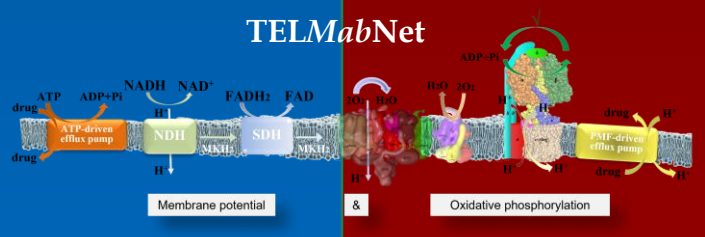
3rd Annual Symposium:
Innovations in anti-mycobacterial Drug Discovery

27th - 28th May 2024

Venue: School of Biological Sciences, Nanyang Technological University, Singapore

TEL*Mab*Net



Register under:

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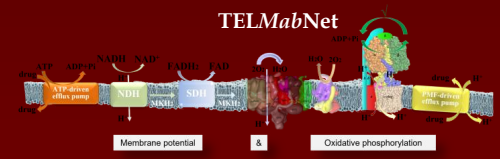
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Mycobacteria can be separated into tuberculosis (TB) causing mycobacteria (*Mycobacterium tuberculosis*, *Mtb*), leprotic mycobacteria, and non-tuberculous mycobacteria (NTM). Approximately one quarter of the World's population is infected with *Mtb* in latent form. TB is of enhanced concern when combined with other diseases, such as HIV and Covid-19. Similar concerns hold true for NTM infections, which are increasing in their prevalence, morbidity and mortality and frequently surpass the global incidence of TB. NTM most commonly cause pulmonary infections, especially among patients with structural airway disease like cystic fibrosis and bronchiectasis, but can also cause lymphadenitis, skin and soft tissue infection, cardiac infection, bone and joint infections, and disseminated disease. Chemotherapy is long and often toxic, includes parenteral drugs, and suffers from poor cure rates.

Mtb and NTM can be considered multidrug resistant superbugs. Therefore, there is an urgent need for more efficacious, well tolerated, and oral antibiotics optimized towards the treatment of NTM diseases and TB.

The *3rd Annual Symposium: Innovations in anti-mycobacterial Drug Discovery* will include presentations from speakers from around the world who have made significant advances in TB- and NTM research and –drug discovery. The goal of this event is to present novel concepts and to provide a platform for vibrant and open discussions between industry, senior scientists, postdoctoral fellows and students from academia.

The symposium is organized by members of TEL*Mab*Net (*Targeting energy of life for the development of drug combinations to eradicate antibiotic-tolerant Mycobacterium abscessus, a clinical nightmare, Network*), an excellence cluster funded by the Singapore National Research Foundation.



Organizers

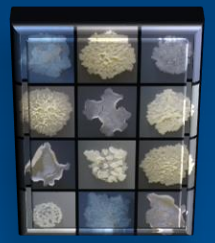


Gerhard Grüber
Lead-PI of TEL*Mab*Net
Nanyang Technological University, Singapore



Thomas Dick
Center for Discovery and Innovation, Hackensack Meridian Health, USA

Speakers





Courtney Aldrich
University of Minnesota, Minneapolis, USA
Editor-in-Chief of *ACS Infectious Diseases*

Title: *Development of a pre-clinical TB candidate targeting biotin biosynthesis that kills through the insidious accumulation of toxic metabolites*



Yossef Av-Gay
University of British Columbia, Life Sciences Institute, Vancouver, Canada

Title: *Chemical and genetic discovery of host directed targets against Mycobacterium tuberculosis*



Daniel Barkan
The Hebrew University of Jerusalem, Israel

Title: *A soluble, ribosome-associated ABC-F ATPase mediates macrolide sensitivity in multiple mycobacteria*



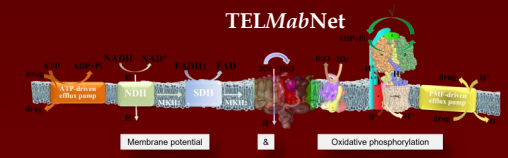
Lucas Boeck
University of Basel, Department of Biomedicine, Switzerland

Title: *Linking mycobacterial behaviours, antibiotic action and clinical outcomes*



