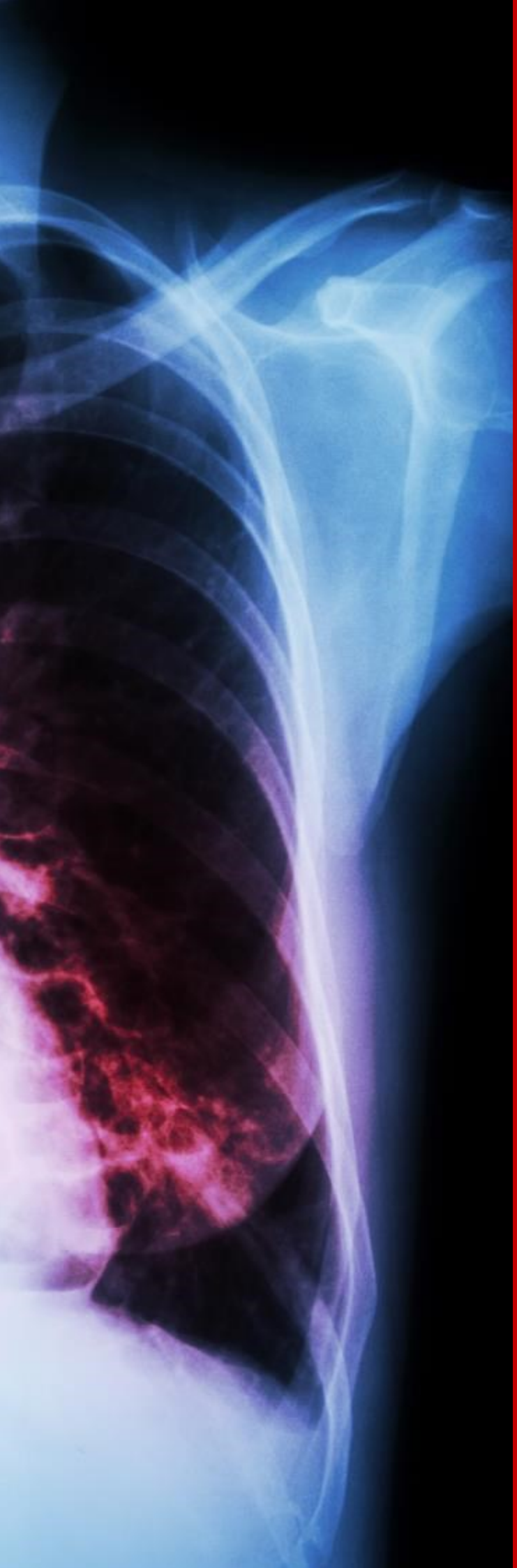


SPRINT TB

SINGAPORE
PROGRAMME OF RESEARCH
INVESTIGATING NEW APPROACHES
TO TREATMENT OF TUBERCULOSIS

ANNUAL REPORT 2015

NUS National University of Singapore

Yong Loo Lin School of Medicine

SPRINT TB

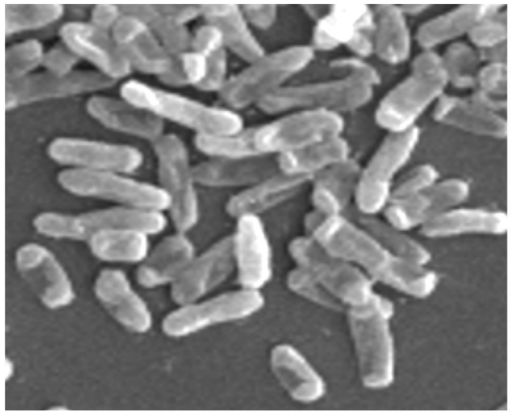
Fighting
TUBERCULOSIS
through Research

CONTENTS

TUBERCULOSIS

QUICK FACTS

- Tuberculosis (TB) is an infectious disease caused by a bacterium, *Mycobacterium tuberculosis*.
- One-third of the world's people carry TB in its inactive form. About 10% of these individuals will develop active disease over their lifetime.
- In 2014, 9.6 million people were diagnosed with TB and 1.5 million died of it.
- Multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB is on the rise, constituting nearly 0.5 million of total TB cases in 2014.
- Treatment for drug-sensitive TB has not changed for the past 40 years and involves 6 months intensive antibiotic therapy. Improved, shorter and more effective combination treatments are urgently needed.
- Treatment for drug-resistant TB is 18-24 months long and involves multiple expensive oral and injectable medications with many serious adverse effects. Nevertheless, nearly half of these patients die, as the existing drugs cannot efficiently clear the disease.



THE WORLD HEALTH ORGANIZATION AIMS TO END TB BY 2035, WHICH IS NOT ACHIEVABLE WITH THE CURRENT RATE OF GLOBAL TB INCIDENCE DECLINE OF LESS THAN 2% ANNUALLY.
TO MAKE TB ERADICATION A REALITY, NEW TOOLS ARE ESSENTIAL AND THEIR DEVELOPMENT DEPENDS ON RESEARCH FUNDING.

$1.3 BILLION

US DOLLARS OF ADDITIONAL FUNDING FOR TB RESEARCH IS NEEDED EVERY YEAR TO MEET THE DISEASE ERADICATION GOALS.

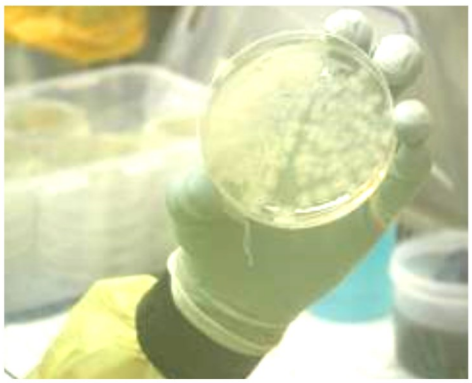
WHO Global TB Report 2015

THE BIGGEST KILLER

"IN 2014, TB KILLED
1.5 MILLION PEOPLE...
TB NOW RANKS ALONGSIDE
HIV AS A LEADING CAUSE
OF DEATH WORLDWIDE."

WHO Global TB Report 2015

Photo: WHO/David Rochkind



TB IN SINGAPORE

- With 49 TB cases for 100,000 people in 2014, Singapore is classified by WHO as a medium TB burden country.
- High prevalence of diabetes and the aging population drives the high incidence of TB cases in Singapore.
- Nearly 60% of the world's TB is in Asia. Singapore is surrounded by high TB incidence countries.
- International travel and commerce further fuel the incidence of TB (including drug-resistant TB) among Singaporeans.

SPRINT TB

SPRINT-TB, A COMPREHENSIVE BENCH-TO-BEDSIDE TUBERCULOSIS RESEARCH PROGRAMME LED BY NATIONAL UNIVERSITY OF SINGAPORE, FOCUSES ON DISCOVERING, DEVELOPING AND DELIVERING NOVEL TREATMENTS FOR THIS HIGH PRIORITY DISEASE.

THROUGH OUR INNOVATIVE RESEARCH, WE ARE WORKING TOWARDS A WORLD FREE OF TB.

MISSION

To discover, develop and deliver new treatments that ultimately save lives of people infected with tuberculosis.

VISION

By 2019, becoming a leading international academic research programme focused on delivering new treatments for tuberculosis.

AIMS

By 2019...

- *Discover at least two new genes essential for dormancy in mycobacteria*
- *Discover at least two new chemically-validated dormancy targets*
- *Deliver one preclinical development compound or one clinical candidate with activity against TB*
- *Identify two or more innovations in the standard TB drug development process (preclinical or clinical) that accelerate or improve the evaluation of new compounds or combination regimens*
- *Establish an Asian TB trials and clinical research network*
- *Complete the evaluation of at least one new or repurposed antibacterial drug (phase 2 or phase 2/3) with potential for regimen shortening*
- *Complete the evaluation of at least one new or repurposed immune-modulatory drug (phase 2 or phase 2/3) with potential for regimen shortening*
- *Identify an effective 2 month regimen for drug-sensitive TB*
- *Identify at least one improvement to treatment delivery systems that improves adherence and/or clinical outcome from TB treatment*

MESSAGE FROM PROGRAMME DIRECTOR

PROFESSOR NICHOLAS PATON

Department of Medicine
Yong Loo Lin School of Medicine
National University of Singapore

SPRINT-TB (Singapore Programme of Research Investigating New Approaches to Treatment of Tuberculosis) was formally established in July 2014 following the award of a substantive **flagship programme grant by the National Medical Research Council (NMRC)**, Singapore. This award indicates recognition of **the importance of tuberculosis (TB)** as a major public health threat, especially in Asia, as well as the **potential for Singapore researchers to make a pivotal contribution to this field.**

SPRINT-TB benefits from the **complementary expertise of four theme principal investigators** (PIs) (p. 6) – spanning basic science, drug development, clinical trials and health systems research. The PIs meet every month to develop a research agenda and inter-linked activities that are truly collaborative and aligned towards common goals. The programme also draws on the scientific and clinical expertise of a huge range of senior investigators from other departments and research institutes in Singapore and internationally. Currently over 100 staff and collaborators are working on projects funded under the programme.

SPRINT-TB has a number of other strengths. Firstly, it is based in Singapore, in the **heart of Asia** – a region with many high TB burden countries and containing nearly 60% of the world's TB cases. SPRINT-TB has succeeded in building **extensive intra-Asian collaborations** (p. 34), including several clinical trials that are currently active in the region. Secondly, the programme is supported by the **extraordinary scientific facilities** in Singapore – such as state-of-the-art imaging at the A*STAR-NUS Clinical Imaging Research Centre (p. 24), the brand new NUS BSL-3 laboratory (p. 33), and the technology platforms at the Experimental Therapeutics Centre (p. 16) and the Genome Institute of Singapore (p. 22). The greatest strength of SPRINT-TB is that it truly spans the **continuum of research from bench to bedside and beyond**, including the essential (but often forgotten) part of addressing the necessary steps of implementing research findings – all aligned to a **common goal of delivering new treatments for TB.**

Notable highlights during the year include identification by Theme 1 of potent **activity of bortezomib** against a new target in the TB bacterium (p. 10). In Theme 2, work has started on finding the **derivatives of bortezomib** that may have greater selectivity in killing bacteria with minimal toxicity (p. 16). Theme 3 has established a platform for testing new drugs and combinations in humans - the **whole blood bactericidal activity assay** (p. 22) - and modified this to be able to test drugs that work against bacteria, as well as that modify the host immune response. This is a powerful new way of fast-tracking the testing of new treatments and combination treatments through to clinical trials. Theme 4 has set up a collaborative effort in TB health services research with the national TB programme in Cambodia and opened the **SPRINT-TB office in Phnom Penh** (p. 31).

The programme also benefits from the oversight of its **Scientific Advisory Board** (p. 36) that convened its first meeting in October 2015, and has been privileged to receive a stream of **key international opinion leaders** in TB (p. 40) who have been very positive about the quality of the research and contribution SPRINT-TB can make.

I hope you enjoy reading this report and welcome any new opportunity to work together with you in the **global effort to fight TB through research.**

Nicholas Paton

SPRINT-TB Director

Research

SPRINT-TB spans four interconnected bench-to-bedside research themes.

Theme 1

BACTERIAL TARGET DISCOVERY

Lead: A/Prof. Thomas Dick
Department of Microbiology and Immunology
National University of Singapore

Using genetic and chemical approaches to identify new mycobacterial targets.

Theme 2

DRUG DEVELOPMENT

Lead: Prof. Alex Matter
Experimental Therapeutics Centre
A*STAR

Conducting screening, medicinal chemistry and pharmacology studies to develop new TB drug candidates.

Theme 3

CLINICAL TRIALS

Lead: Prof. Nicholas Paton
Department of Medicine
National University of Singapore

Conducting clinical trials to evaluate safety and efficacy of new drugs and combination regimens for TB.

