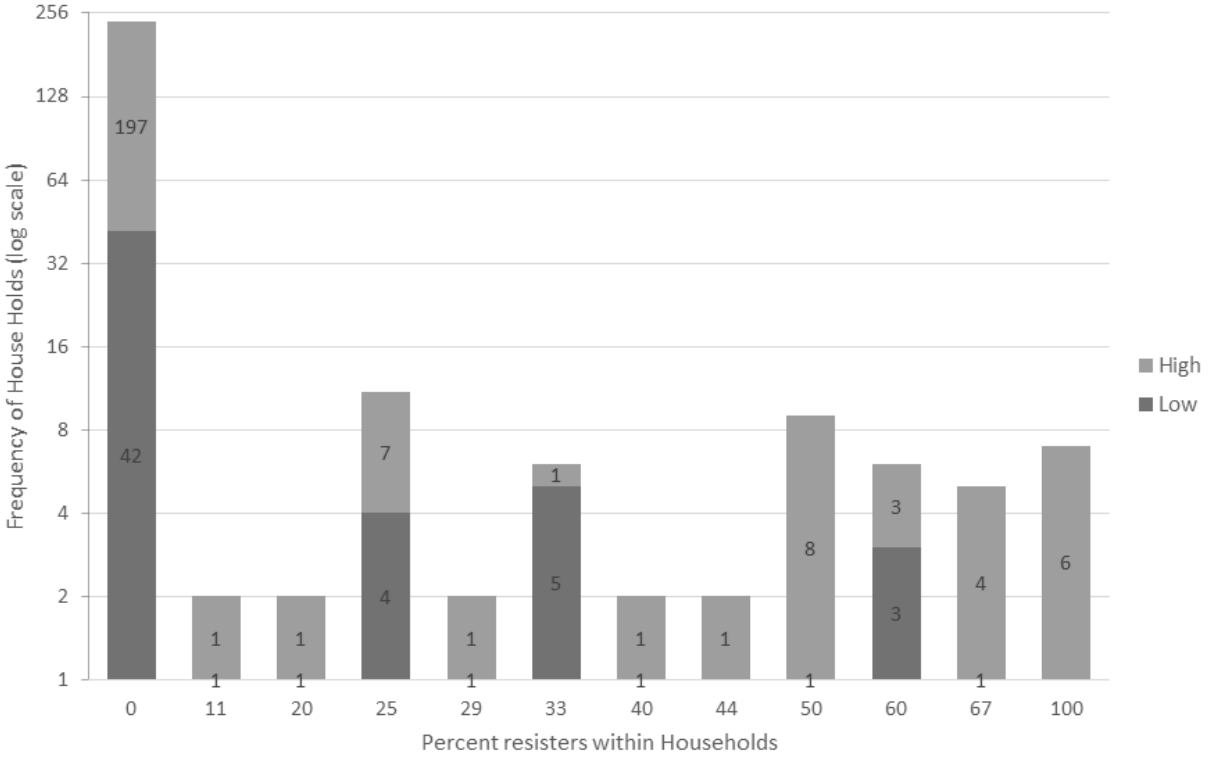
**Background:** Despite high exposure to infectious pulmonary tuberculosis (PTB) cases, some household contacts (HHCs) never acquire TB infection (TBI), and are often referred as "resistors" of TB infection. Characterizing these HHCs is highly relevant to translational science research to identify the target immunologic profile to inform development of TB vaccines.

**Methods:** Between August 2014 and May 2017, as part of Cohort for TB Research with Indo-US Medical partnership (C-TRIUMPH) study, we prospectively enrolled HHCs of adult PTB patients in India. HHCs underwent tuberculin skin test (TST) and QuantiFERON® TB Gold Test-in-tube (QGIT) at study entry and if negative by both (<5mm TST and <0.35IU/mL QGIT), underwent follow-up TST and/or QGIT testing at 4-6 and/or 12 months. Using random effects Poisson regression, we assessed factors associated with resistors (defined as no evidence of TBI at 12 months following exposure to culture positive PTB). We calculated the percent of resistors in HHs with high exposure (defined as >6 score for adults and >5 score for children using a published score) to PTB.

**Results:** Of 570 HHCs in 293 HHs exposed to culture positive PTB, 59 (10%) from 38 HHs were resistors. 2 of 33 diabetics and 0 of 8 HIV-infected HHCs were resistors.14 (24%) shared the same bed as the index case, 13 (22%) shared 3 or more meals per day and 46 (78%) spent more than 6 hours in a day. Resistors were younger in age (<6 years: relative risk (RR), 9.61; 95% CI, 1.99 - 46.45 and 6-15 years: RR, 8.8; 95% CI, 1.97 - 39.30) and more educated (RR, 9.30; 95% CI,1.08 - 80.49). 31 (53%) resistors had high TB exposure score; 21 HHs had >50% of its members who were resistors despite high exposure (Figure).

**Conclusions:** Despite high exposure to PTB, a small subset of individuals appears to resist the development of infection. Notably, this group tends to cluster in HHs suggesting unique genetic and immunologic mechanisms for resistance to TB infections.

**Funding Sources and Conflicts of Interest:** CTRIUMPH is part of the RePORT consortium funded with Federal funds from the Government of India's (GOI) Department of Biotechnology (DBT), the ICMR, the USA National Institutes of Health (NIH/NIAID) and the Office of AIDS Research. The authors declare that they have no conflict of interest.



## PD-33

### Incidence of Mycobacterium tuberculosis infection among household contacts of adult pulmonary tuberculosis cases in India

**Mandar Paradkar[1],** Kavitha Dhanasekaran[2], Aarti Kinikar[3], Rajesh Kulkarni[3], Renu Bharadwaj[3], Sanjay Gaikwad[3], Rahul Lokhande[3], Sushant Meshram[3], CK Dolla[2], Sriram Selvaraju[2], Lakshmi Murali[2], Kannan Thiruvengadam[2], Divyashri Jain[1], Saranathan Rajagopal[2], Vandana Kulkarni[1], Neeta Pradhan[1], Shalini J[2], Rewa Kohli[1], Rani Nayagam[2], Shrivijay Bala Yogendra Shivakumar[1,3], Nishi Suryavanshi[1], Akshay Gupte[4], Nikhil Gupte[1,4], Padmapriyadarshini Chandrasekaran[2], Vidya Mave[1,4], Amita Gupta[4] for the CTRIUMPh Study Team

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**Background:** Evaluating incident tuberculosis infection (TBI) in household contacts (HHC) of tuberculosis (TB) cases in high burden settings such as India is vital for TB biomarker and vaccine development.

**Methods:** CTRIUMPH study prospectively enrolled HHCs (adults/children living in same house with adult pulmonary TB case) in Pune and Chennai, India. Tuberculin skin test (TST, 5TUs) and Quantiferon Gold-In Tube test (QGIT) were performed at enrollment, and at 4 months and 12 months among HHCs without TBI at previous visit. Incident TBI was defined as TST induration ≥5mm or positive QGIT (>0.35 IU/mL) at follow up. We calculated incidence rates by Poisson regression and Kaplan-Meier estimate for cumulative incidence, for TST, QGIT and either. A published exposure score was used to quantify the TB exposure. Cox proportional hazards regression was performed. Models adjusted for age, gender and exposure score. McNemar's test was performed to compare the age-specific incidence by TST and QGIT.

**Results:** 706/999 (70.6%) HHCs enrolled had TBI at baseline. 199 HHCs (Age in years- <6=25, 6-<15=54, 15-<25=38, 25-45=66, >45=16) without baseline TBI completed 12 months follow-up and were analyzed. 83 (41.7%) seroconverted by 12 months. TBI incidence by QGIT, TST and either test positivity was 280, 557 and 702 per 1000 person-years respectively. Figure 1 shows cumulative TBI incidence by index smear/culture status. HHC age>45 years was independently associated with TBI by TST (aHR=3.98, 95%CI 1.29-12.2, p=0.02) and TST and/or QGIT (aHR=3.70, 95%CI 1.30-10.52, p=0.01). Males (aHR=1.26, 95%CI 1.06-1.97, p=0.04) and high TB exposure score (aHR=1.58, 95%CI 1.33-2.68, p=0.04) were associated with TBI by TST and/or QGIT. TBI was higher by TST than QGIT in HHCs aged 15-<25 (p-0.003) and <45 years (p=0.008).

**Conclusion:** Among our cohort of Indian HHCs recently exposed to TB, incidence of TBI was impacted by type of TBI test used, index smear status, age, male sex and by TB exposure score.

**Funding Sources and Conflicts of Interest:** CTRIUMPH is part of the RePORT consortium funded with Federal funds from the Government of India's (GOI) Department of Biotechnology (DBT), the Indian Council of Medical Research (ICMR), the USA National Institutes of Health (NIH), the National Institute of Allergy and Infectious Diseases (NIAID), the Office of AIDS Research (OAR), and distributed in part by CRDF Global. This work was also supported by the National Institutes of Health (NIH 1R01A1I097494-01A1), the NIH funded Johns Hopkins Baltimore-Washington-India Clinical Trials Unit for NIAID Networks (U01 AI069497). Aarti Kinikar, Rajesh Kulkarni and Rahul Lokhande are supported by the BJGMC JHU HIV TB Program funded by the Fogarty International Center, NIH (Grant# D43TW009574).

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## PD-34

### Immunogenicity of AERAS-404 or BCG revaccination in a prevention of established M. tuberculosis infection efficacy trial

**Virginie Rozot[1],** Elisa Nemes[1], Hennie Geldenhuys[1], Asma Toefy[1], Frances Ratangee[1], Lebohang Makhethe[1], Mzwandile Erasmus[1], Nicole Bilek[1], Ann M. Ginsberg[2], Kathryn Rutkowski[2], Devin Hunt[2], Robert Ryall[3], Sanjay Gurunathan[3], Carlos DiazGranados[3], Robert Hopkins[2], Thomas J. Scriba[1], Mark Hatherill[1], the C040-404 Study Team

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Persons with recently acquired M. tuberculosis (M.tb) infection are at greater risk of tuberculosis (TB) disease than uninfected or remotely infected individuals. A vaccine that prevents an established M.tb infection (measured by interferon-gamma release assay (IGRA)-conversion) would likely have a major impact on incidence of TB disease, M.tb transmission, and control of the epidemic. Vaccine-mediated prevention of IGRA conversion would provide valuable proof-of-concept data required for advancing candidates to efficacy trials that test prevention of TB disease. The first prevention of M.tb infection trial, C-040-404 (NCT02075203), is a Phase II randomized, controlled, partially blinded trial, conducted in a region endemic for TB. This trial aimed to determine the safety, immunogenicity, and prevention of IGRA conversion of AERAS-404 and BCG revaccination in previously BCG vaccinated, IGRA-negative adolescents. Here we sought to determine the immunogenicity of AERAS-404 and BCG revaccination in participants of the C-040-404 trial.

Participants were randomized in a 1:1:1 ratio to receive either two doses of AERAS-404 (15 μg H4 in 500 nmol IC31) or placebo, administered by intramuscular injection 56 days apart; or one dose of BCG (2-8x105 CFU) administered by intradermal injection. Whole blood from 90 adolescents (30 from each arm) was collected before and after vaccination and a whole blood intracellular cytokine staining assay was performed. Blood was stimulated with peptide pools representing the mycobacterial antigens Ag85B and TB10.4 (H4 antigen in AERAS-404) or with viable BCG from the vaccine vial. We quantified expression of IFN-γ, IL-2, TNF-α, IL-17 and IL-22 by classical CD4 and CD8 T cells, γδ T cells, NKTlike and MAIT cells as well as NK cells by flow cytometry.

Analyses are complete but participant allocation to vaccine arm is still blinded. Unblinded immunogenicity data will be presented at the conference.