Thomas Dick
Center for Discovery and Innovation, Hackensack Meridian Health, Nutley, USA

Title: *Redesign of rifamycin for the treatment of Mycobacterium abscessus lung disease*





Laurent Kremer
Université de Montpellier, Montpellier, France

Title: *New therapeutic strategies for Mycobacterium abscessus infections - Untapping the mycolic acid pathway*



Barbara Laughon
National Institute of Allergy and Infectious Diseases, NIH, USA
Co-Chair of the *Working Group for new drugs* (WGND)

Title: *The landscape of TB and NTM drug development*



Albert Y. H. Lim
Department for Respiratory and Critical Care Medicine, Tan Tock Seng Hospital, Singapore

Title: ***NTM pulmonary disease phenotypes***



Vladimir Marshansky
President & CEO (Founder) of *Neuro-Horizon Pharma Inc* (NHP), USA

Title: *Neuro-Horizon Pharma Inc. - Cellular Rotary Nano-Motors Company: From Scientific Discovery to Pharmaceutical Drug Targeting and Development*



Vikneswaran Mathiyazakan
School of Biological Science, Nanyang Technological University, Singapore

Title: *Atomic structure of the mycobacterial cytochrome oxidase supercomplex paves the way for the development of next-generation therapeutics*

Speakers





Florian Maurer
Institute of Medical Microbiology, Virology and Hygiene, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Title: *Closing the gap: Towards a better alignment of antimycobacterial drug development and susceptibility testing in the Clinical Microbiology laboratory*



Nicholas Paton
National University of Singapore, Singapore

Title: *TB treatment duration: how short can we go?*



Kevin Pethe
Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore

Title: *Combinatorial drug strategies for mycobacterial diseases*



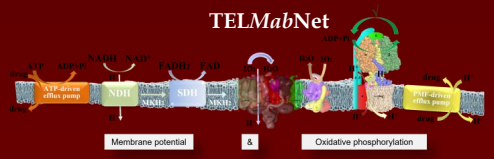
Priya Ragunathan
School of Biological Science, Nanyang Technological University, Singapore

Title: *In vitro and in vivo potency of non-tuberculous mycobacterial F-ATP synthase inhibitors*



Peter Sander
Co-Director of the National Reference Center for Mycobacteria, Institute of Medical Microbiology, University of Zurich, Switzerland

Title: *Innate and acquired drug-resistance mechanisms of Mycobacterium abscessus and how to overcome them*





Ulrich Schaible
CEO of the Borstel Research Center, Leibniz Center for Medicine and Biosciences, Germany

Title: *New therapeutic approaches against mycobacterial infections*



Amit Singh
Centre for Infectious Disease Research, Indian Institute of Science, Bangalore-560012, India

Title: *Reprogramming mitochondrial bioenergetics to target drug tolerance in Mycobacterium tuberculosis*



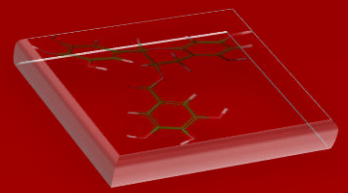
Amit Singhal
A*STAR Infectious Diseases Labs, Singapore

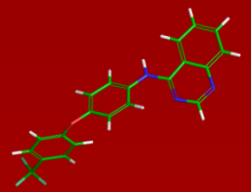
Title: *Host-directed therapies for TB*



Mhairi Skinner
Director & CSO of *Neuro-Horizon Pharma Inc* (NHP), USA

Title: *Neuro-Horizon Pharma Inc. - Cellular Rotary Nano-Motors Company: From Scientific Discovery to Pharmaceutical Drug Targeting and Development*





Program schedule

Monday 27th May

8:30 – 9:15 **Registration**

Session I: Chair Gerhard Grüber, SBS, NTU

9:15 – 9:30 **Opening and Welcome**
Kanaga Sabapathy, Chair of the School of Biological Sciences (SBS) and
Simon Redfern, Dean of the College of Science, NTU, Singapore

9:30 – 10:00 ***The landscape of TB and NTM drug development***
Barbara Laughon, National Institute of Allergy and Infectious Diseases, NIH, USA

10:00 – 10:30 ***TB treatment duration: how short can we go?***
Nicholas Paton, National University of Singapore, Singapore