The four research themes of SPRINT-TB reflect sequential stages in the drug discovery, development and delivery pathway. The themes work closely together towards the broader vision while maximizing the identification of any potential synergies that would enhance the programme's output.

New Approaches to TUBERCULOSIS Treatment

Theme 4

TREATMENT DELIVERY

Lead: Prof. Richard Coker
Saw Swee Hock School of Public Health
National University of Singapore

Developing solutions to the individual and systemic barriers that hinder successful provision of effective combination therapy.

Find out more about SPRINT-TB research at www.sprinttb.org/research .

Theme 1

Bacterial Target Discovery

Research under this theme is focused on delivering chemically and genetically *in vitro* as well as *in vivo* validated targets with bactericidal potential. The theme evaluates existing candidate targets and develops target-based whole cell, as well as biochemical assays that enable lead finding and optimization carried out under Theme 2. Research under Theme 1 also furthers the understanding of the biology of mycobacteria and the host response to infection.

Lead: **Associate Professor Thomas Dick**

Department of Microbiology and Immunology
National University of Singapore

> Theme 1 performs fundamental research in mycobacterial biology, drug target discovery and candidate compound identification. We have developed a new strategy—target-based whole cell screens—that has enabled us to identify several novel compounds with growth inhibitory properties.

A/Prof. Dick obtained his PhD in molecular bacteriology at the University of Heidelberg, Germany, and headed the Mycobacterium Biology Laboratory at the A*STAR Institute of Molecular and Cell Biology, Singapore, before joining the Novartis Institute for Tropical Diseases, Singapore, to lead its TB unit.

Currently A/Prof. Dick heads the antimicrobial drug discovery laboratory and is Director of the BSL-3 Core Facility at National University of Singapore. His research focuses on mycobacterial target discovery with a goal to identify new targets and lead compounds for the development of more effective TB chemotherapy.

Theme 1 Bacterial Target Discovery

BORTEZOMIB INHIBITS MYCOBACTERIAL GROWTH

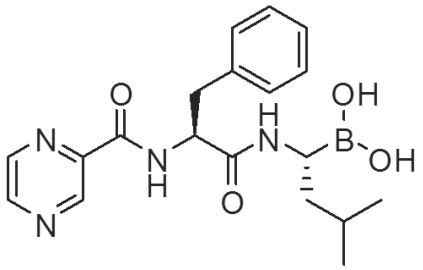
Theme 1 researchers have identified bortezomib (or Velcade®, which is currently approved for treatment of multiple myeloma) as a novel whole cell-active mycobacterial caseinolytic protease (Clp) inhibitor. Clp constitutes a key degradative proteolytic machinery involved in central proteome homeostasis in mycobacteria. By employing the target-based whole cell screening approach, Clp was found to be potently inhibited by bortezomib and its derivatives, causing mycobacterial growth cessation. The discovery established Clp as a new validated drug target and bortezomib as an attractive lead compound for the development of new TB drugs.

A provisional US patent application for the repurposed use of bortezomib was filed on February 6, 2015. This invention is a product of collaboration between Eric Rubin's group at Harvard T. H. Chan School of Public Health, USA, Theme 2 researchers at the A*STAR Experimental Therapeutics Centre, Singapore, and Thomas Dick's group at the Department of Microbiology and Immunology, National University of Singapore.

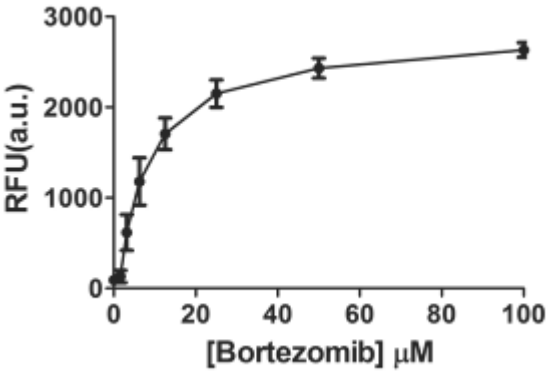
The discovery was published in MBio in May 2015.

Bortezomib and its related compounds are currently undergoing further preclinical and early stage clinical investigations under SPRINT-TB. Theme 2 chemistry team (p. 16) are testing a range of bortezomib derivatives in order to increase the compound's selectivity towards *M. tuberculosis* Clp as opposed to human proteasomes, while Theme 3 researchers (p. 22) will be conducting a clinical study to assess the efficiency of bortezomib in mycobacterial killing.

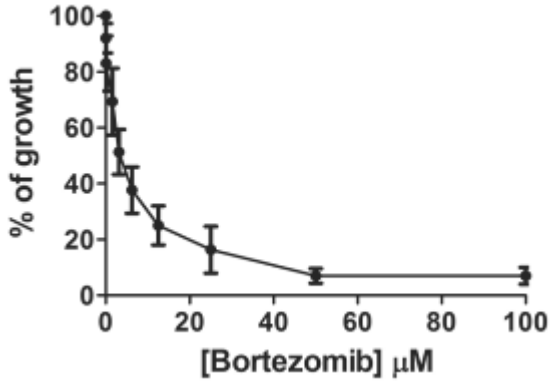
Image on the right:
Bortezomib inhibits ClpP1P2 activity and mycobacterial growth (*Moreira et al, 2015*).



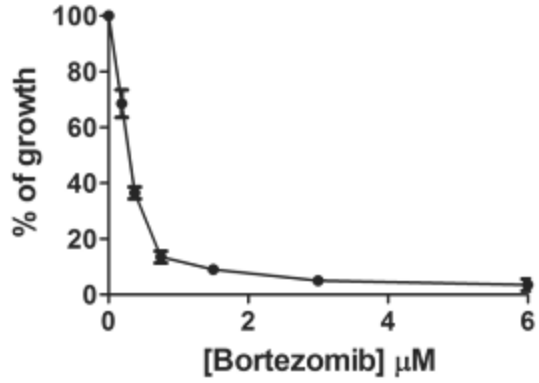
Structure of bortezomib



ClpP1P2 inhibition (p38-mRFP-SsrA)



***M. smegmatis* growth inhibition**



***M. bovis* BCG growth inhibition**

Photo above:
Dr. Wilfried Moreira, Clp screen project lead.

Photo below:
Dr. Yoshiyuki Yamada, whole cell screen project lead.

WHOLE CELL SCREEN

The major barrier to developing new drugs for TB is the lack of attractive targets with their associated, whole cell-active lead compounds for target-based lead optimization campaigns. Theme 1 employs a new strategy, a target-based whole cell screen, to identify such target-lead couples for the development of new clinical TB drug candidates.

The whole cell screening strategy enables to select compounds with antimicrobial activity without any pre-existing assumptions of which cellular mechanisms might be 'essential'. It also has the benefit of probing the complete set of cellular targets (at least 600 genetically essential genes in *Mycobacterium tuberculosis*) in a single assay.

This approach has been successfully applied by Theme 1 previously and generated several target-lead couples with compounds showing efficacy against mycobacteria. Further pathway screens are in the process of identifying target-lead couples for development of new clinical TB drug candidates over the next several years.

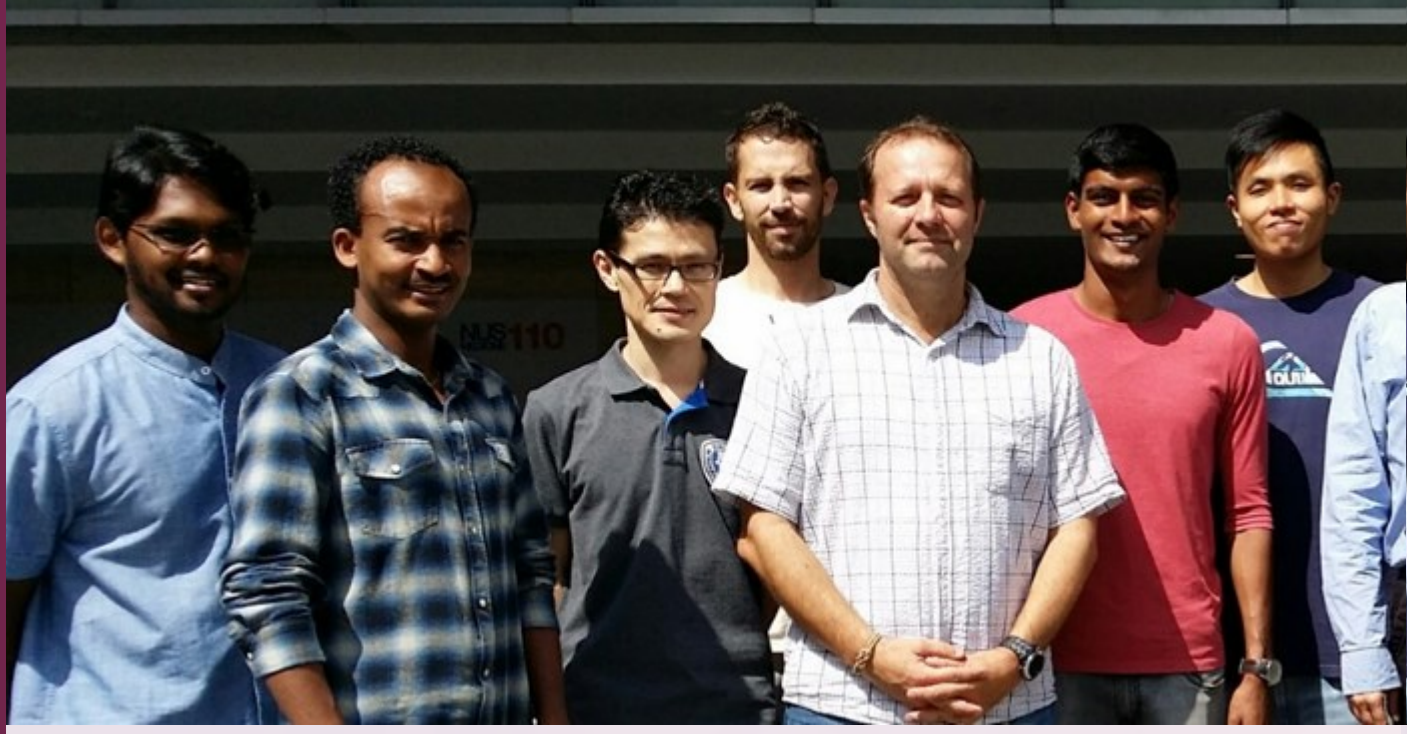


Photo above: Theme 1 Team
Left side: Mr. Sasikumar Rajandran, Mr. Wassihun Wedajo Aragaw, Dr. Yoshiyuki Yamada, Dr. Wilfried Moreira, Dr. Goran Biukovic, Mr. Jickky Palmae Sarathy, Mr. Low Jian Liang.

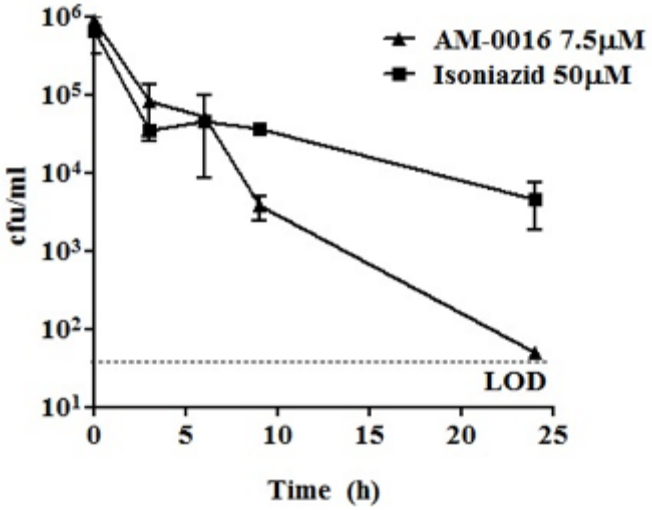
MANGOSTEEN AGAINST TUBERCULOSIS

A new class of compounds found in mangosteen fruit was identified by Prof. Roger Beuerman's group at the Singapore Eye Research Institute (SERI). The compounds, xanthone derivatives, are based on the α-mangostin scaffold and were found to exhibit antimicrobial properties.