**Funding Sources and Conflicts of Interest:** Aeras, Sanofi

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# PD-35

## Phase 1 clinical trial to evaluate the safety and immunogenicity of an adenovirus-based tuberculosis vaccine (Ad5Ag85A) administered by aerosol to healthy volunteers

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Respiratory mucosal (RM) vaccination is the most effective way to generate mucosal-associated protective immunity against pulmonary TB. RM vaccination with a recombinant, replication-deficient serotype 5 adenovirus-based TB vaccine (Ad5Ag85A) conferred robust protection by creating long-lasting tissue resident memory T cells in the lung of experimental animals. The vaccine was safe and immunogenic after intramuscular (IM) vaccination in BCG-primed healthy human volunteers. However the potential of Ad5Ag85A for RM use in humans remains to be evaluated. We have begun enrolment of a clinical trial to evaluate the safety and immunogenicity of aerosol delivery of a low and medium dose of Ad5Ag85A to the respiratory tract of 16 healthy human subjects with a history of BCG vaccination, and will compare aerosol delivery of the highest tolerated dose with IM delivery in a further 20 participants. A single dose of Ad5Ag85A will be aerosolized and inhaled via mouthpiece and tidal breathing using the AeroNeb® Solo Mesh Nebulizer. This device produces aerosol particles with a diameter of 3.4μm and efficiently delivers vaccine to the lung. Safety observations will be made up to 16 weeks after vaccination. Bronchoalveolar lavage (BAL), induced sputum (IS) and blood will be collected before vaccination and at 2 and 8 weeks. BAL, IS and blood samples will undergo immunophenotyping and antigen-specific immune analyses by cytokine ELISA, cell surface immunostaining and intracellular cytokine staining. We will study vaccine-trained innate immunity in the lung by examining imprinted memory alveolar macrophages and examine vaccine-induced tissue resident memory T cells in the lung. By comparing circulating T cells post-aerosol and IM vaccination, we hope to identify biosignatures of protective T cells. We expect that aerosol vaccination will induce dose-dependent memory innate cell and Ag-specific T cell responses in the lung. Preliminary safety and immunogenicity data will be presented.

**Funding Sources and Conflicts of Interest:** Canadian Institutes of Health Research

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## PD-36

### Dose definition of the novel TB vaccine ID93 + GLA-SE for TB endemic countries

**Adam Penn-Nicholson[1]*,** Michele Tameris[1]*, Erica Smit[1], Tracey A. Day[2], Munyaradzi Musvosvi[1], Lakshmi Jayashankar[2], Julie Vergara[2], Simba Mabwe[1], Nicole Bilek[1], Hendrik Geldenhuys[1], Angelique Kany-Kany Luabeya[1], Ruth Ellis[3], Ann M Ginsberg[3], Willem A. Hanekom[1], Steven G. Reed[2], Rhea N. Coler[2], Thomas J. Scriba[1]**, Mark Hatherill[1]** and the TBVPX-114 study team
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**& ** contributed equally*

**Rationale:** A new effective tuberculosis (TB) vaccine is needed to halt transmission in endemic regions by prevention of infectious pulmonary TB in adults.

**Objectives:** This randomized, double-blind, controlled trial aimed to evaluate safety and immunogenicity of three administrations of ID93 + GLA-SE vaccine in previously BCG-vaccinated South African adults (NCT01927159).

**Methods:** Mycobacterium tuberculosis (M.tb) infection was defined by QuantiFERON (QFT) status. Cohort 1 QFT-negative participants received 10g ID93 + 2ug GLA-SE or placebo; thereafter QFT-negative or positive participants in subsequently enrolled cohorts received escalating doses of vaccine, or placebo. Specific immune responses were measured by intracellular cytokine staining, flow cytometry and ELISA.

**Measurements and Main Results:** ID93 + GLA-SE was well tolerated; no severe or serious vaccine-related adverse events (AEs) were observed. Vaccine dose did not influence frequency and severity of AEs, but mild injection site AEs and flu-like symptoms were common in QFT-positive participants. Vaccination induced durable antigen-specific IgG and Th1 cellular responses, which peaked after 2 administrations. Vaccine dose did not influence magnitude, kinetics or profile of antibody and cellular responses. Response kinetics and cytokine profiles to individual antigens differed in QFT-positive participants; Rv3619 and Rv3620-specific IgG was higher, and specific CD4 T cells were more differentiated and effector-like than Rv2608 or Rv1813-specific cells, suggesting priming by natural M.tb infection.

**Conclusions:** Escalating doses of ID93 + GLA-SE induced similar antigen-specific CD4 T cell and humoral responses, with an acceptable safety profile in BCG-immunized, M.tb-infected persons. These data support efficacy testing of two administrations of the lowest (2ug) ID93 vaccine dose in TB endemic populations.

**Funding Sources and Conflicts of Interest:** This work was supported by co-funding from Aeras and the Paul G. Allen Family Foundation.

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## PD-37

### The Toll-like Receptor 4 agonist adjuvant, GLA-SE, improves magnitude and quality of immune responses elicited by the ID93 tuberculosis vaccine

**Tracey Ann Day[1],** Lenette Lu[2], Rhea N. Coler[1], Galit Alter[2], Julie Vergara[1], Tom Rolf[1], Anna Marie Beckmann[1], David Hokey[3], Ann Ginsberg[4], Steven G. Reed[1], TBVPX-113 Study Team: Ruth Ellis[5], Franco M. Piazza[6], Lakshmi Jayashankar[7], Robert Walker[8], Jill Ashman[1], Zachary Sagawa[1], Tom Evans[4], Sadritdin Ishmukhamedov[4], Casey Johnson[9]

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**Background:** Tuberculosis (TB) is the leading cause of infectious death worldwide. Development of improved TB vaccines that boost or replace BCG are a major global health goal. ID93 + GLA-SE is a novel fusion protein TB vaccine candidate comprised of Rv1813, Rv2608, Rv3619, and Rv3620 antigens combined with the Toll-like Receptor 4 agonist adjuvant, GLA-SE. Preclinical

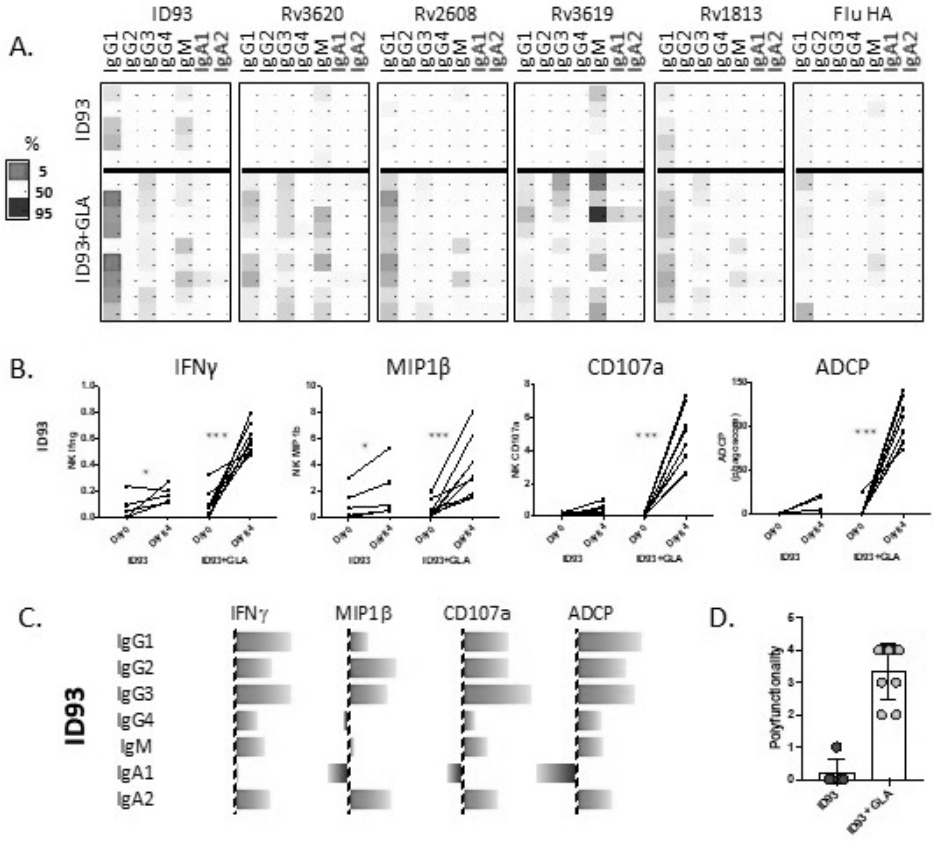
studies show that prophylactic vaccination with ID93 + GLA-SE is protective against TB and therapeutic vaccination can reduce the duration of antibiotic treatment and improve outcome over antibiotics alone. A first-in-human Phase 1 trial was conducted in healthy adults in the US. In this study, all dose levels appeared safe and immunogenic. Here, we describe new results further characterizing the quality and functionality of vaccine-induced immune responses.

**Methods:** A Phase 1, randomized, double-blind, dose escalation clinical trial was performed to evaluate the ID93 antigen alone or in combination with the GLA-SE adjuvant, in 60 BCG-naïve, QuantiFERON negative, healthy adults in the US. Vaccine specific cellular responses were evaluated from a whole blood intracellular cytokine staining assay. Antibody subclass analysis was performed using ELISA. Functional properties of antibodies were assessed using a THP1 phagocytosis assay and an NK cell activation assay.

**Results:** Compared with ID93 protein alone, subjects vaccinated with ID93 + GLA-SE elicited higher titers of ID93-specific antibodies, a preferential increase in IgG1 and IgG3 subclasses, and a multifaceted Fc effector function response. The addition of GLA-SE also enhanced the magnitude and polyfunctional cytokine profile of T-helper 1 type CD4+ T cells.

**Discussion and Conclusion:** The data demonstrate that the GLA-SE adjuvant drives a functional humoral and T-helper 1 type cellular response.

**Funding Sources and Conflicts of Interest:** This study was funded by Aeras and the Paul G Allen Family Foundation.




**Vaccine induced antibody response profiles**

A. Changes in ID93 and control Flu HA specific antibody isotype titers. B. Changes in ID93 specific antibody induced NK cell production of IFNγ, MIP1β, and CD107a, and antibody dependent cellular phagocytosis. C. Spearman correlation coefficients between ID93 antibody specific isotypes and effector functions. D. ID93 specific antibody effector functions per individual.

## PD-38

### Safety and Immunogenicity of H56:IC31 in HIV negative adults with and without latent tuberculosis(TB) infection

**Angelique Kany-Kany Luabeya[1],** Sara Suliman[1], Hennie Geldenhuys[1], Michele Tameris[1], Soren T. Hoff[2], Zhongkai Shi[3], Dereck Tait[4], Ingrid Kromann[2], Morten Ruhwald[2], Kathryn Tucker Rutkowski[3], Barbara Shepherd[3], David Hokey[3], Willem Hanekom[1], Peter Andersen[2], Thomas J. Scriba[1], Mark Hatherill[1]

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**Background**: H56:IC31 is a novel TB vaccine comprising a fusion protein of Mycobacterium tuberculosis (Mtb) antigens Ag85B, ESAT-6, and Rv2660c, formulated in IC31 adjuvant, in development for prevention of adult TB disease.

**Objectives**: Determine safety and immunogenicity, and select dose level and regimen of H56:IC31 in HIV(−), Mtb-uninfected and Mtb-infected adults for further development.

**Methods**: We enrolled HIV(-), BCG-vaccinated, South African adults. Mtb infection was defined by QuantiFERON (QFT) assay. The study was conducted in 2 phases. First, dose evaluation was performed in QFT(-) participants to select an H56/IC31 dose (5g/500nmol, 15g/500nmol, or 50g/500nmol). Subsequently, the dose selected was used to determine regimen in both QFT(+) and (-) participants who were randomized to receive 2 or 3 vaccinations. Participants were followed for 292 days for safety and immunogenicity.

**Results:** 399 adults were screened and 98 were enrolled. Fifty QFT(-) subjects were randomized into 3 groups (or placebo) in the first phase. H56:IC31 was well tolerated at all dose levels and 5g /500nmol was selected for the follow-up phase, as higher doses were not significantly more immunogenic. Subsequently, 16 QFT(-) and 32 QFT(+) subjects received either 2 or 3 vaccinations or placebo. Two and three doses of H56:IC31 were well tolerated with similar safety profiles. No vaccine-related severe or serious AEs were observed. Pain at injection site, fatigue, and myalgia were the most frequent solicited AEs reported. Most AEs were mild or moderate. H56:IC31 induced dominant Th1-cytokine expressing CD4+ T-cell responses to Ag85B and ESAT-6, but not Rv2660c, which persisted up to 8 months after the last vaccination. Three doses appeared to be slightly more immunogenic in LTBI(-) but not LTBI(+) subjects.

**Conclusion:** Our data suggest that 2 or 3 5g/500nmol doses are safe and immunogenic in LTBI(+) and (-) subjects and H56:IC31 should be further evaluated for prevention of TB disease.