10:30 – 10:50 **Coffee / Tea break**

Session II: Chair Pablo Bifani, Lee Kong Chian School of Medicine, NTU

10:50 – 11:20 ***Chemical and genetic discovery of host directed targets against Mycobacterium tuberculosis***
Yossef Av-Gay, University of British Columbia, Life Sciences Institute, Vancouver, Canada

11:20 – 11:50 ***Reprogramming mitochondrial bioenergetics to target drug tolerance in Mycobacterium tuberculosis***
Amit Singh, Centre for Infectious Disease Research, Indian Institute of Science, Bangalore, India

11:50 – 12:20 ***Host-directed therapies for TB***
Amit Singhal, A*STAR Infectious Diseases Labs, Singapore

12:20 – 13:20 **Lunch break and poster session**

Session III: Chair Thomas Dick, Center for Discovery and Innovation, Hackensack Meridian Health, USA

13:20 – 13:50 ***Development of a pre-clinical TB candidate targeting biotin biosynthesis that kills through the insidious accumulation of toxic metabolites***
Courtney Aldrich, University of Minnesota, Minneapolis, USA

13:50 – 14:20 ***A soluble, ribosome-associated ABC-F ATPase mediates macrolide sensitivity in multiple mycobacteria***
Daniel Barkan, The Hebrew University of Jerusalem, Israel

14:20 – 14:50 **Coffee / Tea break**

14:20 – 15:10 ***New therapeutic approaches against mycobacterial infections***
Ulrich Schaible, Borstel Research Center, Leibniz Center for Medicine and Biosciences, Germany

15:10 – 15:40 ***Closing the gap: Towards a better alignment of antimycobacterial drug development and susceptibility testing in the Clinical Microbiology laboratory***
Florian Maurer, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

15:40 – 17:00 **Poster session with refreshments**

Program schedule

Tuesday 28th May

Session I: Chair Weidong Hao, Experimental Drug Development Centre, Singapore

9:15 – 9:45 ***NTM pulmonary disease phenotypes***
Albert Y. H. Lim, Department for Respiratory and Critical Care Medicine,
Tan Tock Seng Hospital, Singapore

9:45 – 10:15 ***Innate and acquired drug-resistance mechanisms of Mycobacterium abscessus and how to overcome them***
Peter Sander, **Institute of Medical Microbiology, University of Zurich, Switzerland**

10:15 – 10:40 **Coffee / Tea break**

Session II: Chair Stefan Oehlers, A*STAR, Infectious Diseases Labs, Singapore

10:40 – 11:10 ***Linking mycobacterial behaviours, antibiotic action and clinical outcomes***
Lucas Boeck, University of Basel, Department of Biomedicine, Switzerland

11:10 – 11:40 ***New therapeutic strategies for Mycobacterium abscessus infections – Untapping the mycolic acid pathway***
Laurent Kremer, Université de Montpellier, Montpellier, France

11:40 – 12:10 ***Redesign of rifamycin for the treatment of Mycobacterium abscessus lung disease***
Thomas Dick, Center for Discovery and Innovation, Hackensack Meridian Health, Nutley, USA

12:10 – 13:25 **Lunch break and poster session**

Session I: Chair Gerhard Grüber, SBS, NTU

13:25 – 13:50 ***Atomic structure of the mycobacterial cytochrome oxidase supercomplex paves the way for the development of next-generation therapeutics***
Vikneswaran Mathiyazakan, School of Biological Sciences, NTU, Singapore

13:45 – 14:15 ***Combinatorial drug strategies for mycobacterial diseases***
Kevin Pethe, Lee Kong Chian School of Medicine, NTU, Singapore

14:15 – 14:40 ***In vitro and in vivo potency of non-tuberculous mycobacterial F-ATP synthase inhibitors***
Priya Ragunathan, School of Biological Sciences, NTU, Singapore

14:40 – 15:00 ***Neuro-Horizon Pharma Inc. - Cellular Rotary Nano-Motors Company: From Scientific Discovery to Pharmaceutical Drug Targeting and Development***
Vladimir Marshansky and Mhairi Skinner, *Neuro-Horizon Pharma Inc* (NHP), USA

15:00 – 15:10 **Closing remarks**

Abstracts (Monday 27th)