In collaboration with SERI, Theme 1 tested twenty five xanthone derivatives against *Mycobacterium tuberculosis.* Rapid cidal activity and potency against phenotypically drug-resistant dormant bacteria was observed. The selected lead compound, AM0016, exhibited low spontaneous resistant mutation frequency. Further tests utilizing scanning electron microscopy showed that exposure to AM0016 induced damage to the mycobacterial cell envelope, which inversely correlated with cell viability.

Xanthone compounds thus represent a novel, fast acting chemotype and a promising lead against *M. tuberculosis*. The compounds are undergoing further studies under SPRINT-TB.

Image on the right:
AM0016, a compound derived from mangosteens, is effective against mycobacteria.



Time-dependent activity of AM0016 against *M. smegmatis.*

Right side: A/Prof. Thomas Dick, Ms. Hayden Yeo Hui Yu, Ms. Annanya Shetty, Ms. Devika Mukherjee, Ms. Carolyn Mulu Wu, Ms. Grace Ngan Jie Yin, Ms. Michelle Yee Mei Kheng, Ms. Jia Jie Lim, Ms. Pooja Gopal.

MORPHOLOGICAL PLASTICITY IN MYCOBACTERIA

Generally mycobacteria are viewed as non-differentiating aerobic bacilli: they do not form specialized resting cells, need oxygen and are rod shaped. Mycobacteria can survive shock starvation in phosphate buffered saline in a non-replicating state without any apparent morphological differentiation.

Theme 1 had another look at this adaptation. Rather than shock starving the bacilli in saline, they added traces of a carbon source to the saline and observed the response of the bacteria. Interestingly, providing traces of a carbon source to *M. smegmatis* in saline (as opposed to shock-starving the microorganism), resulted in the formation of a small-cell morphotype: reductive cell division generated very short rod-shaped cells with increased long-term viability. Upon addition of rich medium, these small resting cells grew back to larger standard cells before commencement of the regular cell division cycle. The fact that a new morphotype can be so easily generated by slight changes in culture conditions supports the notion of a surprising morphological plasticity of mycobacteria.

MECHANISM OF ACTION OF PERCHLOZONE SOLVED

Perchlozone®, a new thiosemicarbazone class drug, was approved for treatment of multidrug-resistant tuberculosis (MDR-TB) in Russia in 2012. The mechanism of action of the drug was unknown.

Theme 1 performed a comparative *in vitro* analysis of perchlozone and thiacetazone, a well-studied thiosemicarbazone TB drug. The two compounds were found to have an identical spectrum of activity. Spontaneous drug-resistant mutants exhibited cross-resistance, which was mapped to the FASII dehydratase complex HadABC and the monooxygenase EthA, thereby suggesting that perchlozone, like thiacetazone, is activated by EthA with its principal target being HadABC. The study was published in the International Journal of Antimicrobial Agents in April 2015.

Photo below:
Ms. Pooja Gopal, perchlozone project lead.

Theme 2

Drug Development

Research under this theme is focused on characterizing compounds discovered by Theme 1 and by external sources. Theme 2 conducts high-throughput screening, medicinal chemistry and pharmacology for lead finding, optimization and preclinical development to deliver new TB drug candidates for clinical development.
The theme also develops imaging biomarkers that can provide an early indication of activity of drugs or combination regimens against TB bacilli and works on TB models to conduct preclinical development studies in order to support investigational product use in humans.

Lead: **Professor Alex Matter**

Experimental Therapeutics Centre
A*STAR

> Our theme bridges fundamental research of Theme 1 to clinical development in Theme 3 by guiding early stage scientific discoveries to clinical trials in man via a rigorous comprehensive preclinical drug development and optimization process.

Prof. Matter held a position as Director of the Novartis Institute for Tropical Diseases, Singapore, and was Global Head of Oncology Research for Novartis Pharmaceuticals Corporation, where he played an important role in the success of several anticancer drugs.

Currently Prof. Matter is CEO of the Experimental Therapeutics Centre at A*STAR, Singapore and Honorary Adjunct Professor at National University of Singapore.

Prof. Matter is a recipient of multiple prestigious international scientific awards. His research interests lie in drug discovery and experimental therapeutics.

LEAD OPTIMIZATION PROJECTS

Theme 1 screens and identifies novel compounds active against new TB targets, which advance to Theme 2 for lead optimization.

Optimization starts with selecting the leads from secondary screening with proven specificity, the highest binding affinity to the target of interest, and an initial structure-activity relationship. The process not only focuses on enhancing the affinity of the drug candidates towards the target, but also improving their pharmacokinetics, namely, absorption, distribution, metabolism, and excretion, to render properties which are required for optimal drug action and reduction of potential side effects.

Candidates are tested for solubility in variable formulations before being assessed for their *in vivo* pharmacokinetic properties in preclinical studies. The drug candidates that have optimal properties in potency, metabolic stability, permeability, minimal CYP450 inhibition and induction, as well as adequate bioavailability are selected for further evaluation.

The first compound successfully identified and tested by Theme 1 as a candidate for TB treatment, bortezomib (p. 10), is currently undergoing studies by Theme 2 medicinal chemistry team to enhance its selectivity to mycobacterial Clp target versus the human proteasome.

Photo below:
Drug development facilities at the Experimental Therapeutics Centre, A*STAR, Singapore.

Photo on the right:
PET imaging being performed at the Singapore Bioimaging Consortium's state-of-the art imaging facility.

ANTI-TNF-α MONOCLONAL ANTIBODY AS TB TRACER

Theme 2 aims to develop new tracers for PET (positron emission tomography) imaging of pulmonary TB based on labelled monoclonal antibodies. Tumour necrosis factor-α (TNF-α) is a critical cytokine in the immune response and clinical symptomatology of TB. Labelling infliximab, one of the clinically-licensed monoclonal antibodies against TNF-α, will be the first step in testing this approach.

The tracer doses of labeled anti-TNF-α antibody used in PET imaging are too small to have any notable biological effect, but will enable the localization and quantification of TNF-α secretion. Previous studies of the human TB immune response have largely been limited to measuring TNF-α levels in peripheral blood or bronchoalveolar lavage fluid. Having a method to measure TNF-α secretion *in situ* could provide valuable new insights into the disease pathogenesis, as well as act as a potentially useful indicator of drug activity.

The initial proof-of-concept study is in progress in collaboration with the Singapore Bioimaging Consortium, A*STAR, using the humanized mouse model developed at the Institute of Molecular and Cell Biology, A*STAR (p. 18). The concept will later be translated to clinical studies.

The developed method may have further applications to other pathologies characterized by high local TNF-α levels that have been shown to respond to therapeutic anti-TNF-α monoclonal antibodies (rheumatoid arthritis, inflammatory bowel disease). This approach may also be extended to label other monoclonal antibodies for use in TB imaging and treatment or relapse monitoring.

Photo below:
Collaborators in the anti-TNF-α antibody for TB imaging project: Dr. Julian L. Goggi, Prof. Kishore K. Bhakoo and Dr. Edward G. Robins, Singapore Bioimaging Consortium , A*STAR, Singapore.

DEVELOPMENT OF NOVEL TB RELAPSE MODELS

Murine models have been extensively used for investigating aspects of human TB by assessing the effects of drugs on bacterial clearance rather than testing sterilising activity using a relapse model. One of the main challenges in developing a useful relapse model has been the fact that acute TB models (BALB/c or C57BL/6) lack lesions with typical human TB pathology. Such lesions provide a spectrum of microenvironments in which *M. tuberculosis* bacilli can reside, allowing the pathogen to exist simultaneously in physiological stages ranging from active replication to dormancy.

Theme 2 is taking an approach of adopting alternative models. For instance, the C3HeB/FeJ (Kramnik) model has shown the ability to form lesions more representative of the TB pathology seen in humans. Furthermore, the Institute of Molecular and Cell Biology (A*STAR) in Singapore has developed a humanized mouse model that may be of high value as a TB model by formation of granulomas consisting of human cells, thus mimicking human-like pathology.

The project will introduce further refinements to the relapse model: PET/CT (positron emission tomography/computed tomography)-based imaging, which will enable longitudinal assessment and allow for monitoring of relapse, decrease sample size, improve the precision of outcome detection, and more closely resemble the relapse assessment methods used in clinical studies.

The work in developing the novel TB relapse models with PET/CT-based imaging may translate into a new experimental paradigm that transforms how new compounds and drugs for TB are assessed. The developed models will be used in multiple SPRINT-TB preclinical studies (next page).

Photo below:
Inventor of the humanized mouse model Dr. Chen Qingfeng (fourth from the right) and his team at the Institute of Molecular and Cell Biology, A*STAR, Singapore.

Photo on the left:
Dr. Martin Gengenbacher, laboratory head, and Dr. Rupangi Verma, project lead, working on TB model development and preclinical studies.

PRECLINICAL STUDIES OF TB DRUG CANDIDATES

Preclinical evaluation with animal efficacy studies is starting under Theme 2 for several new TB drug candidates. The studies will be using acute and relapse (p. 18) TB models.

The newly-identified mycobacterial Clp inhibitor bortezomib (p. 10) and related compounds (including ixazomib) are currently entering preclinical studies for efficacy against *M. tuberculosis*.

Another novel class of compounds with mycobacterial cidal activity, xanthone derivatives (p. 12), will progress to preclinical testing in the beginning of 2016.

Given strong supporting results in these and other preclinical assessments, the candidate drug compounds will proceed to clinical development under Theme 3 (p. 20).

Photo on the right:
Part of the preclinical research set up at the BSL-3 Core Facility, National University of Singapore.

Theme 3

Clinical Trials

Research under this theme focuses on clinical trials of new drugs and treatment regimens for drug-sensitive TB. The new interventions arise from research in Theme 1 and Theme 2, as well as novel applications of existing compounds and their combinations.

The theme also conducts clinical trials of new or repurposed anti-mycobacterial or immune-modulatory drugs and combination regimens to shorten treatment duration for TB.

Theme 3 also aims to improve trial methodology and to establish collaborations between Asian research centres to form a network to conduct high standard TB clinical trials.

Lead: **Professor Nicholas Paton**

Department of Medicine
National University of Singapore

> Our theme takes compounds developed by Theme 1 & 2, as well as other new or repurposed drugs, and brings them into clinical testing in patients. In addition to antibacterial compounds, we also focus on new treatments that can potentially improve the immune response to TB.

Prof. Paton obtained his medical degree from the University of Cambridge, UK, and has held senior research positions at the Medical Research Council Clinical Trials Unit in UK and National University of Singapore. He has extensive experience in translational research, led multiple large scale trials, including EARNEST and PIVOT, and worked with multiple international research networks.

Prof. Paton currently heads SPRINT-TB and is Director of Research at the University Medicine Cluster. He focuses on TB clinical research with particular interest in treatment shortening approaches. He is the Chief Investigator of the multinational TRUNCATE-TB trial, which aims to shorten drug-sensitive TB treatment to 2 months.