**Funding Sources and Conflicts of Interest:** Aeras

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## PD-39

### Impact of implementing an effective community engagement strategy on retention rates in a Phase 2b TB disease prevention vaccine trial in South Africa, Zambia, and Kenya

**Anja van der Westhuizen[1],** Christina Caporaso[2], on behalf of the TB-018 study group.

The authors want to acknowledge the TB-018 study group which includes the teams at the sites (SATVI, KEMRI, CIDRI, ZAMBART, CIDRZ, Task Applied Science, Setshaba, AURUM, Tembisa, Be PART, PHRU) involved in the TB-018 study, Quintiles, Aeras and GSK.
*[1]Aeras, South Africa; [2]GSK Vaccines, Belgium*

**Background:** TB vaccine efficacy trials require to follow-up thousands of IGRA+ adults, healthy or with stable chronic medical condition(s), living in a TB endemic region for many years to capture sufficient TB disease endpoints. High retention rates are critical to the success of these trials yet challenging to accomplish.

**Methods:** Aeras, GSK, and trial site partners are conducting a multi-centre, Phase IIb, double-blind, randomized, placebo controlled trial (NCT01755598) to evaluate the efficacy, safety and immunogenicity of GSK Vaccines' candidate tuberculosis (TB) vaccine M72/AS01E against TB disease in 3573 subjects aged 18-50 years. The trial is being conducted in South Africa, Zambia and Kenya and requires 3 years' follow-up after vaccination via clinic visits or contact visits to acquire a sufficient number of cases of TB

disease events. During trial planning, drop-out rates of 15.0% over the first 2 years of follow-up were assumed and used to determine the trial sample size. The strategies were developed with the sites and presented by community engagement leads from each trial site at annual investigators' meetings and applied by the sites. Some of the key strategies include retention events for participants, home visits, regular visit reminders, after-hour visit options, and provision of other health care services at the same facility (family planning clinic, social care services).

**Results:** Year 1: 97.3% of participants were retained on the trial by the end of year 1. Year 2: As of 14 September 2017 85.0% of participants had completed Month 24 with retention rates of 96.7%.

**Discussion and Conclusion:** High retention rates can be achieved in TB vaccine clinical trials in South Africa, Kenya and Zambia. Sponsor commitment to retention through mandated development of retention plans, adequate funding for implementation and regular review and adaptation of strategies resulted in high retention rates on a phase IIb TB vaccine trial.

**Funding Sources and Conflicts of Interest:** The Bill & Melinda Gates Foundation, DFID UK Department for International Development and GlaxoSmithKline Biologicals SA. C Caporaso reports personal fees from GSK group of companies, during the conduct of the study and outside the submitted work. A van der Westhuizen has nothing to disclose.

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# PD-40

## Building a portfolio of community engagement projects to enhance TB

**Michele Tameris,** Kelvin Vollenhoven, Marwou de Kock, Mark Hatherill

*South African Tuberculosis Vaccine Initiative (SATVI), Institute of Infectious Disease and Molecular Medicine, Department of Pathology, University of Cape Town, South Africa*

**Background:** The South African Tuberculosis Vaccine Initiative (SATVI) is committed to using novel and effective methods of community engagement (CE).

**Methods:** We describe CE projects conducted by SATVI in the 5-year period 2013 - 2017.

**Results:** 2013 "Karina's Choice": A drama production with high school learners as performers reached > 8000 adolescents and educators at 8 local high schools. Audience members completed pre and post-knowledge assessments showing improved insights into TB.

2015-2016 "Lienkie's Lungs": A series of street performances and taxi theatre addressing TB control and stigma, a drama production performed at clinics, community halls, a correctional facility and an annual Easter festival reached a total audience estimated at 1500. A Beat TB Graffiti Wall was created by festival goers and a Digital Story produced, narrating the impact of this project on the lives of performers and collaborators.

2015-2016 The "Kick TB Schools Program", conducted at 4 Worcester schools in 2015, reached 5000 learners. We expanded the 2016 Program to 25 primary schools, reaching 15880 learners. We introduced the TB Alliance Educational Toolkit for learners and educators for inclusion in the Life Orientation syllabus. 106 learners submitted entries to the Kick TB Poster Design Competition.

2017 University Bridging Bursary Scheme: We received 16 applications and awarded 4 bursaries to local school leavers, to cover registration costs for the University of Stellenbosch SciMathUS programme, covering Science and Mathematics tuition to meet university entrance requirements.

2017 World TB Day involved a month-long program at 4 community libraries, with a Graffiti Wall display; winning entries of Kick TB Poster Competition; screening of TB educational videos and story reading by SATVI staff.

**Conclusion:** A committed TB vaccine research site is capable of sustainable CE, essential for successful, long-term community-based vaccine research in TB-affected communities

**Funding Sources and Conflicts of Interest:** Wellcome Trust International Engagement Awards 099500/Z/12/Z funded Karina's Choice and Wellcome Trust International Engagement Awardand 105063/Z/14/Z funded Lienkie's Lungs

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## PD-41

### Drama as a community engagement tool to raise TB awareness

**Kelvin Edgar Vollenhoven,** Michele Tameris, Marwou de Kock, Mark Hatherill

*South African Tuberculosis Initiative (SATVI), University of Cape Town (UCT), South Africa*

**Background:** Lienkie's Lungs, a drama which aimed to raise awareness about TB, was developed by a partnership between SATVI, UCT Drama School and the Mothertongue Project, a local performing arts group, and funded by a Wellcome Trust International Engagement grant.

**Methods:** The drama, which was performed by actors from the Mothertongue Project and the Worcester community, was developed during a development phase (August to September 2015) with focus groups in the community, followed by a week-long camp with mentoring, guidance and input from the staff and students of the UCT Drama Department. The final theatre production was performed at six rural and urban community health clinics, as well as at community centres, shopping areas and taxis both during the preparation and climaxing at the Worcester Easter Festival in March 2016. The drama was supported by a graffiti wall activity and a stilt walker to generate excitement in the audience. Field surveys conducted during live performances and post festival focus groups were used to assess the impact.

**Results:** This project resulted in a mobile Beat TB Graffiti Wall which was displayed during World TB month (2017) at local libraries; and a Digital storybook titled: "Beat TB Stories of Engagement", an audio-visual storybook documenting the experiences of key actors and role-players in this initiative.

Mothertongue performers and investigators appeared on a national television youth programme, with the graffiti wall as backdrop.

The drama reached an estimated 17 000 community members locally, and an estimated 2.5 million through television. Post festival focus groups and field surveys confirmed audience appreciation and understanding. **Discussion and conclusions:** Drama, is an effective engagement tool to raise awareness about TB in a high burden community.

**Funding Sources and Conflicts of Interest:** Wellcome Trust /No Conflict of interest

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## PD-42

### Leveraging libraries to raise awareness about TB on World TB Day

**Kelvin Edgar Vollenhoven,** Michele Tameris, Marwou de Kock, Mark Hatherill

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**Background:** The South African Tuberculosis Vaccine Initiative (SATVI) partnered with the Breede Valley Municipality libraries in coordinating a community engagement program to raise awareness about Tuberculosis around World TB Day in libraries in the Worcester area.

**Methods:** Eight sessions about TB awareness were conducted by SATVI staff and members of the Community Advisory Board (CAB) at four local libraries through interactive workshop discussions, storytelling, art activities, graffiti wall display, poster art, library book display, and educational videos. The focus of the program was raising awareness about TB prevalence, prevention, transmission and treatment adherence.

**Results:** The program reached 360 adults and children over eight sessions, with the library management expressing the desire to expand the program in 2018.

The program provided a satisfying opportunity for the staff of SATVI and CAB members to engage with the community and children specifically through various activities like story reading and workshop discussions.

This program has created the ideal platform for the distribution of shelf-ready educational materials from resource agencies such as TB Care II, TB Alliance, Department of Health and Aeras.

The program was able to attract local organised community groups like community development workers and community health workers, during workshops aimed at this group.

**Conclusions:** Public libraries are strategically located to engage communities with TB Awareness raising programs during World TB month.

**Funding Sources and Conflicts of Interest:** None

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# PD-43

## Using eCompliance for tracking patients and ensuring accuracy of data in vaccine trials

**Shelly Batra**[1], Sandeep Ahuja[1], Sonali Batra[2]

[1]*Operation ASHA, India;* [2]*mASHA Technologies Private Limited*

**Background:** eCompliance is an Android application loaded onto a tablet and attached to a fingerprint reader. It was developed as a Microsoft Research collaboration. It been used since 2011 in Operation ASHA's core program to ensure adherence to the DOTS protocol of TB treatment.

**Method:** New patients are enrolled into the system by scanning their fingerprints. TB patients must take medication under direct supervision. Using eCompliance, when the patient comes to a DOTS centre, her fingerprint is scanned along with the fingerprint of our health worker and only then is the medication given. This simultaneous scanning of fingerprint proves that the medication was given under direct supervision. If the patient does not come in at the scheduled date and time, the system sends a text message to the health worker who then goes to the patient's house to give her the medication and takes her fingerprint scan as proof of visit. Also GPS tracking confirms worker movements. eCompliance has also been modified and used for other purposes, such as to ensure adherence to treatment of Haemophilia, diabetes and mental health. It has also been used in Telegana to track attendance among school children and identify absentees using an inbuilt algorithm.

**Results:** We have achieved a default rate of less than 3% and treatment success rate more than 89%, which are far better than country averages.

**Discussion:** Biometric tools such as eCompliance ensure adherence. We propose customizing and using eCompliance for vaccine trials to ensure that patients stay within the system for the duration of the trial during which there shall be regular follow ups and tests. This way we can minimize dropouts of patients, ensure timely testing and follow up. Also, data accuracy is ensured. There can be no data fudging and all reports are available at the click of a button. We have recently started enrolling TB patients using Iris prints instead of fingerprints,with similar results.

**Funding Sources and Conflicts of Interest:** 1) Microsoft Research 2) World Bank's development Marketplace 3) USAID 4) Marshall Foundation, France 5) LGT Venture Philanthropy, Switzerland 6) Michael and Susan Dell Foundation, USA 7) Operation ASHA, USA 8) Sahayak Foundation, USA 9) Grand Challenges

## PA-01

# The impact of previous BCG vaccination in enhancing the effectiveness of tuberculosis drugs to control mycobacterial growth ex-vivo

**Satria Arief Prabowo**[1,2], Andrea Zelmer[1,2], Lisa Stockdale[1,2], Steven Smith[1,2], Karin Seifert[1], Helen Fletcher[1,2]

*[1]Department of Immunology and Infection, London School of Hygiene & Tropical Medicine, United Kingdom [2]Tuberculosis Centre, London School of Hygiene & Tropical Medicine, London, United Kingdom*

**Background:** Current effort to effectively control tuberculosis (TB) is hindered by lengthy treatment and the emergence of drug resistance. Combining vaccination with drug therapy will enhance host immune responses and improve the effectiveness of current treatment. Several pre-clinical animal studies suggest the benefit of Bacillus Calmette–Guérin (BCG) vaccination in adjunct to treatment. A proof-of-principle study is needed to identify optimum regimens. Mycobacterial growth inhibition assay (MGIA) is a functional assay that measures the summative ability of host immune cells to inhibit the growth of mycobacteria ex-vivo.

**Methods:** We implemented an ex-vivo MGIA to assess the ability of isoniazid (INH) and rifampicin (RIF) to inhibit the growth of mycobacteria using peripheral blood mononuclear cell (PBMC) from historically BCG-vaccinated and naïve volunteers (n=100). The average time since BCG vaccination was 23.8 years. PBMCs were co-cultured for 4 days with Mycobacterium bovis BCG as an immune target.

**Results:** BCG-vaccinated participants were superiorly capable of inhibiting mycobacterial growth ex-vivo compared to the naïve ($p< 0.0001$). BCG-vaccinated females were better able to control mycobacterial growth than males ($p< 0.05$). BCG vaccination enhanced the ability of INH to control mycobacterial growth at the drug concentrations of 0.01 and 1 ug/ml ($p< 0.05$), and RIF at the concentration of 0.01 ug/ml ($p< 0.005$). BCG-induced inhibition of mycobacterial growth was associated with increased IFN-□ and IP-10 production in the presence of drugs ($p< 0.05$).