The landscape of TB and NTM drug development

Barbara Laughon. National Institute of Allergy and Infectious Diseases, NIH, USA

The pipelines of new anti-tuberculosis (TB) and anti-nontuberculous mycobacteria (NTM) drugs are increasing with new molecular entities discovered by academic and private sector scientists. This presentation will review the current situation and describe recent advances in the field. Important for the introduction of new TB drugs is attention to the safety and effectiveness of novel combinations in newer regimens, and efforts by several international consortia are beginning to address these issues. The situation for the non-tuberculous mycobacteria is also evolving, particularly for *Mycobacterium abscessus* and *M. avium* complex. Newer drug candidates are entering the clinical development pipeline, and additional drug discovery research is underway particularly addressing the antibiotic needs of cystic fibrosis patients. These factors will be summarized in this landscape presentation.



TB treatment duration: how short can we go

Nicholas Paton, National University of Singapore, Singapore

Traditionally, drug-susceptible TB has been treated with a 6-month treatment duration for all. However, it is clear now that most people can be successfully cured with far shorter treatment courses using new drug combinations and a strategic treatment approach. I will present recent data and the approaches taken by ongoing clinical trials and biomarker studies that indicate that we have the potential to transform the current TB treatment paradigm.



Chemical and genetic discovery of host directed targets against Mycobacterium tuberculosis

Yossef Av-Gay, University of British Columbia, Life Sciences Institute, Vancouver, Canada

Chemical and genetic discovery of host directed targets against *Mycobacterium tuberculosis* Tuberculosis (TB) remains a major public health threat with over 1.5 million annual deaths worldwide. TB drugs are highly toxic and display poor efficacy against multi drug resistant (MDR) *M. tuberculosis* (*Mtb*). To overcome these challenges, instead of targeting resistance prone microbial components, host directed therapy (HDT) is envisioned to activate conserved host factors and pathways that enhance the innate ability of the human host to fight infections. Screening of target defined based libraries identified compounds designed against host kinases and receptors with activity against intracellular *Mtb*. Some at low micromolar inhibition of Mtb growth inside human macrophages without toxicity to the host cell or activity against *Mtb* grown in Broth. Genetic validation of two targets associated with active compounds, a protein kinase and a histamine receptor, were carried out using SiRNA and CRISPR knock out experiments, showing that the two corresponding genes have a role in controlling the replication of *Mtb* in human macrophages.

Abstracts (Monday 27th)



Reprogramming mitochondrial bioenergetics to target drug tolerance in Mycobacterium tuberculosis

Amit Singh, Centre for Infectious Disease Research, Indian Institute of Science, Bangalore-560012, India

Mycobacterium tuberculosis (*Mtb*) persists inside the phagocytic cells despite immune pressures and stresses caused by multiple anti-TB drugs. How *Mtb* tolerates immune and drug pressures and survives is a fundamental question in the TB field? We have developed a novel biosensor to image the redox physiology of *Mtb* inside the human host during infection and upon chemotherapy. Using this probe, we identified the role of phagosomal acidity and mitochondrial metabolism in promoting the emergence of a redox-altered subpopulation of *Mtb* that tolerates anti-TB drugs. Importantly, we provide empirical evidence linking intramycobacterial redox balance, mitochondrial bioenergetics, and Hippo signaling pathway in the emergence of drug tolerance during infection. Based on these innovative findings, we developed strategies to reset immuno-metabolism to improve the efficacy of anti-TB drugs during infection.



Host-directed therapies for TB

Amit Singhal, A*STAR Infectious Diseases Labs, Singapore

Inadequacies of traditional pathogen-directed therapies and emergence of drug-resistance are the major barriers to global TB elimination. Disappointing results from the REMOxTB and RIFAQUIN treatment shortening trials highlight the need for novel interventions to cure TB. This led to the emergence of a new paradigm in TB treatment *viz.* host directed therapies (HDTs), which focuses on the modulation of host factors subverted by the pathogens in order to improve disease pathogenesis and pathogen eradication. Such therapeutic approaches could potentially (i) augment the efficacy of conventional anti-microbials, (ii) shorten treatment regimens for drug-susceptible and/or drug-resistant *Mtb* infections, (iii) reduce the immunopathology associated with TB, and (iv) promote development of immunological memory that could protect against relapse and reinfection. In this talk I will provide the current update on the TB-HDTs been tested in clinics and will present our own data towards this direction.