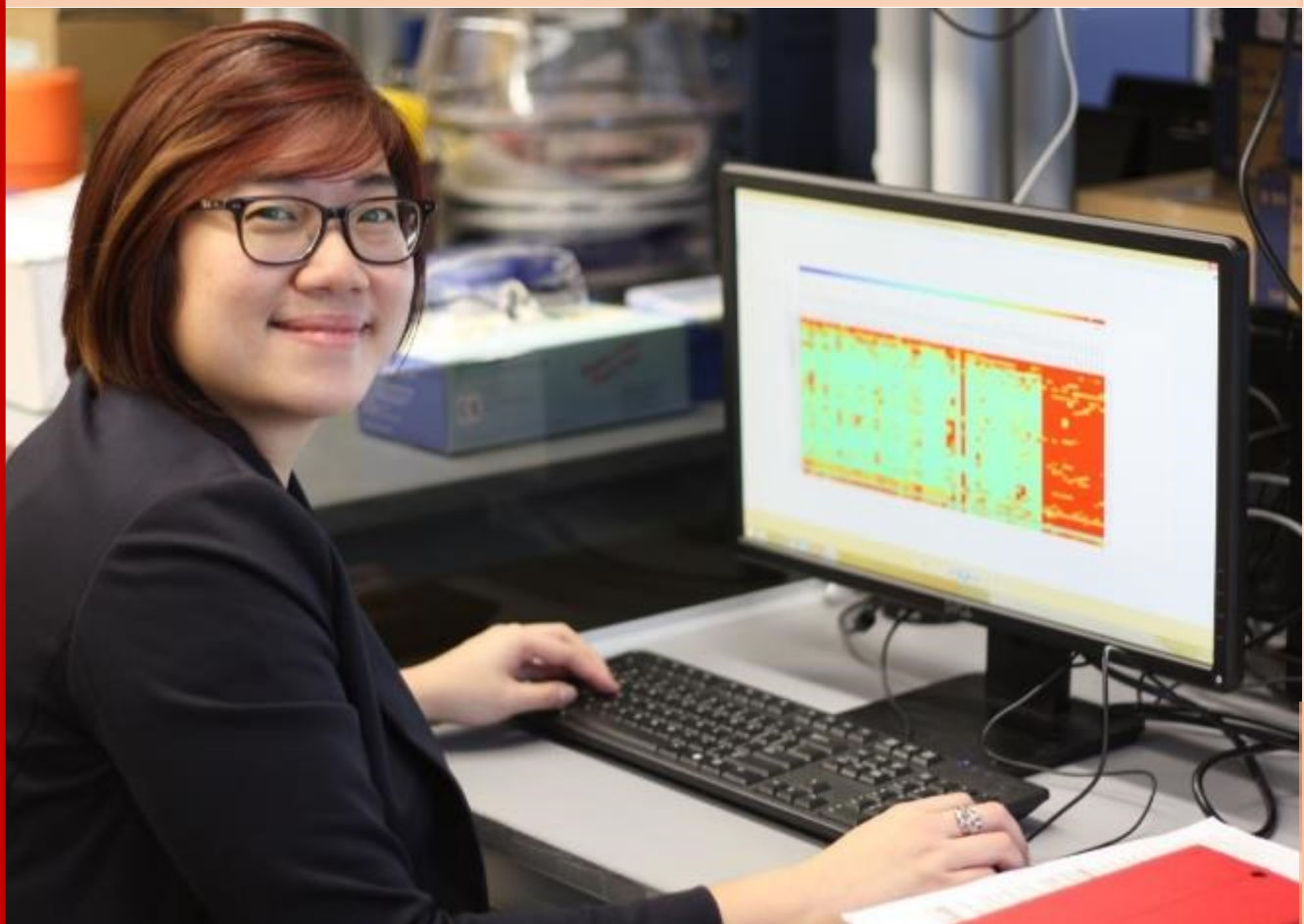
WHOLE BLOOD BACTERICIDAL ACTIVITY ASSAYS

The whole blood bactericidal activity assay (WBA) is an *ex vivo* model for measuring drug effects on mycobacterial sterilization. In a WBA study, healthy volunteers take the study drug and their blood is afterwards taken at predetermined time points. Each blood sample is later infected in the laboratory with TB bacteria, and bacterial killing by circulating drugs and host factors is measured using liquid cultures.

WBA is a novel experimental method which allows for preliminary investigation of sterilizing effects of new TB drugs and drug regimens. Theme 3 uses the assay to evaluate efficacy of various drugs against a range of *M. tuberculosis* strains, as well as to assess the host immune response and changes in the gene expression profile in collaboration with the Genome Institute of Singapore.

Photo above:
WBA project leads: Dr. Meera Gurumurthy, Dr. Claire Naftalin and Dr. Rupangi Verma.

Photo below:
Dr. Lin Wenwei, lead of the WBA transcriptomics studies, reviewing gene expression data produced in collaboration with Prof. Martin Hibberd and Dr. Paola Florez de Sessions from the Genome Institute of Singapore, A*STAR, Singapore.



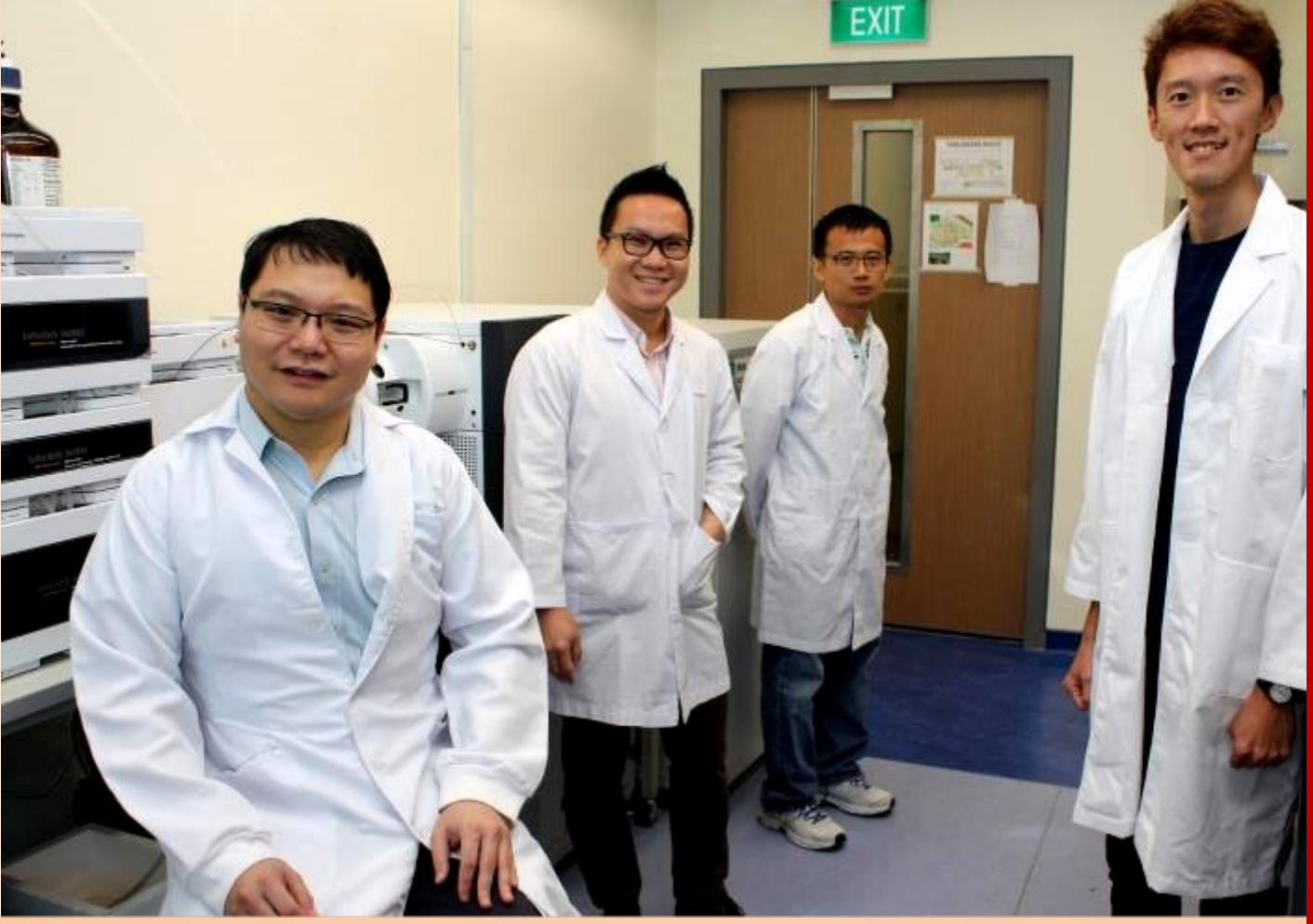


Photo above:
Pharmacokinetics analysis team : A/Prof. Lawrence Lee, Dr. Daryl Hee Kim Hor, Mr. Han Hwan Chour and Mr. Johannesen Leaw Yee Kiat.

The studies are performed with healthy volunteers, who are recruited and dosed at the Investigational Medicine Unit, National University Hospital, Singapore.

Theme 3 has established the WBA assay at National University of Singapore's BSL-3 Core Facility, which is equipped with an automated mycobacterial growth detection system and has a large collection of *M. tuberculosis* strains utilized in the assay.

Pharmacokinetics analysis of the collected blood samples is performed by A/Prof. Lawrence Lee's team at National University of Singapore. The team uses Agilent Triple Quadrupole liquid chromatography and mass spectrometry systems.

The first WBA study was successfully completed in November 2015 and there are multiple drugs and regimens in the ongoing WBA pipeline.

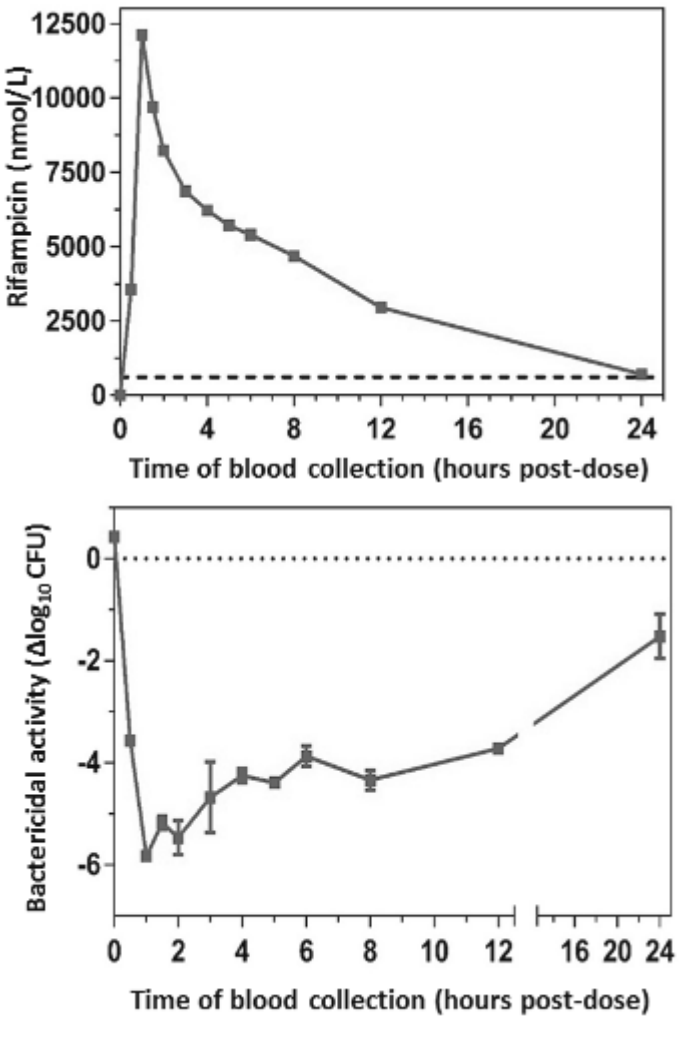


Image on the right:
Serum concentration of rifampicin and the corresponding whole blood bactericidal activity in one healthy volunteer after a single dose of 30 mg/kg of rifampicin.

TB CLINICAL IMAGING STUDIES

There is a pressing need to develop biomarkers that can provide an early indication of activity of drugs or combination regimens against TB, and novel imaging approaches hold promise for this indication. In collaboration with the A*STAR-NUS Clinical Imaging Research Centre, Theme 3 uses the PET/MRI platform to measure the extent and activity of pulmonary TB and evaluate the relationship between the imaging features and clinical, microbiological and immunological markers of TB disease in the course of chemotherapy.

Theme 3 also conducts studies in TB-exposed contacts in order to develop a test that can differentiate between patients with completely quiescent TB, and those with subclinical disease that may later progress into active TB.