**Discussion and Conclusion:** This study provides evidence regarding the benefit of BCG vaccination in enhancing effectiveness of TB drugs ex-vivo. Clinical studies might be warranted to further elucidate the benefit of BCG in adjunct to treatment. Implementation of the MGIA assay to screen optimum combinations of drugs and TB vaccine candidates in early phase clinical trials worth further consideration.

**Funding Sources and Conflicts of Interest:** None

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## PA-02

# The role of DPP4 and antagonist CXCL10 in the pathogenesis of TB, an opportunity for vaccines and HDT?

**Morten Ruhwald**

*Statens Serum Insitut, Denmark*

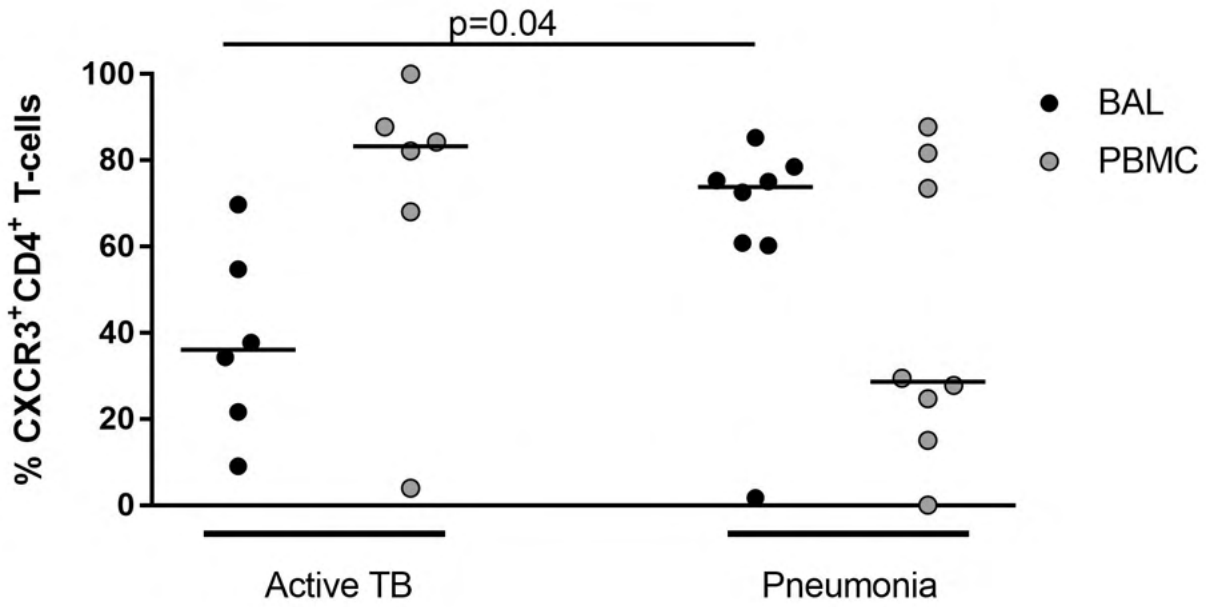
**Introduction:** M. tuberculosis is equipped to establish itself within the human host as a subclinical infection contained by the immune system in a granuloma structure. T cells that are essential for infection control, are recruited to the site of infection by chemokines, predominantly CXCL10. Studies have shown that CXCL10 in the plasma of patients chronically infected with hepatitis C virus is present predominantly in an antagonist form capable of binding its receptor CXCR3, without inducing signaling. This is due to N-terminal truncation by the enzyme DPP4. The aim of this study was to explore whether such CXCL10 antagonism may have an impact on the pathogenesis of TB.

**Results:** Plasma levels of agonist and antagonist CXCL10 were measured by Simoa digital ELISA and DPP4 enzyme activity in plasma was assessed in three groups of patients active TB (n=20), bacterial pneumonia (n=10) and healthy controls (n=10). We found significantly higher levels of total and antagonist CXCL10 and reduced DPP4 enzyme activity in TB patients compared to controls. We traced the source of CXCL10 secretion to M. Tb-infected CD3+ giant cells in the lung by histopathology. Interestingly, these cells co-localized with high numbers of DPP4 (CD26)-expressing CD4+ T cells. Moreover, lymphocytes at the site of TB infection (BAL) had reduced frequency of CXCR3+ T cells compared to T cell in the periphery (figure).

**Interpretation:** Our data suggests that CXCL10 antagonism is an important regulatory mechanism occurring at the site of TB disease. CXCL10 may be inactivated shortly after secretion by membrane bound DPP4, therefore reducing its chemotactic potential. Given the importance of Th1 cell functions in TB, our data suggest an important unappreciated regulatory role of DPP4 in TB.

**Perspectives**: DPP4 is the target for a class of enzyme inhibitors used in the treatment of diabetes. Our results suggest these drugs could be repurposed for host directed immunotherapy.

**Funding Sources and Conflicts of Interest:** None




# PA-03

## Mycobacterium tuberculosis H37Rv cell wall isolated poly L-glutamines as novel Th1-biased adjuvant

**Manish Gupta**[#], Rajesh Mani[#], Rakesh Bhatnagar, Nirupama Banerjee[*]

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[#]Author contributed equally.

**Background:** The immunomodulatory properties of Mtb cell wall components are well-known and classically highlighted by their use in Freund's adjuvant. Here we aim to explore the adjuvant potential of poly-α-l-glutamines (PLG), a lesser-known component of Mtb CW, that are present in abundance, only in pathogenic mycobacteria.

**Methods**: Immunomodulatory properties of PLG were evaluated using Mtb ESAT6 protein as vaccine candidate in C57BL/6J mice model. Different parameters of antigen specific immunity, humoral response, TH cell development, recall memory etc., were monitored using ELISA and flow cytometry. PLG's potency was compared with DDA-MPL, a known Th1-immunity inducing adjuvant. Effect of PLG in modulating protective efficacy of ESAT6 in the mice model is examined after challenge with Mtb, by recording clearance/reduction of bacillary load in the lung and spleen, and long-term survival of the host, in comparison to BCG.

**Results:** PLG adjuvanation triggered a strong humoral response against ESAT6 antigen and resulted in significantly elevated levels of total IgG and its isotypes (IgG1, IgG2-a and IgG2-b). The splenocytes from PLG vaccinated mice upon antigenic stimulation, displayed robust increase in Th1 specific IFN-γ, TNF-α, IL-2 and Th2 specific IL-6 and IL-10 cytokines. Additionally, PLG also activated Th17 response, leading to secretion of significantly high levels of IL-17 cytokine by the splenocytes. The PLG adjuvanted mice recorded 97.4 % and 92.43% reduction in bacterial counts in the lungs and spleens respectively, six weeks after

Mtb challenge. The magnitude of reduction is statistically not different from BCG vaccinated mice. PLG as adjuvant appears better than DDA-MPL in enhancing protective efficacy of ESAT6 ($P < 0.05$).

**Conclusions:** The strong Th1 and Th17 immune response generated by PLG makes it a promising adjuvant candidate for developing effective vaccines against Th1 response dependent diseases like Tuberculosis, Typhoid, etc.

**Funding Sources and Conflicts of Interest:** Indian Council of Medical Research (ICMR), New Delhi, India. No conflict of Interest.

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## PA-04

## De novo arginine biosynthesis pathway of Mycobacterium tuberculosis: A novel drug target and potential vaccine candidate

**Sangeeta Tiwari**[1,2], Vitor Mendes[2], Catherine Vilchèze[3], Tom L. Blundell[4], William R. Jacobs Jr.[1,3]

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Combating tuberculosis (TB) effectively mandates the development of protective vaccine and drug interventions that can rapidly sterilize persistent subpopulations of Mycobacterium tuberculosis (Mtb) leading to formation of drug resistant strains. Till date, only available vaccine is BCG, which is inconsistent in providing protection and have low efficacy in high disease burden areas. BCG can cause severe disseminated disease in HIV infected infants and immunocompromised patients, which restricts its use in high disease prevalent areas. Moreover as been demonstrated in animal models, it provides partial protection and cannot be cleared with time, necessitates the need for more efficaciously protective and safe vaccines. We demonstrate that arginine starvation of Mtb rapidly sterilizes the tubercle bacillus in vitro and in vivo, without the emergence of suppressor mutants. Importantly, independent mutants in arginine biosynthesis pathway are unable to scavenge host arginine resulting in rapid death in both immunodeficient and immunocompetent mouse models. Transcriptomics and flow cytometry analyses revealed accumulation of reactive oxygen species (ROS) and extensive DNA damage, following disruption of arginine biosynthesis, resulting in accelerated Mtb cell death. Our genetic and biochemical approaches, provide strong evidence for Mtb de novo arginine biosynthesis as a promising druggable pathway, with inhibition resulting in oxidative damage mediated cell- death. Further, our study shows that these strains provide protection against Mtb. Thus, this strain in combination with other bactericidal auxotrophy methionine can be used as potential safe whole-cell vaccine strain.

**Funding Sources and Conflicts of Interest:** None

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## PA-05

## Epitope-based vaccine design for Mycobacterium tuberculosis strains through pan-genomic reverse vaccinology

**Ravina Madhulitha Nalamolu,** Chiranjeev Pasala, Sudheer Kumar Katari,

Amineni Umamaheswari *Bioinformatics Centre, Department of Bioinformatics, Sri Venkateshara Institute of Medical Sciences University, India*

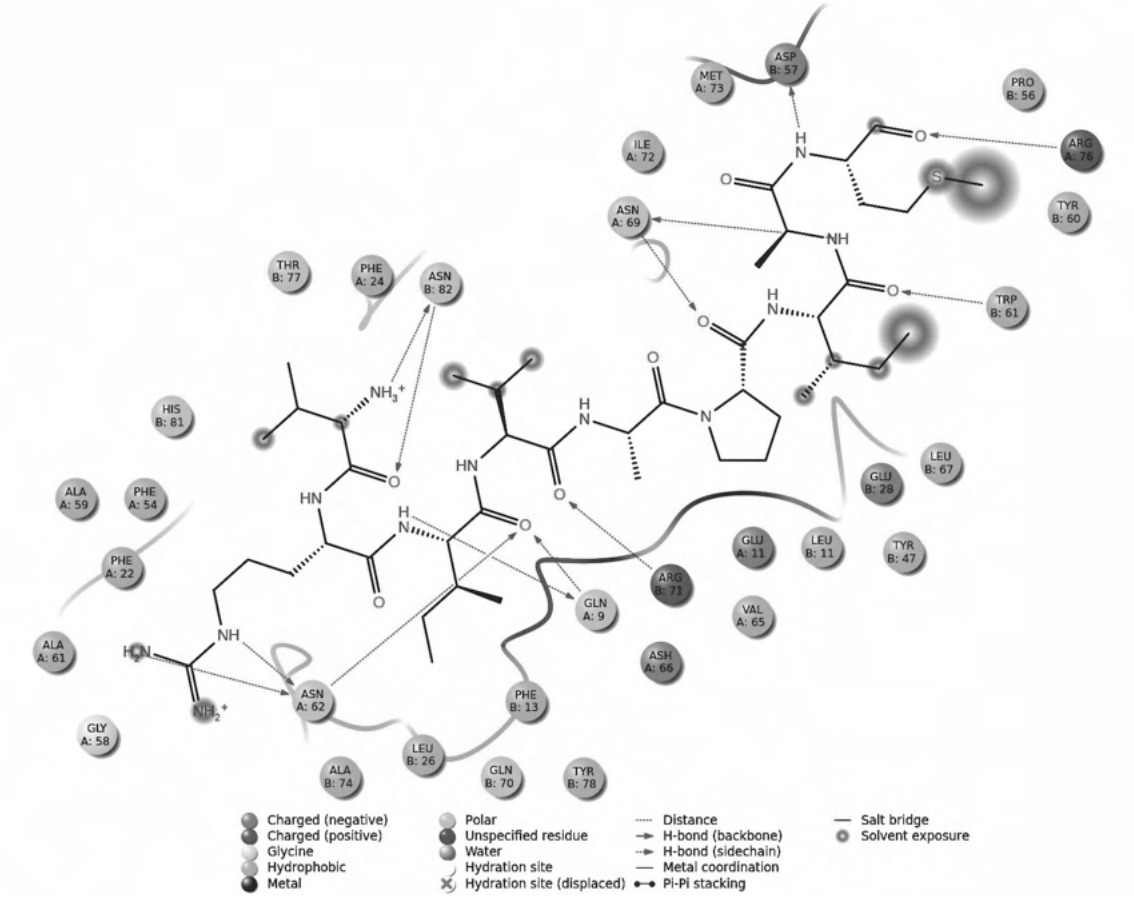
Tuberculosis is an infectious disease caused by Mycobacterium tuberculosis which infects half of the world human population. Developing potent vaccine is an important strategy to tackle the prevention of tb.