Development of a pre-clinical TB candidate targeting biotin biosynthesis that kills through the insidious accumulation of toxic metabolites

Courtney Aldrich, University of Minnesota, Minneapolis, USA

Biotin biosynthesis is a promising target for antibacterial drug discovery as this absent in mammals, conditional silencing of the biotin pathway in vitro and vivo leads to sterilization. Despite the promising genetic validation and intriguing bactericidal phenotype of biotin auxotrophs, potent and selective inhibitors with suitable drug disposition and pharmacokinetic properties have not been described. The identification and optimization of inhibitors of the transaminase BioA and radical-SAM enzyme BioB will be described leading to exceptionally potent compounds that display potent synergy and possess low nanomolar minimum inhibitory concentrations against drug-resistant *Mycobacterium tuberculosis* strains. A multitude of approaches were employed to confirm on-target activity. Mechanism of action studies further revealed biotin inhibition causes alteration of membrane fluidity through remodeling of the cell wall that compromises vulnerable efflux pumps leading to toxic accumulation of key metabolites. Further compound optimization provided candidate compounds with outstanding pharmacokinetic properties.

Abstracts (Monday 27th)



A soluble, ribosome-associated ABC-F ATPase mediates macrolide sensitivity in multiple mycobacteria

Daniel Barkan, The Hebrew University of Jerusalem, Israel

Macrolides, and specifically Azithromycin and Clarithromycin are important part in the treatment of *M. abscessus*, but rarely used against *M. tuberculosis (Mtb*). In both bacteria, the existence of a potent ribosome methylase (Erm) diminished the potency of the drug. However, additional factors exist that may nevertheless potentiate the macrolides to a point of clinical efficacy. These include ribosome-binding ABC-F ATPases, protecting the ribosome from drug binding. We characterized one such soluble ABC-F ATPase by targeted deletions in *M. smegmatis*, *M. abscessus* and Mtb – despite previous erroneous notion the gene was essential. We found the deletion mutants to be substantially slow-growing and highly sensitive to macrolides. Moreover, recombinant strains with an ATPase-defective, mutant proteins were extremely susceptible to macrolides, up to X100 more than WT. Additional physiological roles of these proteins were explored. We believe the ribosome-binding ABC-F ATPases may be an interesting target for potentiating the activity of macrolides against various mycobacteria.



New therapeutic approaches against mycobacterial infections

Ulrich Schaible, *Research Center Borstel, Leibniz Lung Center, Cellular Microbiology, Germany*

Granuloma formation is a hallmark of tuberculosis (TB) pathogenesis to sequester and control the pathogenic agent, *Mycobacterium tuberculosis (Mtb)* but provide a source for TB reactivation later in live. Upon reactivation, granulomas exacerbate to become necrotic foci of uncontrolled *Mtb* growth, cellular necrosis associated with polymorphonuclear neutrophil (PMN) influx and limited access to antibiotics but a source for transmission. PMN, otherwise efficient anti-microbial defence cells, do not only fail to kill *Mtb* but promote Mtb growth in subsequent macrophage host cells. To interfere with both, the pathological process and *Mtb* growth, we use different approaches to improve TB therapy: I) Novel nanocarrier-mediated targeted antibiotic delivery systems targeting *Mtb* within active granulomas; II) host directed therapies targeting PMN to enable better killing of *Mtb* and limit pathology and long-term sequelae; III) assessing new anti-mycobacterial compounds in proper TB infection models.



Closing the gap: Towards a better alignment of antimycobacterial drug development and susceptibility testing in the Clinical Microbiology laboratory

Florian Maurer, Institute of Medical Microbiology, Virology and Hygiene, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Drug susceptibility testing is vital to limit the emergence of acquired resistance against antimicrobials. However, robust and approved assays are still unavailable for several key antimycobacterial drugs. In my talk, I will describe current shortcomings at the interface of antimycobacterial drug development and drug susceptibility testing. I will explain some key concepts from the diagnostic space and raise awareness for the legal and operational challenges that come with using laboratory-developed tests instead of standardized commercial assays. I will explain what data are needed to properly characterise a susceptibility testing assay and the underlying bacterial population as a basis for a clinical breakpoint setting. I will outline how a deeper integration of preclinical antimycobacterial drug development and development of corresponding diagnostic tests could look like in the future so that high-quality testing is widely available once a new drug enters the clinic.