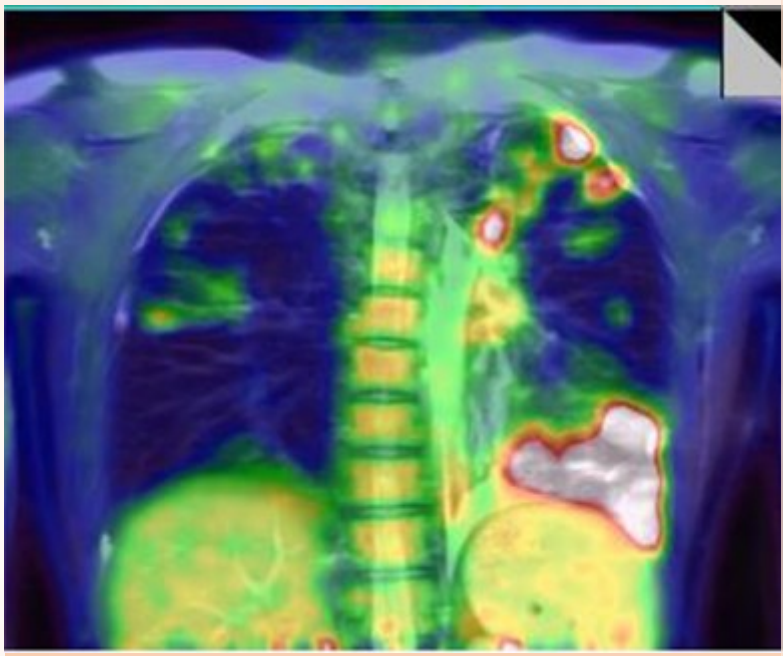


Image above:
PET/MRI scan of a study participant with active pulmonary TB.

The studies are ongoing and initial observations were published in Radiology in September 2015. Theme 3 will also be conducting a range of TB imaging studies using novel tracers.

Photo below:
Study participant undergoing a PET/MRI scan inside an infection control capsule at the A*STAR-NUS Clinical Imaging Research Centre, National University of Singapore.

Photo above:
Participants of TRUNCATE-TB Trial Steering Committee Inaugural Meeting, held on February 11, 2015 at National University of Singapore.

Back row: Dr. Qingshu Lu (Singapore), Dr. Padmasayee Papineni (Singapore), Prof. Guy Thwaites (UK/Vietnam), Dr. Meera Gurumurthy (Singapore), Dr. Geraint Davies (UK/Malawi), Prof. Andrew Nunn (UK), Dato' Dr. Hj. Abdul Razak Muttalif (Malaysia), Dr. Patrick Phillips (UK), Prof. Charles Gilks (Australia), Prof. Nicholas Paton (Singapore), Prof. Shenjie Tang (China), Dr. Sushil Pandey (Australia).
Front row: Ms. Suelyn Lau (Singapore), Dr. Rovina Ruslami (Indonesia), Dr. Sabai Phyu (Singapore).

TRUNCATE-TB TRIAL

Establishing effective short treatment regimens is a priority in combating the TB epidemic. Theme 3 flagship project is the TRUNCATE-TB trial (Two-month Regimens Using Novel Combinations to Augment Treatment Effectiveness for drug-sensitive Tuberculosis). It is a ground-breaking phase 2/3 TB treatment regimen shortening trial, which will recruit over 1,000 patients in 6-8 countries in Asia until its completion in 2019.

The primary aim of the trial is to determine whether a strategy of treating drug-sensitive TB for 2 months with one of a number of novel combination regimens and re-treating relapses with a 6 month course of standard treatment will be non-inferior to the standard 6 month treatment / 6-month re-treatment approach.

The secondary aims are determining whether there are advantages of a 2 month initial treatment strategy for preventing the emergence of drug resistance, improving quality of life and decreasing national TB programme resource use and cost. The study also aims to determine the safety, tolerability and efficacy of a number of novel TB combination regimens.

The study is conducted with Singapore Clinical Research Institute (SCRI) and University College London, UK.

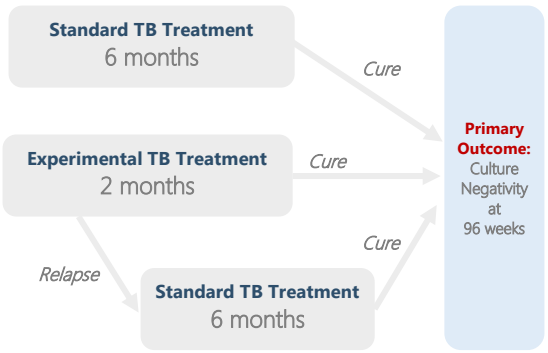


Image on the right:
TRUNCATE-TB trial concept.

HOST-DIRECTED THERAPY

PASCOLIZUMAB TRIAL

There is a strong immunological rationale for targeting interleukin-4 (IL-4) in TB patients as an approach to more rapidly eliminate dormant mycobacteria: TB patients have demonstrable IL-4 in blood and granulomas, while anti-IL-4 antibodies administered to TB-infected Balb/c mice result in marked reduction in colony counts in lung and spleen. Thus, decreasing the Th2 response by blocking IL-4 may accelerate clearance of mycobacteria. A humanized anti-IL-4 monoclonal GMP-grade antibody, pascolizumab, exists and has been made available to SPRINT-TB by GlaxoSmithKline.

Theme 3 is conducting a randomized, double-blind, placebo-controlled proof-of-concept trial in patients with drug-sensitive TB to evaluate efficacy of blocking IL-4 with pascolizumab administered with the standard TB therapy.

The trial is conducted at sites in Singapore, Malaysia, Philippines and Thailand.

Dosing Strategy

(IV infusion with standard Rx for drug-sensitive TB)

Cohort 1
0.05mg/kg single dose; 4 active
Cohort 2
0.5mg/kg single dose; 4 active
Cohort 3
2.5mg/kg single dose: 9 active, 3 placebo
Cohort 4
10mg/kg single dose: 9 active, 3 placebo
Cohort 5
2.5mg/kg x 2, 28d apart: 9 active, 3 placebo
Cohort 6
10mg/kg x 2, 28d apart: 9 active, 3 placebo

Outcome Measures

Primary: Efficacy - time to detection in sputum liquid culture at week 8

Co-primary: Safety in drug-sensitive TB

Secondary: Bacterial clearance, host clinical status, immune response, transcriptomics, lung imaging

Box above:
Pascolizumab trial design.

Photo on the right:
Investigational Medicine Unit (National University Hospital, Singapore) study coordinator Ms. Grace Xie examining a trial participant during one of the study visits.

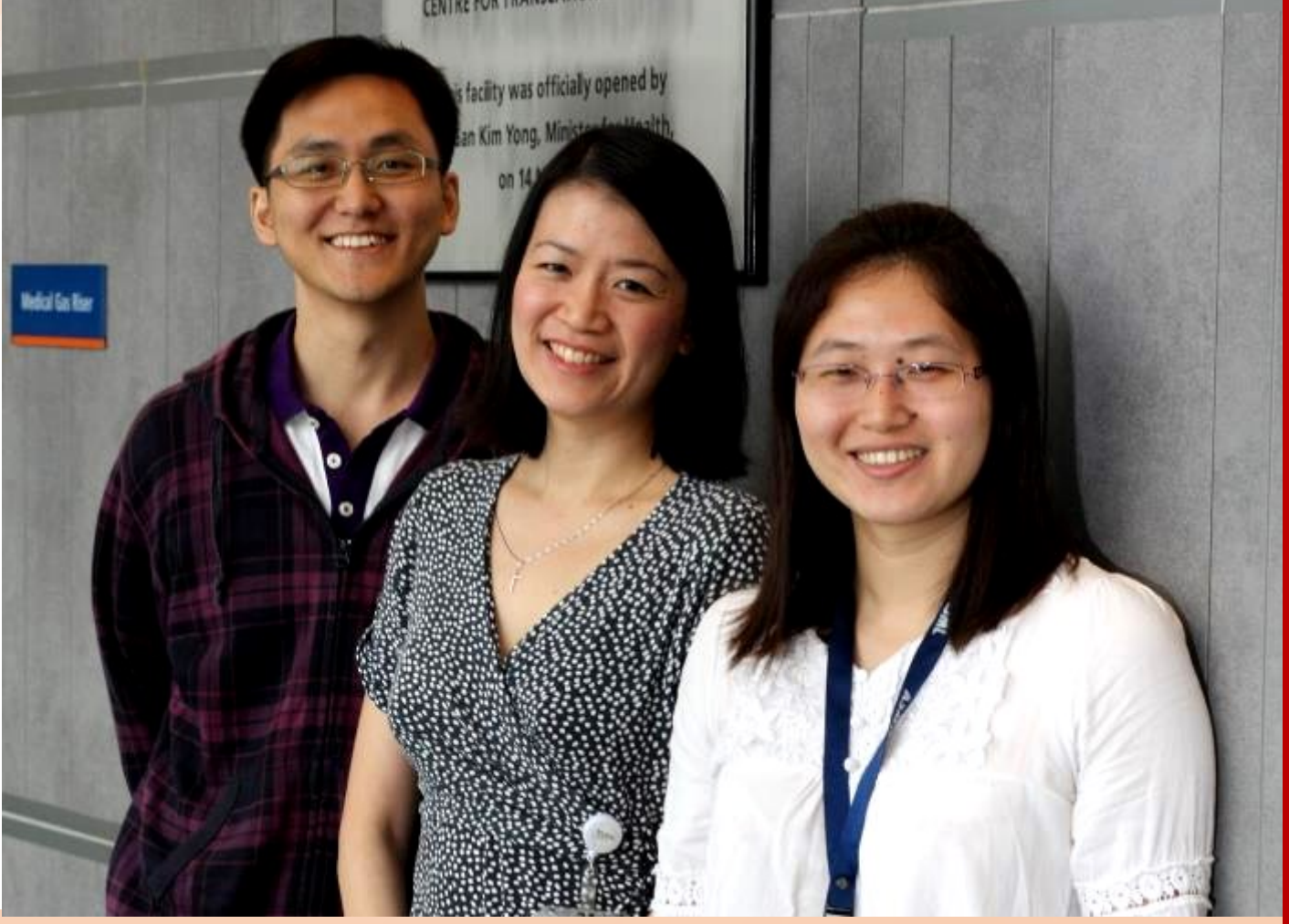


Photo above:
Doxycycline study team: Dr. Eddie Miow Qing Hao, Principal Investigator Dr. Catherine W. M. Ong and Ms. Wang Yu.

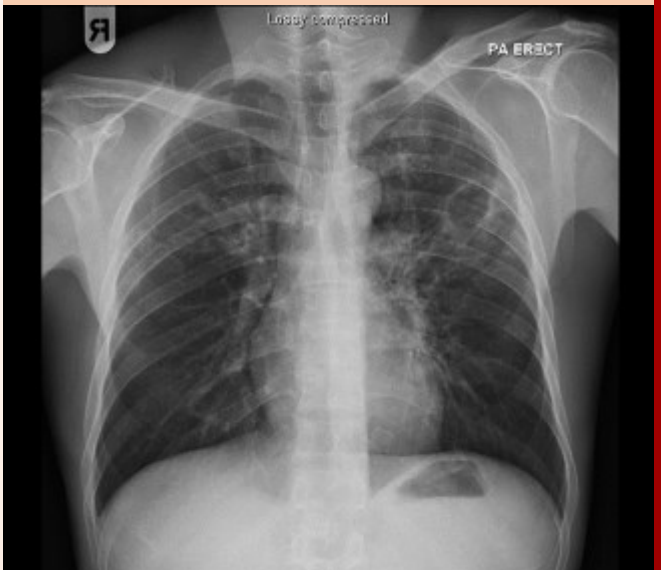
DOXYCYCLINE STUDY

A hallmark of advanced TB is lung cavities, which are caused primarily by patients' inflammatory response. Host proteolytic enzymes, matrix metalloproteinases (MMPs), drive lung tissue destruction in TB infection. MMP inhibition with the antibiotic doxycycline has been shown to improve lung function in patients with chronic lung diseases, but its use in TB treatment has not been sufficiently explored.