R- programming scripts were developed for comparative proteomic analysis of 23 strains of M. tb. Obtained 10 common outer membrane proteins (OMPs) of M. tb strains were analyzed for survival of the pathogen. The essential proteins were annotated for non-homology against human and gut flora. 3 epitopes were predicted using SYFPEITHI, Immune Epitope Database and Jemboss. The epitopes structures (205VRIVAPIAM211 of pstA1 and 84VRSLRPLIL92, 134VVLAQTFVS142 of modB) were built through homology modeling using Modeller 9v15, validated and subjected to protein peptide docking with 5 HLA-DRB alleles using BioLuminate v1.9. The best epitope-HLA-DRB complex stability was analyzed by performing 50 ns molecular dynamics simulations(MDS).

Among 33 docked complexes, the best docked complex for the TH-cell recognition of epitope1 (205VRIVAPIAM211) with HLA-DRB1*0101 (1AQD) possessing Glide Gscore of -13.086 kcal/mol and ΔGscore of -158.109 kcal/mol. Analysis of pstA1-epitope with HLA-DRB1*0101(1AQD) docking complex Phe-24,Phe-54,Gly-58,Ala-61,Asn-62,Val-65 of A chain andLeu-11,Phe-13,Tyr-47,Pro-56,Asp-57,Tyr-60,Gln-70,Arg-71,Ala-74,Thr-77,Tyr-78,Asn-82,His-81 of B chain (Figure1) residues were interacted and correlated with control peptide of 1AQD (103GSDWRFLRGYHQYA117). The simulations results revealed that the epitope–HLA-DRB complex was stable throughout the 50 ns MD run time with an average potential energy of -209159.59 kcal/mol, RMSD of 1.72 Å and RMSF of 1.10 Å.

We reported 3 potent epitopes and their binding affinities with 11 structures of 5 HLA-DRB alleles. MDS revealed that the HLA-DRB1*0101 (1AQD) epitope1 complex was stable. The putative epitope designed by reverse vaccinology will be presented on the surface exposed for immunogenic functions against tb.

**Funding Sources and Conflicts of Interest:** This research was supported by DBT, Ministry of Science & Technology, BIF program, Govt. of India (No. BT/BI/25/037/2012 SVIMS-T).




# PA-06

## Development of a recombinant BCG vaccine expressing a monomeric form of ESAT-6

**Makram Essafi[1],** Riadh Hmaidi[1], Houcemeddine Othman[1], Amira Refai[1], Rania Bouzeyen[1], Ramandeep Singh[3], Mohamed-Ridha Barbouche[1], Najet Srairi-Abid[1]

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Translocation of Mycobacterium tuberculosis (Mtb), from phagosome to the cytosol, is essential for the optimal presentation of antigens to CD8 T cells and the establishment of a robust adaptive immune response against tuberculosis. This translocation is

enabled by Mtb virulent effector ESAT-6 which permeabilizes the phagosomal membrane. In ESAT-6-deficient trains, like BCG, the bacteria remain enclosed in the vacuole. ESAT-6-induced translocation of Mtb can only occur when it is dissociated from its chaperone CFP-10. In absence of CFP-10, recombinant ESAT-6 always aggregates in a homodimeric inactive form (defective in membrane permeabilization). Here we aim to generate a recombinant BCG vaccine that expresses the monomeric active form of ESAT-6 through mutating the residues involved in ESAT-6 homodimer assembly. We performed a bioinformatic study on ESAT-6/CFP-10 complex as well as on the hypothetical interaction model of ESAT-6/ESAT-6 in order to estimate the free energy of each residue involved in the hydrophobic interaction between the two peptides. Four methods have been used, namely the Molecular mechanics generalized born surface area (MM-GBSA), Anchor, Rosetta and the Presaging Critical Residues in Protein interfaces (PCRPI) server. The study revealed the possible involvement of seven residues (L28, L39, W43, W58, L65, L72 and I76) in the formation of ESAT-6 homodimer. Only four residues (L28, L65, L72, I76) have been selected for mutagenesis assays to avoid disturbing the secondary structure of the protein and seven mutants have been generated. Work is in progress in order to express in E.Coli a recombinant monomeric active form of ESAT-6 before its transfer to a parental BCG. Having a BCG strain expressing exclusively the monomeric form of ESAT-6 will allow the exit of the bacteria, at early stage of infection, to the cytosol and the optimal presentation of the antigens to CD8 T cells, conferring then an effective adaptive immune response against TB

**Funding Sources and Conflicts of Interest:** Tunisian Ministry of Higher Education and Scientific Research

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## PA-07

## Insights into mycobacterial membrane vesicles: a potential subunit vaccine candidate

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[*]Equal contribution to work

**Introduction:** Recent vaccine against serogroup B Meningococcus exploited Outer Membrane Vesicles of Neisseria. Mycobacteria too generate Membrane Vesicles (MVs). However, reports show, upon Mtb challenge, mice primed with BCG/H37Rv-derived MVs exhibit exacerbated virulence.

While (i) isolating recombinant MVs from a non-pathogenic mycobacterium expressing specific immunogenic Mtb proteins and (ii) evaluating if MVs-derived from clinical M. tuberculosis (Mtb) isolates may be protective, we obtained the following insights.

**Results:** Interestingly, a third of M. smegmatis (mc2155), and a fifth of Mtb (H37Rv & Ra) MVs proteome constitute proteins with ability to bind nucleic acids (NAs). We hypothesized if NAs are in MVs. Indeed, both DNA and RNA get precipitated from MVs preps of Msmeg and Mtb. During growth progression, RNA but not DNA accumulates in these MVs preps. Across growth progression, Live Dead assay showed 98% of cells being alive. Treatment of intact MVs with DNase I and RNase A indicate NAs external to MVs. TEM-immunogold staining indicate approx. 5-10% of darkly stained 20-30 nm sized MVs carrying RNA on their surface.

**Methods:**

-MVs enrichment – as per published protocols.

-Negative and immunogold staining with Transmission electron microscopy (TEM)

-ESI-Tandem Mass Spectrometry (MS) with Orbitrap (Thermo Scientific; All MVs samples from biological triplicates).

-Phenol & chloroform-based NAs extraction – as per standard protocols

**Discussion and Conclusion:** Unlike Gram-negatives, mycobacteria, seem to harbor NAs outside MVs. Presence of NAs and proteins with NAs associating capability raises concern on accuracy of cataloging MVs proteome. To obtain accurate MVs proteome, we first treat intact MVs with Dnase I, RNase A and Proteinase K to eliminate NAs and their associating proteins. Currently we are comparing how the untreated and treated MVs stimulate macrophages.

**Funding Sources and Conflicts of Interest:** DBT, Govt. of India, India

# PA-08

## Assessment of the protective effect, against tuberculosis, of a new vaccine composition

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BCG failure to induce long term protection has been endowed to its inability to escape the phagolysosome of phagocytes, leading to weak antigen presentation and mild activation of CD8+ T-cell responses, the major component of a robust immune response against TB. Infected-host apoptosis plays an important role in immunopotentiating dendritic cells-mediated priming of CD8 T-cells, a process defined as "crosspriming" that improve immunity against Mtb infection. We previously reported that apoptosis of BCG infected macrophages relies on activation of FOXO3, a transcription factor negatively regulated by the prosurvival activated threonine kinase (Akt). Priming macrophage apoptosis during BCG vaccination, through FOXO3 activation, may lead to higher cross-priming of T-cells, conferring then better protection against TB.

Several chemicals and pro-apoptotic drugs, used to treat cancer, are inhibitors of Akt that act through FOXO3 activation. We therefore propose to assess the protective effect, against TB, of a new vaccine composition made of an inhibitor of Akt, mixed to the parental BCG, compared to the parental BCG vaccine alone.

In vitro treatment with the Akt inhibitor boosted BCG-induced apoptosis of THP1-derived macrophages (TDMs) as shown by Annexin V/7-AAD staining, along with the dephosphorylation of Akt and its target FOXO3. Moreover, real-time quantitative PCR analysis of the expression profile of BCG-infected macrophages showed an upregulation of the pro-apoptotic targets of FOXO3, NOXA and the apoptogenic mitochondrial proteins AIF and EndoG. Treatment with the Akt inhibitor also improved the clearance of BCG from macrophages.

Experiments are in progress to evaluate the protective effect of our new vaccine composition in mice model of infection.

This study suggests that enhancing apoptosis of BCG infected macrophages, through FOXO3 activation, may potentiate BCG-induced immunity and improve protection against MTB.

**Funding Sources and Conflicts of Interest:** The Tunisian ministry of Science and Research and the Indian ministry of Sciences & Technology Department of Biotechnology.

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# PA-09

## Immunological activity of the fusion protein containing major secretory protein of Mycobacterium tuberculosis

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Studies on subunit vaccines using purified protein from microorganisms or inactivated toxins have been actively conducted. Purpose of these studies is to find an antigen that has highest immunogenicity among the microbial antigen and significantly induces immune response. Mycobacterial heat-shock proteins(HSPs) including HSP65 have been reported to induce a strong immune response against tuberculosis(TB). In previous study, we identified and characterized protein Rv22xx (heat-shock protein 90 family), which effectively induced Dendritic cells(DCs) maturation. Based on this result, two kinds of fusion protein, RAE6(Rv22xx-Ag85B-ESAT6), AE6(Ag85B-ESAT6), were constructed using major secretory proteins and Rv22xx. The immunological activity of these proteins were compared with each other. All protein induced DCs and Macrophages maturation, and increased expression of the surface molecule (MHC class I, II, CD80,86) and production of pro-inflammatory cytokines. Among these, RAE6 showed better immunological activity than the individual single proteins as well as the AE6 protein. RAE6 induced these effect by TLR4 receptor and stimulated its downstream NF-kB and MAPK pathways. Our findings suggest that recombinant fusion protein RAE6 is a promising candidate for the rational design of an effective multi-antigenic TB vaccine.

**Funding Sources and Conflicts of Interest:** National Research Foundation of Korea (NRF) Grant funded by the Korean Government (MSIP) (No. 2017R1A5A201538)

## PA-10

### Synthetic polysaccharide conjugate vaccines expressing Mycobacterium tuberculosis antigens induce high-titer antibody responses in mice, guinea pigs, and rabbits

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*[1]Aeras, US, [2]CanSino, China, [3]Tianjin University of Science & Technology, China*

**Background:** There has been renewed interest in the potential role of antibodies to provide protection against tuberculosis (TB). Mycobacterium tuberculosis expresses numerous polysaccharides on its outer capsule that present an attractive target for antibodies. However, it has been reported that mice respond poorly to polysaccharide conjugate vaccines, while rabbits are known to generate potent antibody responses against such constructs. Here we evaluate the immunogenicity of synthetic arabinomannan (AM) and phenolic glycolipid conjugates in three commonly used models of TB. We also evaluate the efficacy of these conjugates in the mouse model.

**Methods:** Dose-response immunogenicity studies were performed in mice, guinea pigs and rabbits, and included the evaluation of multiple adjuvants. Antibody endpoint titer and isotype analyses were performed, and the data used to design an HN878 mouse challenge. Before challenge, mice were given either active immunization using different adjuvant formulations of the conjugate vaccine or iv dose of high-titer sera from immunized rabbits. Bacterial burden in the lungs and spleen was assessed 3 weeks after challenge.

**Results:** Vaccination induced high-titer responses in each model. Mice demonstrated a clear dose-response effect with titers increasing after each immunization. A clear dose-response effect was not observed in guinea pigs or rabbits. Analysis of antibody isotypes in mice revealed induction of qualitatively different responses dependent upon the adjuvant used. Vaccination with the AM conjugate demonstrated a 0.75log10 CFU reduction in the spleen which did not reach statistical significance. No other vaccine (apart from BCG) demonstrated any effect.

**Conclusion:** The data support the use of these models in evaluating polysaccharide conjugate vaccines, though identification and optimization of protective antigens remains a key priority.