Abstracts (Tuesday 28th)



NTM pulmonary disease phenotypes

Albert Y. H. Lim, Department for Respiratory and Critical Care Medicine, Tan Tock Seng Hospital, Singapore

Non-tuberculous mycobacterial pulmonary diseases (NTM-PD) are increasing worldwide. This phenomenon may be due to ageing population, increasing in awareness, increasing prevalence of diseases that are susceptible to it, such as bronchiectasis and COPD, and advancement in testing for NTM. NTM-PD phenotypes are varied according to the underlying respiratory diseases, the NTM species and the severity of NTM-PD. The understanding of the clinical phenotypes is crucial for clinical evaluation and treatment of NTM-PD. More research is urgently needed for phenotyping of NTM-PD and to provide useful data for evaluation of the effectiveness of NTM-PD therapies.



Chemical and genetic discovery of host directed targets against Mycobacterium tuberculosis

Peter Sander, Institute of Medical Microbiology, University of Zurich, Switzerland

Mycobacterium abscessus has the reputation as an antibiotic nightmare, due to its high level of innate drug resistance mechanisms, leaving limited treatment options which are only partially successful. Clinically acquired drug-resistance mechanisms towards frontline drugs from the class of macrolides (clarithromycin, azithromycin) and aminoglycosides (amikacin) have been elucidated decades ago. In contrast, innate drug-resistance mechanisms could only be deciphered recently following the development of tools for genetic manipulation of the bacteria. Our investigations contributed to the elucidation of resistance mechanisms for the class of rifamycins (rifampicin, rifabutin) by the ADP-ribosyltransferase Arr, aminoglycosides and peptide antibiotics (amikacin and capreomycin) by the acetyltransferase Eis2, streptomycin by the aminoglycoside phosphotransferase Str(3'') and spectinomycin by the transporter MAB_2780c, amongst others. Elucidation of these antibiotic resistance mechanisms at the molecular level pave the way for the rational development of novel compounds which overcome innate drug resistance mechanisms.



Linking mycobacterial behaviours, antibiotic action and clinical outcomes

Lucas Boeck, University of Basel, Department of Biomedicine, Switzerland

Drug development and antibiotic treatments are based on *in vitro* measures of bacterial growth inhibition. Much less is known about antibiotic killing and the consequences of prolonged bacterial survival, also known as drug tolerance. Our study introduces Antimicrobial Single-Cell Testing, a novel high-throughput imaging-based method to assess antibiotic killing. Applying this technology to *Mycobacterium abscessus*, an increasingly prevalent and frequently incurable pathogen, we analysed over 20,000 time-kill curves. Our findings reveal that antibiotic tolerance is different from resistance, but similarly crucial for treatment outcomes. We demonstrate that drug tolerance is conserved within antibiotic classes and driven by the bacterial genetic background. Through, genome-wide associations we identified mechanisms underlying bacterial survival and potential treatment failures. Our work establishes a large-scale framework to assess antibiotic killing, thereby offering targets for drug discovery and providing metrics for drug development and clinical decision making.

Abstracts (Tuesday 28th)



New therapeutic strategies for Mycobacterium abscessus infections - Untapping the mycolic acid pathway

Laurent Kremer, Université de Montpellier, Montpellier, France

Treatment options against *Mycobacterium abscessus* infections are very limited. New compounds are needed to cure *M. abscessus* pulmonary diseases. While the mycolic acid biosynthetic pathway has been largely exploited for the treatment of tuberculosis, this metabolic process has been overlooked in *M. abscessus*, although it offers many potential drug targets for the treatment of this opportunistic pathogen. Recent studies highlighted the importance of MmpL3 and the enoyl-ACP reductase InhA involved in the transport and synthesis of mycolic acids, respectively, as two major vulnerable drug targets in *M. abscessus*. Chemical inhibition of these two proteins strongly impacts on *M. abscessus* growth *in vitro,* in macrophages and in zebrafish. This validates the mycolic acid pathway as an attractive drug target to be further exploited for the treatment of *M. abscessus* lung diseases. Future work is required to improve the activity and pharmacological properties of these inhibitors and their evaluation in pre-clinical models.