A proof-of-concept study conducted by Dr. Catherine W. M. Ong, National University of Singapore, aims to test whether MMP inhibition with doxycycline will decrease tissue destruction in TB. Patients with pulmonary TB are randomized to receive doxycycline or placebo to be taken for 14 days together with the standard TB treatment. For comparison, healthy volunteers receive only doxycycline for 14 days. At designated time points, clinical test are performed and specimens are collected for analysis.

The study will evaluate whether doxycycline can decrease the host inflammatory response in TB and reduce immunopathology. It will be a springboard to a large randomized control trial to examine if doxycycline can mitigate tissue destruction in human TB. This entirely novel approach utilising an antibiotic with a proven safety profile to reduce TB-associated inflammatory pathology will play an important role in shaping future host-directed immunomodulatory interventions in TB.

Image below:
Chest X-ray showing lung cavities in a TB patient.



Theme 4

Treatment Delivery

Theme 4 studies factors that hinder provision of TB therapy to people who need it and develops solutions to these issues. It conducts observational studies to define individual or systematic barriers (regulatory, financial, health systems) that impair the success of effective combination therapy or that impair outcomes from combination therapy, and drives interventional studies of new approaches to address these problems.
The theme also focuses on TB treatment delivery, such as novel models of observed therapy and inducing behavioral changes to enhance adherence to treatment.

Lead: **Professor Richard Coker**

Saw Swee Hock School of Public Health
National University of Singapore

> Our theme performs TB and associated health systems research with the focus on Asia. With almost 60% of world TB cases found in Asia, developing countries in the region would be the beneficiaries of new systems allowing unhindered provision of TB therapy.

Prof. Coker trained at Imperial College Medical School and currently leads TB research at Saw Swee Hock School of Public Health, National University of Singapore. He is also Professor at London School of Hygiene and Tropical Medicine and heads the Communicable Diseases Policy Research Group based in Thailand, which provides a focus of expertise on the diverse public health problems associated with communicable disease control internationally.

Prof. Coker's research interests include emerging infectious diseases, tuberculosis, health systems analysis and strategic planning, policy analysis, and pandemic preparedness.

Theme 4 Treatment Delivery

MOBILE INTERACTIVE SUPERVISED THERAPY (MIST)

Patient compliance is essential for TB treatment success, but it is challenging to sustain for the whole six month duration of the treatment. Current means of ensuring the adherence is Directly Observed Therapy (DOT), where patients need to report daily to a clinic and take their medication under direct observation of a healthcare worker. This may be inconvenient and costly to patients and also strain the resources of national TB control programmes.

As an alternative patient-centered approach, Theme 4 has developed MIST (Mobile Interactive Supervised Therapy), a platform for smartphone-based treatment supervision to enhance TB treatment regimen adherence. It enables patients to submit videos of themselves taking pills, thereby removing the need for them to attend the DOT clinic in person.

MIST has been tested with healthy volunteers and found to be acceptable and effective in supporting adherence to pill taking. The study will further expand to the countries in the region to test the approach in TB patients.

Photo above:
MIST project lead Dr. James Molton testing the app prototype on the Android platform.

Photo below:
MIST project research coordinator Ms. Pang Yan reviewing submitted videos.

Photo above:
Principal investigator A/Prof. Teo Yik Ying (front row, third from the left) and project lead Dr. Rick Ong (front row, second from the left) with mTB genomic database project regional collaborators at the Genomic Epidemiology of Infectious Diseases workshop held February 2-6, 2015.

MTB GENOMIC DATABASE FOR RESISTANCE SURVEILLANCE

MTB genomic database project, led by Principal Investigator A/Prof. Teo Yik Ying and project lead Dr. Rick Ong Twee Hee at Saw Swee Hock School of Public Health, National University of Singapore, aims to create a comprehensive genomic database of clinical *M. tuberculosis* isolates within Asia, correlating whole genome sequence data and corresponding phenotypic drug susceptibility results in order to differentiate neutral phylogenetic-informative polymorphisms from mutations associated with drug resistance. The database, coupled with rapid high-throughput sequencing technologies could be used as a rapid molecular diagnostic method to facilitate active genomic surveillance in TB patients, enabling clinicians to monitor emergence of drug resistance and thus personalize the therapy for effective treatment. *M. tuberculosis* clinical isolates for the development of the database are obtained in partnership with collaborators in Singapore, Thailand, Vietnam, Malaysia, Indonesia, Myanmar and Cambodia.

TB HEALTH SYSTEMS RESEARCH IN CAMBODIA

Cambodia consistently ranks amongst the 22 highest burden countries with the second highest incidence and mortality rates in Asia. Approximately 64% of the population is infected with either latent or active TB and although free TB treatment is available, there is a substantial number of cases that remain undetected as indicated by the low 62% case detection rate for all forms of TB. The prevalence of multidrug-resistant TB (MDR-TB) is also increasing in Cambodia.

Multidisciplinary TB health systems research has been initiated in Cambodia by Prof. Richard Coker and Dr. Mishal Khan from Saw Swee Hock School of Public Health, National University of Singapore, in 2014. The aim of this research is to generate evidence that will inform policy-makers about optimal allocation of limited resources in order to achieve long term reductions in TB and MDR-TB. Projects are structured around a transmission dynamics framework, involving qualitative, epidemiological, genomic, economic and modelling studies.

As part of the project activities, SPRINT-TB's first regional office was set up and opened in Phnom Penh, Cambodia to conduct the TB health systems research. The project is anticipated to run for the next five years.

Photo below:
TB management unit in a provincial government hospital in Phnom Penh, Cambodia.

SPRINT-TB LABORATORY

The SPRINT-TB Laboratory is at the core of SPRINT-TB research, including most of Theme 1 and Theme 2 drug discovery and preclinical development projects, as well as the array of clinical and public health studies conducted under Theme 3 and Theme 4.

Photo below:
Cross-theme TB Research Laboratory: Mr. Dereje Abate Negatu, Ms. Issac Simi, Mr. Wassihun Wedajo Aragaw, Dr. Rupangi Verma, Ms. Annanya Shetty, Ms. Michelle Yee Mei Keng, Dr. Martin Gengenbacher (Head of Laboratory and Deputy Director of BSL-3 Core Facility), Dr. Yoshiyuki Yamada, Mr. Chen-Yu Tsai, Mr. Joe Liu Jiajun.

Photo above:
SPRINT-TB BSL-2 facilities at the Center for Translational Medicine, National University of Singapore.

Singapore's largest research Biosafety Level-3 (BSL-3) Core Facility at National University of Singapore is licensed for the usage of various mycobacterial strains and animal models and is extensively used for SPRINT-TB research projects. SPRINT-TB currently boasts twelve fully-trained staff and students authorized to work in the BSL-3 facilities.

Photo on the right:
SPRINT-TB research in the BSL-3 Core Facility, National University of Singapore.

SPRINT-TB CLINICAL RESEARCH NETWORK

SINGAPORE NETWORK

SPRINT-TB has developed a Singapore-wide clinical research network for the conduct of the programme's clinical trials and studies. Using National University Hospital (NUH) as its home base, SPRINT-TB collaborates with major hospitals in Singapore in its TB clinical trials.

BILATERAL COLLABORATIONS IN ASIA

SPUTUM TRANSCRIPTOMICS STUDY
Fakulti Medicine Universitas Indonesia

In collaboration with Dr. Erlina Burhan and Dr. Anis Karuniawati, this Theme 3 study aims to describe changes in the bacterial gene expression following TB treatment initiation. It will present opportunities for the development of biomarkers and enhanced diagnostic methods for TB.

EPIDEMIOLOGICAL ANALYSIS
National TB Program, Myanmar

The bilateral collaborative study conducted by Theme 4 identifies risk factors of the development of MDR-TB cases in Myanmar.

TB HEALTH SYSTEMS RESEARCH
National TB Program, Cambodia

The study will generate evidence that will inform policy makers about optimal allocation of limited resources in order to achieve long-term reduction in TB incidence.

ASIAN TB RESEARCH AND CLINICAL TRIALS INTEGRATED ORGANISATIONAL NETWORK (A-TRACTION)

Delegates from ten countries gathered for the 3rd ASEAN Medical Deans' Summit, held in September 2014 at National University of Singapore. The A-TRACTION project, presented by SPRINT-TB Director Professor Nicholas Paton to the summit, was identified as a top-tier priority for ASEAN medical research collaboration. Receiving follow-up interest from the ASEAN member countries, SPRINT-TB is looking forward for productive collaboration in building and expanding the A-TRACTION network.

Multiple SPRINT-TB clinical studies and trials, such as pascolizumab trial (p. 26), TRUNCATE-TB trial (p. 25), mTB genomic database (p. 31) and others have warranted regional multi-centre collaborations in order to efficiently and timely recruit TB patients eligible for the studies. With the facilitation of SPRINT-TB, the clinical sites in Singapore and overseas will coalesce into the Asian TB Research and Clinical Trials Integrated Organisational Network (A-TRACTION), which will provide a platform for standardizing laboratory and data management, as well as conducting high quality multicenter collaborative TB studies and facilitating intra-Asian capacity building.

MORE ABOUT SPRINT-TB

SCIENTIFIC ADVISORY BOARD

SPRINT-TB is overseen by the Scientific Advisory Board, which meets annually to review the progress of the programme, make phase transition decisions, and prioritize activities for allocation of funding.

PROFESSOR DAVID SHERMAN

Center for Infectious Diseases Research USA

Prof. Sherman is the Tuberculosis BL-3 Director and full Professor at the Center for Infectious Disease Research, USA. He is an established expert in the TB molecular research field, with interests including virulence and latency of *M. tuberculosis* and TB drug discovery.

PROFESSOR BRIAN ANGUS

University of Oxford UK

Prof. Angus is the Director of the Oxford Centre for Clinical Tropical Medicine, UK. He has conducted pharmacokinetics studies in severe malaria and melioidosis in tropical countries, and his current research focus is on clinical trials in tropical infectious diseases.

PROFESSOR SABINE EHRT

Weill Cornell Medical College USA

Prof. Ehrt is a renowned authority in the molecular basis of *M. tuberculosis* resistance to host defence mechanisms and metabolic adaptation in the host. Her research focuses on elucidation of mycobacterial genes required for growth and persistence at various stages of infection.

COLLABORATORS

ACADEMIC AND CLINICAL

Experimental Therapeutics Centre, A*STAR
Singapore

Singapore Eye Research Institute
Singapore

Singapore Bioimaging Consortium, A*STAR
Singapore

Institute of Molecular and Cell Biology, A*STAR
Singapore

Nanyang Technological University
Singapore

Singapore Clinical Research Institute
Singapore

Investigational Medicine Unit,
National University Hospital
Singapore

BSL-3 Core Facility,
National University of Singapore
Singapore

Clinical Imaging Research Centre, A*STAR-NUS
Singapore

Singapore-MIT Alliance in Research and Technology
Singapore

Genome Institute of Singapore, A*STAR
Singapore

University College London
UK

London School of Hygiene and Tropical Medicine
UK

Max Planck Institute for Infection Biology
Germany

New Jersey Medical School-Rutgers University
USA

Harvard T. H. Chan School of Public Health
USA

University of Minnesota
USA

INDUSTRY

GlaxoSmithKline
UK

Janssen Pharmaceutica
Singapore

JSC Pharmasynthez
Russia

Otsuka Pharmaceuticals
Switzerland

Refer to p. 34 for the list of collaborating hospitals and clinical institutions in Singapore and the region.