**Funding Sources and Conflicts of Interest:** Bill & Melinda Gates Foundation

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## PA-11

### Rv2882c-Rv20xxc, a novel immunostimulatory antigen of Mycobacterium tuberculosis, activates bone-marrow derived dendritic cell

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*College of Medicine, Chungnam National University, South Korea*

**Background:** Tuberculosis is a disease that requires long treatment with the advent of the Multidrug-resistant tuberculosis and the extensively drug-resistant tuberculosis, that more difficult to treatment. So the therapy tuberculosis vaccine developments become important.

**Method:** To search for more effective tuberculosis therapy subunit vaccines, we study expressed in latent stage protein (Rv20xxc) and macrophage-activating protein (Rv2882c). Thus, produced fusion protein Rv2882c-Rv20xxc.

**Result:** We confirmed that recombinant Rv2882c-Rv20xxc fusion protein maturated dendritic cells to secrete pro-inflammatory cytokines, such as TNF-α, IL-6 and IL-12p70, and surface molecules. Differentiation of Th1 and Th17 of CD4 + T cells is important in the mechanism of tuberculosis vaccine. Therefore, we confirmed that maturation of dendritic cells by Rv2882c-Rv20xxc differentiates naïve CD4+ T cells into Th1 and Th17 cells. Finally, we determined the therapeutic effect of Rv2882c-Rv20xxc in a chemotherapy mice model.

**Conclusion:** Our findings suggest that Rv2882c-Rv20xxc is an excellent candidate for the effective multiantigenic tuberculosis vaccine.

**Funding Sources and Conflicts of Interest:** National Research Foundation of Korea (NRF) Grant funded by the Korean Government (MSIP) (No. 2017R1A5A201538)

# PA-12

## Mycobacterium tuberculosis protein Rv2299c fused-ESAT-6 subunit vaccine confers improved protection against the hypervirulent strain HN878 in mice

**Seunga Choi**

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**Background:** Understanding functional interactions between dendritic cells and antigens is necessary for achieving an optimal and desired immune response during vaccine development.

**Method:** We make a fusion protein Rv2299c (heat-shock protein 90 family), which effectively induced dendritic cell maturation, fused ESAT-6. The Rv2299c-ESAT-6 fused protein was evaluated for its immunostimulatory potential on dendritic cells and determined the Rv2299c-ESAT-6 fusion protein has a vaccine potential against tuberculosis.

**Result:** The Rv2299c-ESAT-6 fused protein-maturated dendritic cells showed increased expression of surface molecules and production of proinflammatory cytokines. The Rv2299c-ESAT-6 fused protein-maturated dendritic cells also showed an induced Th1 cell response with bactericidal activity. Furthermore, boosting Bacillus Calmette–Guérin (BCG) with the fused protein significantly reduced hypervirulent Mycobacterium tuberculosis HN878 burdens post-challenge. The pathological study of the lung from the challenged mice assured the efficacy of the fused protein. The fused protein boosting also induced Rv2299c-ESAT-6-specific multifunctional CD4+ T-cell response in the lungs of the challenged mice.

**Conclusion**: Our findings suggest that Rv2299c is an excellent candidate for the rational design of an effective multiantigenic tuberculosis vaccine.

**Funding Sources and Conflicts of Interest:** National Research Foundation of Korea (NRF) Grant funded by the Korean Government (MSIP) (No. 2017R1A5A201538)

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# PA-13

## Evaluation of attenuated strains as auxotrophic vaccines against Mycobacterium tuberculosis

**Tannu Priya Gosain[1],** Rania Bouzeyen[2], Mamta Singh[1], Prabhakar Tiwari[1], Garima Arora[1], Saqib Kidwai[1], Ramandeep Singh[1]

*[1]Translational Health Science and Technology Institute, India, [2]Institut Pasteur de Tunisia, Tunisia*

**Background:** Tuberculosis remains of the major diseases with a higher mortality rate worldwide. Interplay of various metabolic pathways enables the bacterium to adapt and survive under different stress conditions. Stringent response pathways and inorganic polyphosphate are key players in this stress adaptation. The genome of M. tuberculosis encodes for enzymes in involved in PolyP synthesis (PPK-1) and PolyP utilization (PPX and PPK-2).

**Methods:** We have purified these enzymes by affinity chromatography. The mutants for PolyP metabolic enzymes were generated by homologous recombination using temperature sensitive mycobacteriophages. The survival of these mutants and parental strain has been compared in different stress conditions. We have used aerosol infected guinea pigs to compare the growth kinetics of mutant and wild type strains in lungs and spleens.

**Results:** Previously, we have shown these enzymes are functional in M. tuberculosis. We have also shown that accumulation of PolyP occurs in different growth and stress conditions. Both PolyP deficient and accumulating strains are severely attenuated in chronic stage of infection. In addition PolyP deficiency also enhances the susceptibility of M. tuberculosis to front line TB drugs. Experiments are in progress to evaluate these mutant strains as auxotrophic vaccines in mice model of infection. We are also studying various immune parameters in various immunized groups.

**Discussion/Conclusion:** The genome of M. tuberculosis encodes for functional polyphosphate kinase and polyphosphatase enzymes. PolyP accumulation in (p) ppGpp dependent and enables M. tuberculosis to adapt to different stress conditions. PolyP dysregulation impairs the ability of M. tuberculosis to cause disease in animals. These attenuated strains are good candidates to be evaluated as auxotrophic vaccines.

**Funding Sources and Conflicts of Interest:** Department of Biotechnology, Government of India

## PA-14

### Miniaturized Fluorescence adapter for Fluorescence Sputum Smear Microscopy using bright-field microscope.

**Mamta Rani[1],** Vikas Pandey[1], Pooja Singh[1], Saumya Singh[1], Nashreen Z Ehtesham[2], Seyed E. Hasnain[3], Ravikrishnan Elangovan[1]

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**Background:** Tuberculosis is a major healthcare burden for developing countries. WHO plans to eradicate TB by 2050, for this goal the number of cases must decrease 16% per year. Currently it is a huge challenge as only 58% of TB infected get diagnosed and treated. Delay in diagnosis of people with active TB further spread the new infections. Despite recent advances in rapid diagnostics, the bright field sputum smear microscopy (SSM) remains the most commonly used method for MTB diagnosis in India. In contrast, Light-Emitting Diode Fluorescence Microscopy (LED-FM) for sputum smear examination is recommended by WHO for detection of acid-fast bacilli in high tuberculosis (TB) burden countries. The availability of fluorescent microscope at most DOT centers, district hospitals and community healthcare centers is still scanty. We have developed a novel patented (2673/DEL/2015) planar waveguide-based illumination technology called compact Total Internal Reflection Fluorescence (cTIRF) to observe fluorescent sample using bright-field microscope without any hassle of optical filters, lens installation, and expensive instrumentation.

**Methods:** The cTIRF system is a compact approx size of a calculator and cost effective way of fluorescence observation. The cTIRF can easily be used with different wavelength excitation based on sample staining. The sputum sample processing, smear slide preparation and auramine O staining remains same as recommended by WHO.

**Result:** The proof of concept of the cTIRF system has been established in the laboratory at IIT Delhi. The optical performance of cTIRF has been benchmarked against Olympus IX71 fluorescence microscope with varying fluorescent and biological samples.

**Discussion & Conclusion**: According to WHO, LED-FM shows improved sensitivity over conventional Ziehl Neelsen microscopy. We propose the cTIRF device in all the DOT centers for high sensitive fluorescence SSM diagnosis of MTB cells.

**Funding Sources and Conflicts of Interest:** Ministry of Human Resource & Development

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## PA-15

### Development of an innovative, rapid, affordable and automated system for selective enrichment, isolation and detection of MTB in sputum sample.

**Saumya Singh[1],** Saurabh Singh[2], Pooja Singh[1], Mamta Rani[1], Naresh Arora[2], Neha Quadir[3], Nasreen Z Ehtesham[3], Seyed E Hasnain[2], Ravikrishnan Elangovan[1],

*[1]Department of Biochemical Engineering & Biotechnology, IIT Delhi, India, [2]Kusuma School of Biological Sciences, IIT Delhi, India, [3]National Institute of Pathology, Safdarjung Hospital Campus, India*

**Background:** Mycobacterium tuberculosis (MTB) is a major global health burden that claims 1.5 million deaths annually. Approximately 4.3 million TB cases remainun-diagnosed every year globallythat leads tonew infections. The sputum smear microscopy (SSM) and nucleic acid amplification test (NAAT) are routinely used methods for the diagnosis of MTB. The specificity of the SSM test at DOTS center in India isapproximately 50%. While, the highly sensitive NAAT is expensive and unaffordable for developing countries even after subsidy. There is a dire need for a high sensitive, deployable diagnostic test that cater above issues. We have developed a cost-effective, novel and deployable immuno-magnetic cell capture (iMC2) system that enables selective isolation and detection of MTB cells from complex sputum sample.

**Methods:** The iMC2system has two components, the platform device and the capture bottle. The capture bottle is prefilled with iMC2 reagent along with thinning solution, to liquefy the sputum and release Mycobacterium tuberculosis in solution. The iMC2 reagent contains super paramagnetic nanoparticles coated with anti-Mycobacterium tuberculosis antibody. The capture bottle is kept in platform device to isolate the bacteria into very small volume (50µl). The enriched MTB cell can further be detected using microscope.

**Results:** The iMC2 system enables MTB cells separation and concentration from sputum with 80% efficiency. The enrichment of MTB cells occur without background mucus debris which improve the detection sensitivity highly.

**Discussion & Conclusion:** The device components are designed with scalability in mind and manufactured using injection molding. All the reagents are prepared to be stable in room temperature and assay automated to minimize human intervention. Additionally, iMC2 TB is compact, portable, and cost effective method for MTB detection with 1 hour turnaround time.

**Funding Sources and Conflicts of Interest:** Ministry of Human Resource & Development

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# PA-16

## Comparison of pellicle and liquid grown BCG reference strains in standard BCG batch release assays and protection studies

**Megan Fitzpatrick**[1], Mei Mei Ho[2], Simon Clark[3], Belinda Dagg[2], Bhagwati Khatri[2], Faye Lanni[3], Ann Williams[3], Dominick Laddy[1], Barry Walker[1]

*[1]Aeras, USA, [2]Bacteriology Division, MHRA-NIBSC, UK, [3]Public Health England, Porton Down, UK;*

A global BCG vaccine shortage of 16.5M doses occurred in 2015, largely caused by increased country requirements, buffer stock replenishments, and production issues. This global shortage has impacted both preclinical studies and clinical trials of new TB vaccines. Stakeholders met at McGill University in Montreal that same year to discuss the shortage and potential mitigation strategies. Manufacturing BCG through a more scalable liquid fermentation process instead of the traditional pellicle growth method was considered. This pilot study aimed to generate a supportive data package by comparing pellicle-grown and liquid-grown BCG strains in selected quality control assays as well as mouse and guinea pig protection studies.

BCG Lyophilized WHO Reference Reagents (Danish, Moreau, Russia, Tokyo strains) were obtained from the National Institute for Biological Standards and Control UK (NIBSC). Strains were grown in liquid, in shake flasks, and glycerol stocks prepared. The pellicle-grown, lyophilized reference strains were compared to the liquid-grown, glycerol stocks prepared for this study using assays as required in the BCG vaccine monograph of European Pharmacopeia: cultural viable count, identity by PCR, excessive dermal reactivity, absence of virulent mycobacteria, and delayed hypersensitivity. Preparations were also compared for their efficacy in mouse and guinea pig protection studies.

Liquid-grown BCG culture preparations met the requirements of quality control testing at NIBSC. Except for BCG Russia, there were no significant differences in lung colony forming units (CFUs) between liquid-grown and pellicle-grown preparations in mouse and guinea pig protection studies. For BCG Russia, the liquid-grown preparation protected better in mice (P=0.0010), but the pellicle-grown preparation protected better in guinea pigs (P=0.0011).

Producing BCG vaccines by a more scalable liquid growth process could be a viable solution to the global BCG shortage.

**Funding Sources and Conflicts of Interest:** None

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# PA-17

## Functional, antigen-specific stem cell-like memory (Tscm) CD4+ T cells are induced by human Mycobacterium tuberculosis infection

**Cheleka Anne-Marie Mpande,** Virginie Rozot, Mark Hatherill, Elisa Nemes and Thomas J. Scriba *South African Tuberculosis Vaccine Initiative, Institute of Infectious Disease and Molecular Medicine, Division of Immunology, Department of Pathology, University of Cape Town, South Africa*

**Background:** A better understanding of the Mycobacterium tuberculosis (M.tb)-specific memory T cell repertoire, particularly during the early stages of M.tb infection is needed to inform vaccine strategies. Virus-specific CD8+ stem cell memory T cells (TSCM) are associated with maintenance of long lasting immunity. However, little is known about bacteria-specific CD4+ TSCM function. We aimed to determine if M.tb infection generates antigen-specific CD4+ TSCM and if so, characterise their functional ontology.

**Methods**: We studied immune responses to natural M.tb infection in PBMCs from a longitudinal adolescent cohort of recent QuantiFERON (QFT) converters (n=41) and cross-sectional adult cohorts (n=20). M.tb-specific CD4 T cells were detected by flow cytometry using MHC-class II tetramers (M.tb-tet) bearing Ag85, CFP-10 and ESAT-6 peptides, or by intracellular cytokine staining after PBMC stimulation with M.tb-antigens. Expression of memory markers, chemokine receptors, cytotoxic molecules and functional markers was detected using flow cytometry.

**Results:** M.tb-Tet+ TSCM were induced by primary M.tb infection and maintained thereafter. M.tb-Tet+ TSCM expressed CD95 and CXCR3, classical TSCM markers. M.tb-Tet+ TSCM expressed significantly higher levels of CCR5, CCR6, CXCR3, Granzyme A, Granzyme K and Granulysin than bulk naive T cells or bulk TSCM. Analysis of the functional (IFN-γ, IL-2, TNF-α, CD40L and CD107a expression) profile of M.tb-specific TSCM in recent QFT converters is currently on-going.

**Conclusion:** M.tb-specific CD4+ TSCM are induced during primary M.tb infection and are distinct from bulk naive T cells and TSCM. M.tb-specific CD4+ TSCM displayed chemokine receptor profiles consistent with memory Th1/17 cells and expressed effector functions including cytotoxic markers.

**Funding Sources and Conflicts of Interest:** Funding: South African Medical Research Council and the US National Institutes of Health

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## PA-18

## Activation of L-type voltage gated calcium channel in macrophages suppresses protective responses during Mycobacterium tuberculosis infection

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*University of Delhi, India*

The prevalence of Mycobacterium tuberculosis (M. tb) strains eliciting drug resistance has necessitated the need for understanding the complexities of host pathogen interactions. The regulation of calcium homeostasis by Voltage Gated Calcium Channel (VGCCs) upon M. tb infection has recently assumed importance in this area. Our work previously showed a suppressor role of VGCC during M. tb infections and recently reported the mechanisms of its regulation by M. tb. Here we characterize the role of VGCC in mediating defence responses of macrophages during mycobacterial infection. We report that activation of VGCC during infection synergistically downmodulates the generation of oxidative burst (ROS) by macrophages. This attenuation of ROS is regulated in a manner which is dependent on Toll like Receptor (TLR) and also on the route of calcium influx, Protein Kinase C (PKC) and by Mitogen Activation Protein Kinase (MAPK) pathways. VGCC activation during infection increases cell survival and downmodulates autophagy. Concomitantly, pro-inflammatory responses such as IL-12 and IFN-γ secretion and the levels of their receptors on cell surface are inhibited. Finally, the ability of phagosomes to fuse with lysosomes in M. bovis BCG and M. tb H37Rv infected macrophages is also compromised when VGCC activation occurs during infection. The results point towards a well-orchestrated strategy adopted by mycobacteria to supress protective responses mounted by the host. This begins with the increase in the surface levels of VGCCs by mycobacteria and their antigens by well-controlled and regulated mechanisms. Subsequent activation of the upregulated VGCC following tweaking of calcium levels by molecular sensors in turn mediates suppressor responses and prepare the macrophages for long term persistent infection.

**Funding Sources and Conflicts of Interest:** University Grant Commission, India

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## PA-19

## Role of phosphorylation on secretion in Mycobacterium tuberculosis and its impact on its survival

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Mycobacterium tuberculosis faces numerous environmental stresses upon entering the host. A common mode of regulation of the cell's response is through phosphorylation/ dephosphorylation of specific target proteins. One such mechanism is modulated

through two component phosphosignaling pathways. In addition to the classical Two-Component system, M. tuberculosis is equipped with 11 eukaryotic like serine threonine protein kinases (STPKs) and one tyrosine kinase. Reports have suggested that these eukaryotic like STPKs regulate a wide array of functions inside the pathogen such as cellular metabolism, transcriptional regulation, cell wall biosynthesis and cell division. We are working towards the identification of novel substrates to better understand the effect of phosphorylation on overall cellular physiology and growth of pathogen. Towards this we have performed phosphoproteome and phosphosecretome analysis to identify novel targets and secretory proteins that are phosphorylated. We also used proteomics to identify the secretome of mycobacteria, which contributes enormously towards pathogenesis. We have identified two very important secretory proteins of Type VII Seceretory System (T7SS) to be phosphorylated. We investigated the impact of phosphorylation on protein-protein interaction, secretion and eventual survival of pathogen in the host.

**Funding Sources and Conflicts of Interest:** NII core fund

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# PA-20

## Challenges in detecting TB drug resistance in a field setting in Southwestern Uganda

**Patrick Orikiriza**

*Mbarara University of Science and Technology*

**Introduction:** There are limited data from the field about the challenges of detecting anti tuberculosis drug resistance (TB) using molecular methods. We assessed the challenges based on ease of technique and interpretation of results using culture positive isolates in a research Laboratory, in southwestern Uganda. Our aim is to guide regional laboratories on planning for investigations as this may have some cost implications.

**Methods:** We tested archived isolates for first line susceptibility using Hain and Xpert MTB/RIF. A subsample of isolates selected randomly for geographic variability was also tested for second line. To confirm resistance, isolates were tested further using sequencing and MGIT.

**Results:** of the 190 isolates tested for MTBDR plus, 26(13.68%) had non interpretable results for rifampicin and isoniazid-susceptibility. Among 92 isolates tested for second-line, 21 (23%) had non interpretable results. Among the Xpert tests, 25 (13.2%) were repeated because of errors. Considering that the MTBDR plus, MTBDRsl and Xpert MTB/RIF costs 23.46 USD (Shah et al., 2013), 39.4 USD and 14.96 USD (Shah et al., 2013), this would require approximately 610 USD, 826 USD and 299 USD in extra for each investigation respectively. Because of difference in resistance patterns between Xpert and MTBDRsl, we performed sequencing in an external laboratory in Belgium. Considering the cost of shipment plus the technique itself, there were too many costs that we had not anticipated and the results were still contradictory. On repeating the MTBDRsl, in another Laboratory in Kenya, the 7 isolates initially resistant were found susceptible.

**Conclusion:** The discrepancy in resistance results by the three approved methods makes diagnosis difficult and requires establishment of an optimum global second line testing strategy. In addition, development of robust vaccines would avoid all these challenges and greatly contribute to sustainable development goals.

**Funding Sources and Conflicts of Interest:** None

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# PA-21

## Calcimycin induced autophagy decreases mycobacterial growth in THP-1 cells through P2RX7 dependent pathway mediated by intracellular calcium

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**Introduction:** Calcium ionophores like calcimycin show in vitro antimicrobial activity against gram-positive bacteria and fungi but its effect on mycobacteria is not known. In our study, we found that calcimycin is bactericidal in action against mycobacteria by inducing autophagy. We also found the central role of intracellular calcium in regulating autophagic process through ATP-dependent purinergic receptor P2X7 (P2RX7) pathway in calcimycin treated cells.

**Methods:** Western blotting was employed to study the expression of major autophagy markers in calcimycin treated and infected samples. Mycobacterial growth and P2RX7 mRNA expression in treated samples was assessed by CFU plating and qRT-PCR respectively. Intracellular calcium level and ATP secreted in culture supernatants was quantified using Fluo-4 Direct™ calcium Assay and BacTiter-Glo microbial cell viability kit respectively. Docking studies were also performed to ascertain the interaction between calcimycin and P2RX7. P2RX7 inhibitor,1-[N,O-bis(5-Isoquinolinesulfonyl)-N-methyl-L-tyrosyl]-4-phenylpiperazine (KN-62) or intracellular calcium chelator,1,2-Bis(2-aminophenoxy)ethane-N,N,N′,N′-tetraacetic acid tetra (acetoxy-methyl) ester (BAPTA-AM) was used to study the role of P2RX7 or intracellular calcium in regulating autophagy induced by calcimycin.

**Results:** We show that treatment with calcimycin led to decrease in intracellular mycobacterial growth by enhancing autophagy and increases P2RX7 mRNA expression in THP-1 cells. We also demonstrate that calcimycin binding with P2RX7 led to increase in intracellular calcium level that regulates the extracellular release of ATP. Blocking of either P2RX7 expression by KN-62 or reducing intracellular calcium levels by BAPTA-AM abrogated the antimycobacterial activity of calcimycin.

**Conclusion:** Calcimycin exerts its antimycobacterial effect by regulating intracellular calcium-dependent ATP release that induces autophagy in a P2RX7 dependent manner.

**Funding Sources and Conflicts of Interest:** None

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## PA-22

## Phenotypic adaptation to drug treatment in Mycobacterium tuberculosis is mediated by DNA gyrase

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Persistence to clinically used drugs is one of the emerging issues responsible for the failure of current anti-tuberculosis (TB) therapy. Fluoroquinolone (FQ), targeting DNA gyrase, is known for experimental induction of persisters in many bacteria. Although FQs are currently used as second-line drugs for treatment of MDR TB cases, but little is known about the modulation of DNA gyrase expression and fate of persister formation in mycobacterium upon FQ treatment.

In view of this, the current study explores the gyrase-depleted strain of M. tuberculosis (Mtb) to better understand its role in mycobacterial physiology. Differential expression levels of gyrA and gyrB transcripts under a variety of growth conditions suggest that Mtb achieves survival benefit under stress by regulating the intracellular DNA gyrase activity. Further, we show that gyrase depletion by CRISPRi in Mtb induces lexA-mediated SOS response, which is known to affect tolerance of other bacteria to clinically used drugs. Based on these observations, next we examined the possible link of DNA gyrase and emergence of persisters in Mtb. Interestingly, we found that gyrase deficient Mtb shows phenotypic tolerance, and not genetic resistance, to first-line anti-TB drugs. Furthermore, marked changes in intracellular ATP levels and NADH/NAD+ ratio together with the presence of Nile-red stained lipid bodies in gyrase knockdown strain, strongly suggest the role of bacterial gyrase activity in emergence of persister Mtb population.

The above results thus conclude that upon exposure to different clinically approved drugs Mtb switches to drug tolerant persister state, which in-turn is triggered by alteration in DNA gyrase activity. Importantly, our study suggests a careful design of anti-TB drug regimen to minimize the emergence of FQ-induced persister population in clinical settings.

**Funding Sources and Conflicts of Interest:** Department of Biotechnology, India/None

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# PA-23

## Assessment of anti-mycobacterial activity of some selected Congolese medicinal plants

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Tuberculosis is an infectious disease that kills approximately 3 million people annually worldwide. The emergence of multidrug resistant, extensively drug resistant and lengthy therapy reduces the patient compliance and therefore comprises control strategies. The problem is worsened with the coinfection with HIV while BCG vaccine is inefficient for the adult population. There is a need of new vaccine efficient for children and adults as well of new drugs that can overcome the resistance of this pathogen to current antibiotics, thus the alternative to the use of medicinal plants. In this study, the leaves of Terminalia ivorensis, Carapa procera, Fagara macrophylla,, Anacardium occidentale, Ficus spp. and Drepanoalpha were extracted with petroleum ether, ethyl acetate and methanol in order to assess the anti-mycobacterial activity against M. tuberculosis H37Rv and Mycobacterium tuberculosis spp. on Lowenstein-Jensen medium and Middlebrook 7H10 agar using a qualitative approach. The activity was determined as to whether there was growth or not and the crude extracts were screened for the presence of phytochemicals namely alkaloids, flavonoids, tannins, anthocyanins, leucoanthocyanins, total polyphenols and saponins. These extracts were found to be active against mycobacteria culture strains in Middlebrook 7H10 agar where there was inhibition of the growth than in Lowenstein-Jensen slants where only the methanolic extract showed good activity on both strains. The presence of phytochemicals like alkaloids, flavonoids, tannins, saponins, anthocyanins, quinones known to be of medicinal importance point out a possible source for anti-mycobacterial agents to address the problem of multidrug resistance. The in vitro findings of this study provide a partial support for the use of these plants in the management of various infectious diseases as lead to drug discovery and should be reiterated and recommend for a clinical trial using an animal model.