NON-GOVERNMENTAL ORGANISATIONS

International Union Against Tuberculosis and Lung Disease, Asia-Pacific
Singapore

TALENT DEVELOPMENT

STUDENTS & RESEARCH FELLOWS

Since SPRINT-TB's inception in July 2014, the programme has become a training and career development ground for a large number of postgraduates, undergraduate students and research fellows. At present, seven PhD students and six honours students work towards their degrees under SPRINT-TB. The programme employs over ten postdocs, including three clinical research fellows.

RESEARCH MEETINGS

Every three months SPRINT-TB principal investigators, research staff, students and collaborators assemble for a discussion and networking meeting. Theme leads give overviews of their respective themes, and project leads update on the progress of their projects.

Once a year the team gathers for a day-long SPRINT-TB Annual Retreat, which enables more in-depth discussion of research projects and team interactions.

BSL-3 TRAINING

The BSL-3 laboratory provides a foundation for multiple projects of SPRINT-TB, and its staff and students receive comprehensive biosafety level-3 training and certification at National University of Singapore's BSL-3 Core Facility. SPRINT-TB currently has twelve BSL-3-certified users.

GOOD CLINICAL PRACTICE TRAINING

Everyone in SPRINT-TB's clinical research team undergoes training and certification for the Singapore Guideline for Good Clinical Practice (SGGCP).

JOURNAL CLUB

SPRINT-TB students, research fellows and staff gather bi-weekly to present and discuss selected new publications in the TB field. The club has over thirty regular attendees and is chaired by Dr. Wilfried Moreira (research fellow representative) and Ms. Annanya Shetty (student representative).

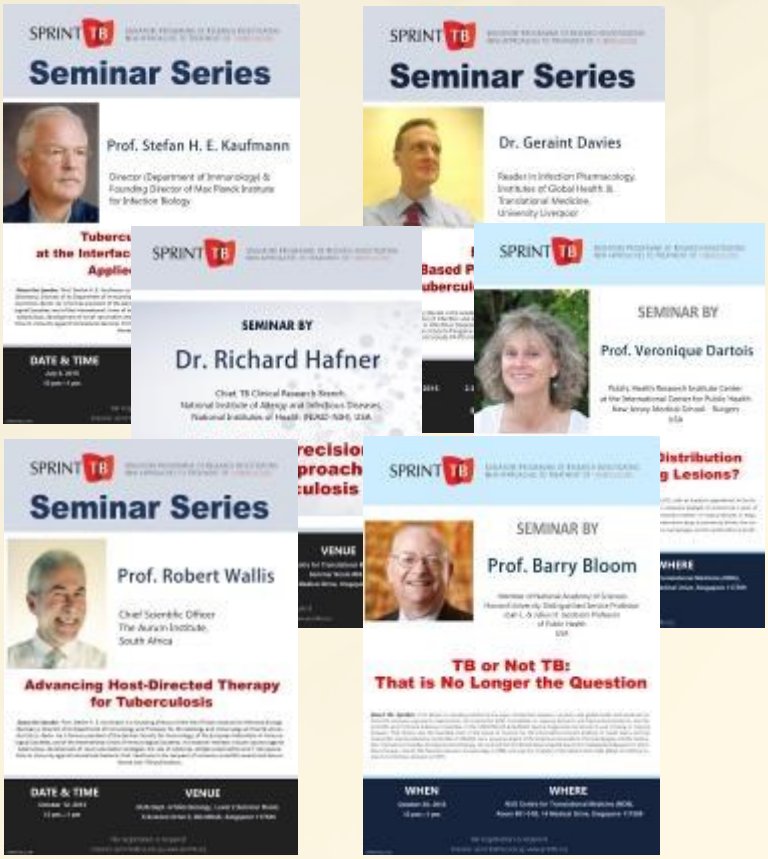
The translational multidisciplinary research team of SPRINT-TB discusses advancements in the TB field ranging from fundamental mycobacterial biology research, target and drug discovery to clinical trials and public health.

EVENTS

SEMINARS

SPRINT-TB regularly hosts scientific seminars, which feature talks from world-renowned researchers in the field of TB. Since the launch of the seminar series, speakers included Prof. Stefan H. E. Kaufmann (Max Planck Institute for Infection Biology, Germany), Dr. Geraint Davies (University of Liverpool, UK), Dr. Richard Hafner (National Institutes of Health, USA), Prof. Veronique Dartois (Rutgers University, USA), Prof. Robert Wallis (The Aurum Institute, South Africa) and Prof. Barry R. Bloom (Harvard University, USA).

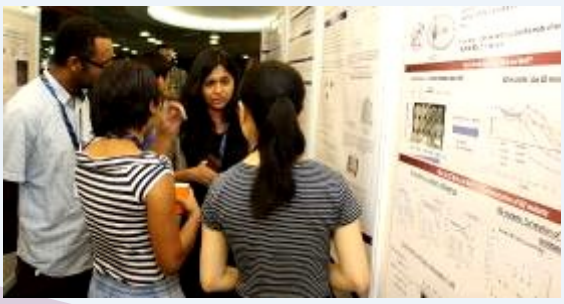
The talks are open to public and the information about current and upcoming seminars is available at *www.sprinttb.org/events.*



ANNUAL SYMPOSIUM

SPRINT-TB Inaugural Annual Symposium: Advances in Tuberculosis Therapy Research was held at National University of Singapore on September 18, 2015. SPRINT-TB will host these events annually, each year featuring renowned scientists, clinicians and key opinion leaders in TB.

This year's symposium programme included presentations on mycobacterial targets, new TB drug candidates, clinical trials of novel TB treatment regimens and public health. The symposium welcomed over one hundred attendees and renowned speakers such as Prof. Eric Rubin (Harvard T. H. Chan School of Public Health, USA). Dr. I. D. Rusen (International Union Against Tuberculosis and Lung Disease), and Dr. Davide Manissero (Qiagen, UK). The event was concluded with a panel discussion about collaborative research overseas. The panel comprised of international and local experts, including Dr. Jeffery Cutter from the Ministry of Health, Singapore.



RESEARCH OUTPUT

PUBLICATIONS AND SCIENTIFIC ABSTRACTS

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Thomas Dick. Target-based whole cell screen: a TB example. Drug Screening & Discovery Technologies Asian Forum 2015, Shanghai, China, 21-22 January 2015.

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Mei Lin Go. Functionalized indoles as potential anti-tuberculosis agents. Ist GIN-RSC Symposium on Organic and Bioorganic Chemistry, Singapore, 13 April 2015.

Nicholas Paton. New Approaches to Evaluating TB Drugs. First Beijing International Tuberculosis Summit, Beijing, China, 21 May 2015.

Nicholas Paton. New Approaches to Evaluating TB Drugs. The 12th NUS-Nagasaki Joint Symposium: Innovations and Insights in Infection and Immunity, Singapore, 11-12 June 2015.

Nicholas Paton. The TRUNCATE-TB trial: trial design from a clinician perspective. NIH workshop on Developing Novel Strategies to optimize Design of TB Drug Combinations, Rockville, MD, USA, 17 June 2015.

Wilfried Moreira. A Target mechanism-based whole cell screen identifies Bortezomib as an inhibitor of caseinolytic protease in mycobacteria. Gordon Research Seminar: Tuberculosis Drug Discovery & Development, Girona, Spain, 11-12 July 2015.

Kristina Rutkute. Fighting Tuberculosis through Research: SPRINT-TB. Singapore Bioimaging Consortium All Laboratories Meeting, Singapore, 30 July 2015.

Wilfried Moreira. A target mechanism-based whole cell screen identifies Bortezomib as an inhibitor of caseinolytic protease in mycobacteria. Singapore Bioimaging Consortium All Laboratories Meeting, Singapore, 30 July 2015.

Kristina Rutkute. A-TRACTION (Asian Tuberculosis Research and Clinical Trials Integrated Organisational Network). APEC 2015 Third Senior Officials' Meeting and Related Meetings – Health Working Group Session, Cebu, Philippines, 28 August 2015.

Nicholas Paton. The Singapore Programme of Research Into Novel Treatment for TB: SPRINT-TB. Lee Kong Chian School of Medicine Respiratory Pathogens Symposium, Singapore, 1 September 2015.

Gail Cross. Evaluating Whole blood Bactericidal Activity of Bortezomib against *Mycobacterium tuberculosis* in healthy volunteers. NUHS Clinician Scientist Unit 'Pitch for Funds' Round, Singapore, 23 September 2015.

Mei Lin Go. Functionalized indoles as anti-tuberculosis agents. 41st Congress on Science and Technology of Thailand: Gateway to ASEAN with Science and Technology, Nakhonratchasima, Thailand, 6-8 November 2015.

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Thomas Dick. Target Mechanism-Based Whole-Cell Screening Identifies Bortezomib as an Inhibitor of Caseinolytic Protease in *Mycobacterium tuberculosis*. Rutgers University, Newark, NJ, USA, 24 November 2015.

PATENTS

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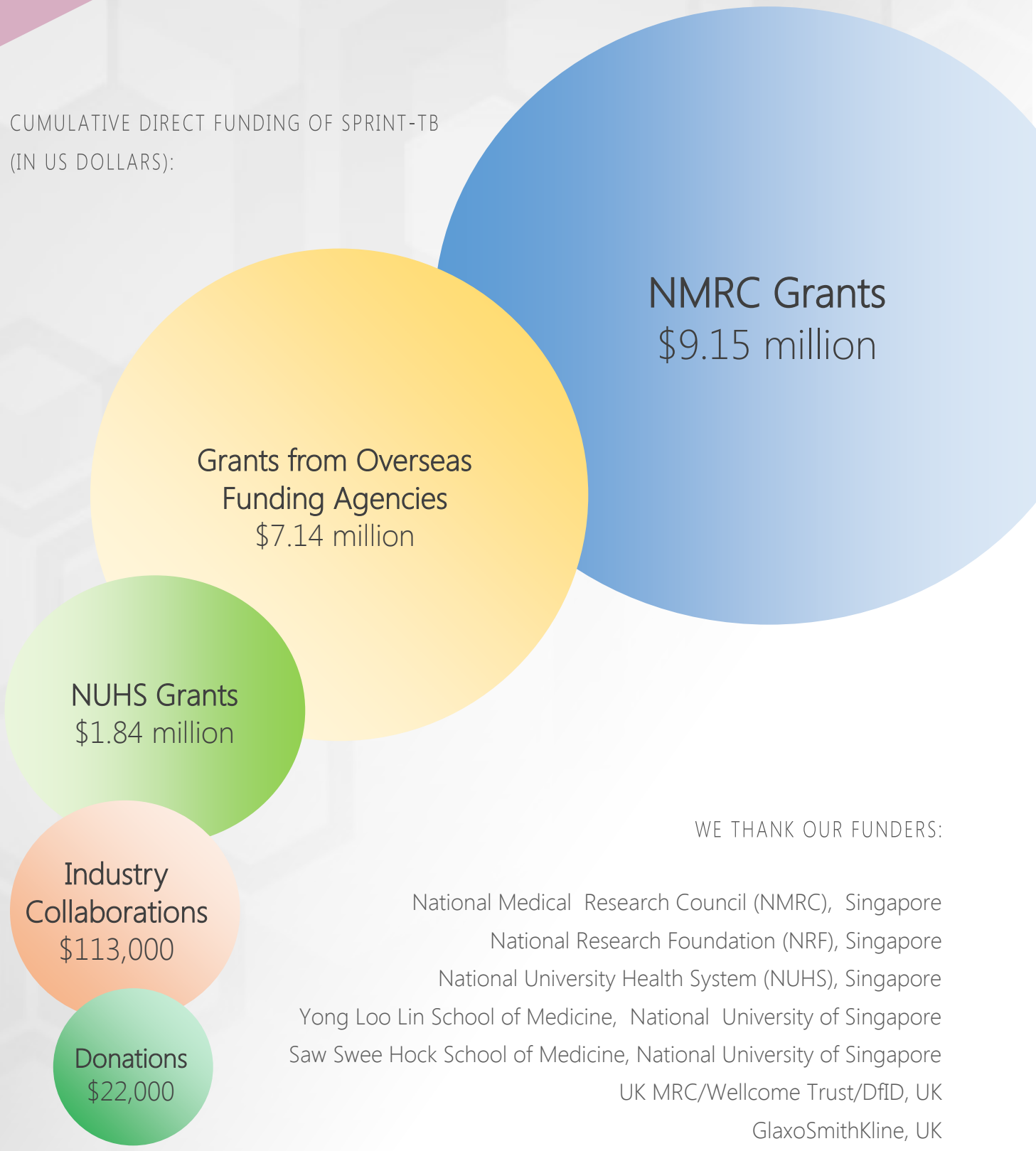
Functionalized Indoles As Potential Anti-Tuberculosis Agents. Inventors: Huan Chen, Wilfried Moreira, Mei Lin Go, Thomas Dick, Tianming Yang. US Provisional Patent Application No.: 62/146,553; Filing Date: April 13, 2015.

FUNDING

CUMULATIVE DIRECT FUNDING OF SPRINT-TB (IN US DOLLARS):



WE THANK OUR FUNDERS:

National Medical Research Council (NMRC), Singapore
National Research Foundation (NRF), Singapore
National University Health System (NUHS), Singapore
Yong Loo Lin School of Medicine, National University of Singapore
Saw Swee Hock School of Medicine, National University of Singapore
UK MRC/Wellcome Trust/DfID, UK
GlaxoSmithKline, UK
Lee Foundation, Singapore

TOP TUBERCULOSIS DRUG DEVELOPMENT RESEARCH FUNDERS IN 2014

Funder	US Dollars (millions)
Otsuka Pharmaceuticals	$53.2
NIAID	$42.7
Bill and Melinda Gates Foundation	$41.7
DFID	$17.1
Company V	$15.4
USAID	$11.9
Company X	$10.0
⇨ Singapore NMRC	$7.2
NIH Other ICs	$5.2
US CDC	$4.5
UNITAID	$3.4
Wellcome Trust	$3.4
European Commission	$3.2
UK MRC	$3.1
Eli Lilly	$2.6

***Source**: Treatment Action Group 2015 Report on Tuberculosis Research Funding Trends*

The funding awarded to SPRINT-TB places it among the best resourced TB drug development research programmes worldwide. This is in keeping with the status of SPRINT-TB as one the leading TB research programmes in the world.

In addition to direct funding, SPRINT-TB is supported by substantial in-kind funding from the host institution, pharmaceutical companies and philanthropic funds. The combined SPRINT-TB spending on TB research in 2015 was estimated at US $4.26 million - an increase of 25% from the previous year, indicating strong growth of the programme.

GIVING

WHY WE FUNDRAISE

The award of substantial public sector research funding (p. 44) and the status of SPRINT-TB as a flagship programme supported by Singapore's National Medical Research Council are a testament to the scientific quality and clinical impact of the work we do. However, the process of securing public sector funding requires substantial time - usually at least 18 months for rigorous international and local review before funding is awarded and available for use.

As shown in this report, SPRINT-TB is at the cutting edge in many areas of TB research, brimming with innovation and ideas. Currently the only limit on the growth of the programme is the funding available to develop these new ideas into initial studies. Some of these may be completed in a short time and others may grow into larger studies that can be put forward for later public sector funding. We rely on donations and other discretionary funding to kick-start these new projects, thereby maximising the contribution that Singapore and SPRINT-TB can make to the to global fight against tuberculosis.

HOW WE USE DONATIONS

Below are some illustrations of how your donated funds may be used in SPRINT-TB research:

- Laboratory materials and equipment for new projects
- Synthesis of compounds and drug candidate molecules
- Support of patient costs in clinical studies
- Volunteer transport and reimbursement for participation in clinical trials
- Coordination of international collaborative projects
- Conduct of clinical trials in regional hospitals

HOW YOU CAN HELP

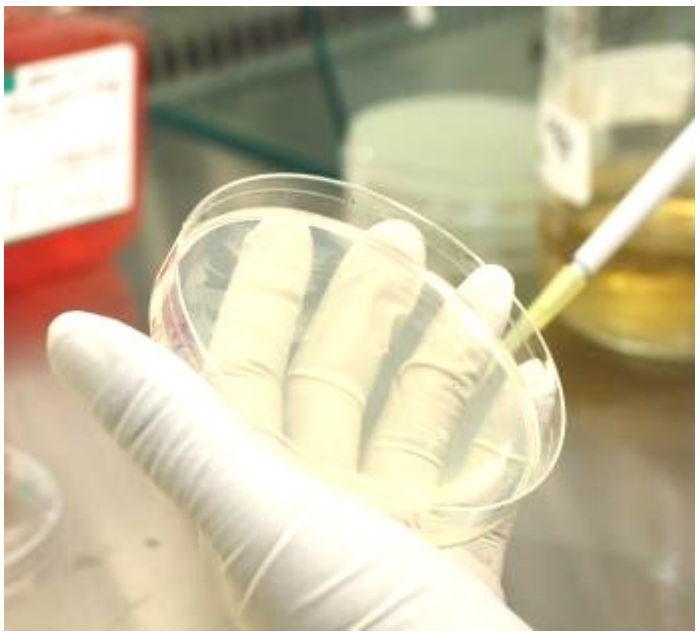
With gratitude, we welcome each and every donation, which will be held by National University of Singapore and used exclusively for SPRINT-TB research activities.

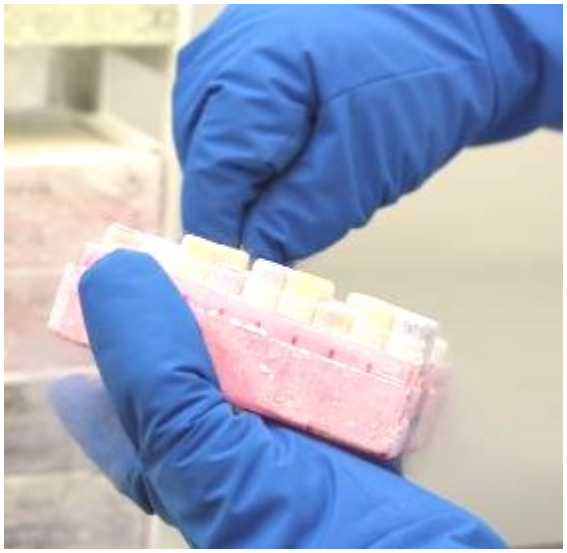
Some ground-breaking ambitious projects may require large sums for execution, while a number of smaller innovative projects can be conducted on a more modest budget. No donation is too big or too small and will be essential in supporting TB research.

We welcome enquiries or proposals at any time. Here is an easy way to contact us:

Dr. Kristina Rutkute
SPRINT-TB Programme Manager
kristina_rutkute@nuhs.edu.sg
+65 6601 5371

Thank you for your support of the fight against TB!





CONTACT

SPRINT-TB

National University of Singapore
Center for Translational Medicine
MD6, Level 15
14 Medical Drive
sprint-tb@nus.edu.sg

PROGRAMME DIRECTOR

Prof. Nicholas Paton
nick_paton@nuhs.edu.sg
+65 6772 6988

PROGRAMME MANAGER

Dr. Kristina Rutkute
kristina_rutkute@nuhs.edu.sg
+65 6601 5371

THEME 1 LEAD

A/Prof. Thomas Dick
Department of Microbiology and Immunology
Yong Loo Lin School of Medicine
National University of Singapore
MD4, Level 5
5 Science Drive 2
Singapore 117545
thomas_dick@nuhs.edu.sg

THEME 2 LEAD

Prof. Alex Matter
Experimental Therapeutics Centre
Agency for Science, Technology and Research (A*STAR)
Nanos, Level 3
31 Biopolis Way
Singapore 138669
amatter@etc.a-star.edu.sg

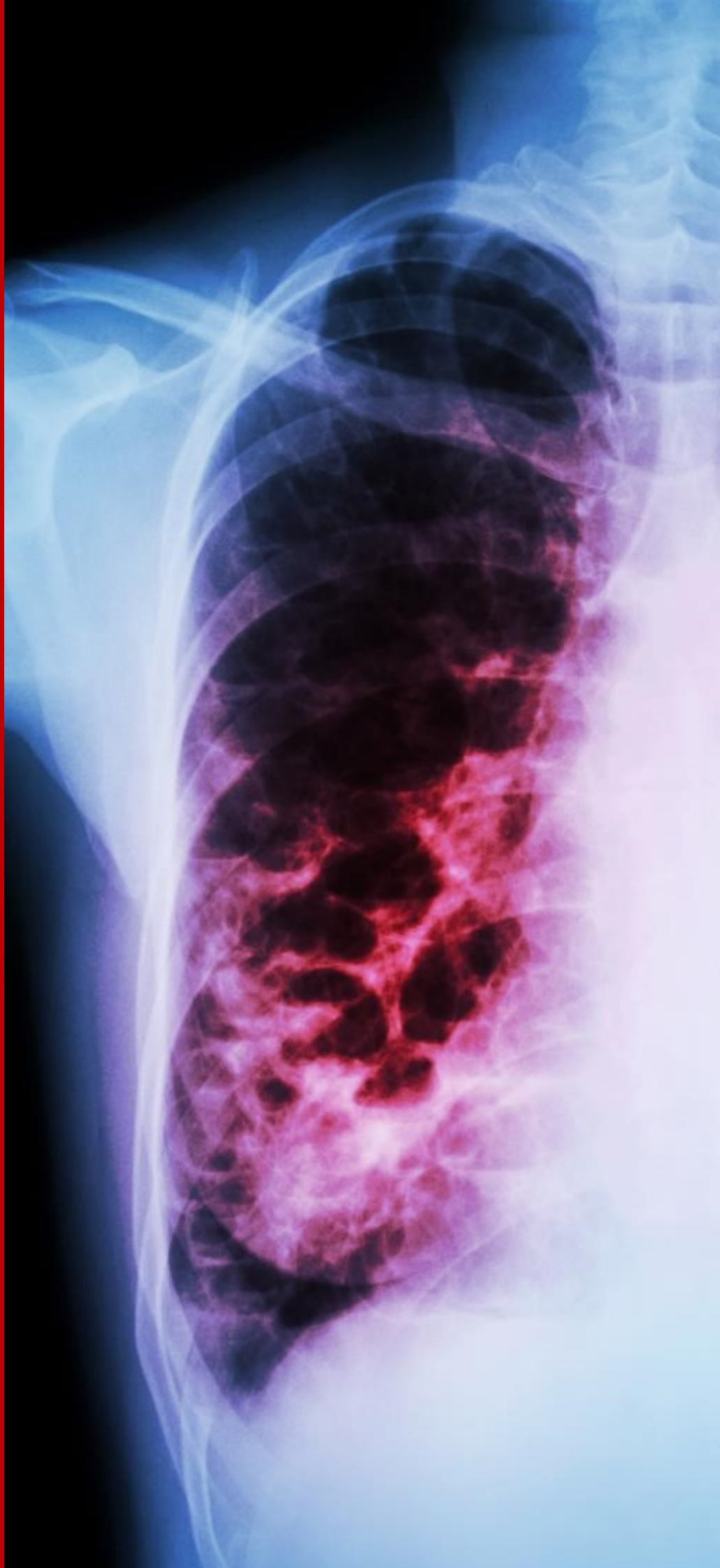
THEME 3 LEAD

Prof. Nicholas Paton
Department of Medicine
Yong Loo Lin School of Medicine
National University of Singapore
NUHS Tower Block, Level 10
1E Kent Ridge Road
Singapore 119228
nick_paton@nuhs.edu.sg

THEME 4 LEAD

Prof. Richard Coker
Saw Swee Hock School of Public Health
National University of Singapore
Tahir Foundation Building
12 Science Drive 2
Level 10
Singapore 117549
richard_james_coker@nuhs.edu.sg

www.sprinttb.org



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National University of Singapore
Center for Translational Medicine
MD6, Level 15
14 Medical Drive
Singapore 117599

www.sprinttb.org