**Funding Sources and Conflicts of Interest:** None

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# PA-24

## Various aspects of GTPases towards its essentiality in survival and pathogenesis of Mycobacterium tuberculosis H37Rv

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**Introduction:** Tuberculosis is the most precarious airborne disease caused by Mycobacterium tuberculosis H37Rv (M. tuberculosis) which spread its terror throughout the world by increasing the human mortality rate every year very promptly. M. tuberculosis acts by inhibiting phagolysosome biogenesis and thereby persistence of bacilli in phagosome. GTP binding proteins are highly conserved genes responsible for its pathogenesis. In this study we authenticate the essentiality of various GTP binding proteins by using molecular and immunological studies, which help in understanding the cellular mechanism of this disease.

**Methods:** Biochemical and biophysical characterization of GTP binding proteins would be done after cloning in appropriate plasmid, which are then purified and checked for GTP binding and hydrolyzing activity by using GTPase assay. Finally mutagenesis, gene disruption and autophosphorylation studies had been carried out to find the essentiality of these genes.

**Results:** In this study we purified and express the selected proteins and also find that these proteins posses GTP binding and hydrolyzing activity. Mutagenesis in the important residue, gene disruption by antisense and autophosphorylation of these genes prove their essentiality in survival of M. tuberculosis. Antiserum raised against these proteins shows its localization in cytoplasm, cell wall, cell membrane and culture filtrate of M. tuberculosis. Bioinformatics results shows importance of these genes as drug target.

**Conclusion:** From the study we can conclude that GTP binding proteins might be an essential molecule in various aspects in terms of pathogenesis of M. tuberculosis. GTP binding and hydrolyzing property carried by these genes play an important role in survival which is also confirmed by from mutagenesis and gene disruption study. These genes can be serve as a potential drug target and may provide a better path in resolving the pathological and survival mechanism of M. tuberculosis.

**Funding Sources and Conflicts of Interest:** None

## PA-25

### Cytokines, matrix metalloproteinases, angiogenic factors and acute phase proteins as biomarkers in Tuberculous Lymphadenitis

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**Background:** Tuberculous lymphadenitis (TBL) is the most common presentation of extra pulmonary tuberculosis. TBL is characterized by decreased antigen-specific IL-1beta, IL-18, elevated type 1/17 cytokines and expansion of T helper (Th)1/Th17 cells. However, the study of cytokines and other related factors as biomarkers of TBL have not been performed.

**Methods:** Thus, we characterized the type 1/17, pro-inflammatory, regulatory cytokines, angiogenic molecules, matrix metalloproteinases (MMPs)/ tissue inhibitor of metalloproteinase (TIMPs) and acute phase proteins as markers discriminating TBL from latent tuberculosis (LTB). Similarly, we assessed the correlation among TBL biomarkers with lymph node (LN) culture grade, size and numbers. Finally, the effect of anti-tuberculosis (pre-vs-post) treatment (ATT) on the expression levels of these markers was assessed.

**Results:** TBL is associated with diminished systemic plasma levels of IL-1beta ($p=0.0019$), IL-18 ($p<0.0001$), vascular endothelial growth factor (VEGF)-A ($p<0.0001$), VEGF-C ($p<0.0001$), MMP-1 ($p=0.0325$) and elevated VEGF-R2 ($p<0.0001$), VEGF-R3 ($p<0.0001$), angiopoietin-2 (Ang-2) ($p<0.0001$), TIE2 ($p<0.0001$) and alpha 2 macroglobulin ($p=0.0099$) when compared to LTB. Receiver operating characteristic (ROC) analysis revealed that IL-1beta, IL-18, VEGF-C/R2, MMP-1 and alpha 2 macroglobulin were important markers discriminating TBL from LTB. No significant relationship was observed between biomarker levels and LN size, numbers or culture grade. Similarly, in response to ATT, IL-1beta, IL-18, VEGF-C, Ang-1, MMP-1 and alpha 2 macro globulin biomarker responses were significantly altered in TBL.

**Discussion and Conclusion:** Hence, pro inflammatory cytokines like IL-1beta, IL-18 or VEGF-C, MMP-1 and alpha 2 macroglobulin could serve as biomarkers for TBL disease progression/ immune protection.

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## PA-26

### Urine IP-10 as a biomarker of therapeutic response in patients with active pulmonary tuberculosis

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**Introduction:** Prior to clinical trials of new TB drugs or therapeutic vaccines, it is necessary to develop monitoring tools to predict treatment outcomes in TB patients. In this study, we assessed IP-10 levels in urine samples from patients with active TB at diagnosis, during treatment, and at completion, and compared these with levels in serum samples collected in parallel from matched patients to determine whether urine IP-10 can be used to monitor treatment response in patients with active TB. Methods: IP-10 was measured enzyme-linked immunosorbent assays in urine and serum samples collected concomitantly from 27 patients with active TB and 21 healthy adults (48 total individuals) in South Korea.

**Results:** The levels of IP-10 in urine increased significantly after 2 months of treatment ($P = 0.039$), but decreased by the completion of treatment ($P = 0.0023$). Serum IP-10 levels exhibited a similar trend, but did not increase significantly after 2 months

of treatment in patients with active TB. Conclusion: Unstimulated IP-10 in urine can be used as a biomarker to monitor treatment response in patients with active pulmonary TB.

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# PA-27

## Sputum sample collection for diagnosis of pediatric pulmonary tuberculosis, does method and site of sample collection matter?

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**Background:** Studies have indicated that tuberculosis killed an estimated 239,000 children in 2015 and nearly all of them were not on TB treatment. This highlights the need for better diagnostic tests and samples which are easy to collect. Several methods and sites for sample collection for PTB diagnosis have been used, however data about which specimen yields better diagnosis remains scarce.

**Methods:** We retrospectively analyzed laboratory data from induced sputum (IS), gastric aspirates (GA), gastric lavage (GL), nasal pharyngeal aspirates (NA) and string test (ST) samples received between January 2011 and June 2017 from < 5 years old children from Mulago national referral hospital, Kampala, Uganda. Laboratory tests were, fluorescent smear microscopy, Lowenstein Jensen (LJ) and mycobacterial growth indicator tube (MGIT) cultures. Samples were compared for smear, culture M. tuberculosis positivity, culture contamination rates and growth of non-tuberculous mycobacteria (NTM).

**Results:** Of the 1,577 samples, 734 (46.5%) were IS, 400 (24.4%) GA, 129 (8.2%) GL, 195 (12.4%) NS, and 119 (7.5%) ST. Samples, 25 (1.6%) were smear positive, 29 (1.9%) and 33 (2.1%) were M. tuberculosis positive on LJ and MGIT culture respectively. Samples 67 (4.2%) grew NTM on MGIT and none on LJ cultures whereas 67 (4.2%) and 288 (18.3%) were contaminated on LJ and MGIT cultures respectively. The diagnostic yield by test, sample and samples received was as in the table below:

**Conclusion:** Diagnosis of pediatric PTB using gastric lavage yields more cases but with high culture contamination rate. This underscores the importance of molecular methods such as the GeneXpert in pediatric TB diagnosis. Extending capacity for collecting GL and IS samples may lead to increased pediatric PTB case detection.

**Funding Sources and Conflicts of Interest:** None

**Table: The diagnostic yield by test, sample type and samples received**

| Samples | Smear n (%) | LJ n (%) | MGIT n (%) | LJ Contaminated n (%) | MGIT Contaminated n (%) | MGIT NTM n (%) | Total |
|---|---|---|---|---|---|---|---|
| **IS** | 13 (1.8) | 16 (2.2) | 12 (1.6) | 31 (4.2) | 143 (19.5) | 30 (4.1) | 734 |
| **GA** | 6 (1.5) | 3 (0.8) | 6 (1.5) | 16 (4.0) | 79 (19.8) | 17 (4.3) | 400 |
| **GL** | 2 (1.6) | 4 (3.1) | 10 (**7.8**) | 15 (**11.6**) | 42 (**32.6**) | 1 (0.8) | 129 |
| **NA** | 3 (1.5) | 4 (2.1) | 4 (2.1) | 2 (1.0) | 16 (8.2) | 11 (5.6) | 195 |
| **ST** | 1 (0.8) | 2 (1.7) | 1 (0.8) | 3 (2.5) | 8 (6.7) | 8 (6.7) | 119 |

## PA-28

### Tuberculosis massive active case discovery in East Jakarta 2016-2017: the role of Ketuk Pintu Layani Dengan Hati (KPLDH) and Juru Pemantau Batuk (Jumantuk) cadre programs

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*Tuberculosis Program Manager of East Jakarta Health Office, Indonesia*

**Background:** Indonesia has the 2nd highest number of incidents of tuberculosis (TB). It accounts for 1.020.000 new cases per year, only 30% of which has been reported. To find the lost 70%, a massive active case discovery was conducted through two programs: Ketuk Pintu Layani Dengan Hati (KPLDH) and Kader Juru Pemantau Batuk (Jumantuk cadres), who also plays a role in child TB screening.

**Methods:** Data was collected and analyzed through Tuberculosis Integrated Online System from 2014 to 2017 involving 129 DOTS facility with 86 primary health centers in East Jakarta.

**Results:** East Jakarta consists of 2.900.722 people. KPLDH program started in February 2016 consisting of 84 teams (310 people). Jumantuk cadres was formed 4 months later (218 orang). The number of new TB cases in East Jakarta (primary health center) from 2014 to June 2017 respectively is as follows: 6.499 (2.637), 7.438 (2.651), 8.948 (3.211), 5.701 (1.830). Meanwhile, the percentage of child TB case discovery in primary health center was 8,5%, 9,8%, 12,1% from 2014 to 2016 respectively. In 2017, child TB case discovery was 13,1% for the first 3 months and 16,5% for the next 3 months.

**Discussion:** Increased TB incidence rate from 2014 to 2017 was 14,4%, 20,3%, and 27,4% respectively in East Jakarta, and 0,5%, 21,1%, and 14% in primary health center. This reveals the positive role of KPLDH and Jumantuk in TB detection and reporting. Likewise, these programs were responsible for the increase in child TB case discovery, especially in the first 3 months of 2017 (Ketuk Pintu TB Day program) and the next 3 months (active TB screening).

**Conclusion:** KPLDH dan Jumantuk are actively involved in increasing TB case discovery in both adults and children.

**Funding Sources and Conflicts of Interest:** none

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## PA-29

### Clinical profile of tuberculous meningitis in a tertiary care center in India

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**Background:** Tuberculous meningitis (TBM) is certainly the most dangerous form of disease with high morbidity and mortality. The current scenario of TBM may provide a thought for urgent need of advances in vaccination against mycobacterium tuberculosis (MTB) to prevent this devastating manifestation.

**Method:** The Study was conducted during December 2014 to August 2016.Institutional ethical permission and patient consent was taken. 60 consecutive cases, more than 12 years of age, diagnosed of TBM using case definition and Lancet Consensus scoring system and admitted in a public tertiary care teaching hospital in Pune, India were included. History and clinical characteristics were studied.

**Results:** Mean age was 35.1 years, there were 55% males and 45% females .43% (26/60) had already received anti tubercular treatment for some form of tuberculosis previously. The most common symptoms were headache, fever, altered sensorium, weight loss and symptoms and signs due to raised intracranial tension . 41.7% patients had cranial nerve palsies. Radiological features were basal meningeal enhancement (93.3%), followed by infarcts(78.3%), tuberculomas(55%) ,basal exudates(30%) and hydrocephalus(25%) .Most common morbidity was neuromuscular weakness followed by ophthalmic complications including blindness, opthalmoparesis due to cranial nerve palsies,colorblindness and cognitive disturbances. The outcome of tuberculous meningitis was very dismal, with a very high mortality rate[46.6 %(28/60)] and those who survived had some form of disability deteriorating the quality of life.Conclusions.T.B.M. has high mortality and morbidity. The current scenario of TBM may provide a thought for urgent need of advances in vaccination against mycobacterium tuberculosis to prevent this devastating manifestation .

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