Redesign of rifamycin for the treatment of Mycobacterium abscessus lung disease

Thomas Dick, Center for Discovery and Innovation, Hackensack Meridian Health, Nutley, USA

Rifamycins are a valuable class of antibiotics for treating infections by mycobacteria due to their potent bactericidal activity against replicating and non-replicating, drug tolerant pathogens. However, the clinical utility of rifamycins against *Mycobacterium abscessus* is compromised by a novel resistance mechanism, namely, rifamycin inactivation by ADP-ribosylation. Using a structure-based approach, we rationally redesign rifamycins through modification of the ansa-chain to block ADP-ribosylation while preserving on-target activity. Validated by biochemical, structural, and microbiological studies, the most potent analogs overcome ADP-ribosylation, restored their intrinsic low nanomolar activity, retained an excellent pharmacokinetic profile, and demonstrated efficacy in a mouse model of *M. abscessus* lung disease.



Atomic structure of the mycobacterial cytochrome oxidase supercomplex paves the way for the development of next-generation therapeutics

Vikneswaran Mathiyazakan, School of Biological Science, Nanyang Technological University, Singapore

The non-fermentative mycobacteria are depending on oxidative phosphorylation to sustain their energy requirements. Oxidation of electron carriers by the oxidative phosphorylation pathway drives the formation of an electrochemical gradient, leading to ATP and water. The later is catalyzed by the reduction of oxygen within the terminal cytochrome cyt-*bcc*:aa_3 oxidase. This catalyst performs multiple roles and remains active in hypoxic environments despite possessing lower affinity towards oxygen compared to cyt-*bd,* the substitute terminal oxidase. The cyt-*bcc*:aa_3 oxidase adopts a unique architecture by forming a supercomplex with cyt-*bcc* (analogous to Complex III in mitochondria), cyt-aa_3 (analogous to Complex IV) and a superoxide dismutase. Here, I present atomic features of the mycobacterial cytochrome oxidase supercomplex, derived from cryo-EM images, unraveling the electron-, oxygen and proton pathways. These insights underscore mechanistic variations of the mycobacterial supramolecular machine and inspire drug discovery efforts.

Abstracts (Tuesday 28th)



Combinatorial drug strategies for mycobacterial diseases

Kevin Pethe, Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore

Tuberculosis (TB) remains a daunting global health challenge, exacerbated by the rise of multi-drug-resistant tuberculosis (MDR-TB). In recent years, several drug candidates progressed to clinical development or were approved for MDR-TB. More important that drug approval, fixed-dose regimen made of complementary drugs are urgently needed for fast treatment of MDR-TB and to limit further emergence of resistant variants. A recent example of promising drug combination is the pretomanid-bedaquiline and linezolid (BPaL) regimen that was recently approved by the US FDA. I will discuss the relevance of targeting bioenergetics for the development of bactericidal drug combinations for tuberculosis and other mycobacterial diseases.



In vitro and in vivo potency of non-tuberculous mycobacterial F-ATP synthase inhibitors

Priya Ragunathan, School of Biological Science, Nanyang Technological University, Singapore

The prevalence, morbidity, and mortality of non-tuberculosis mycobacterium (NTM) infections are rapidly escalating on a global scale. They are notoriously difficult to treat, the cure rate is low, and the bacteria are intrinsically resistant to many antibiotic classes. Many NTM have the capability to enter a metabolically dormant state particular in conditions of low oxygen tension, where the pathogens have to control crucial metabolic processes like oxidative phosphorylation to form ATP. The ATP pool in such dormant state is low and any change to the ATP concentration makes the bacterium vulnerable to drugs that target the maintenance of the ATP:ADP ratio. Hence the mycobacterial F-ATP synthase, which catalyses the synthesis of ATP, has attracted attention as drug target. Here, I present F-ATP synthase inhibitors with high efficacy and specificity against NTM, which also enhance the potency of existing anti-NTM drugs. These findings open the window for new anti-NTM combination therapies.





Neuro-Horizon Pharma Inc. - Cellular Rotary Nano-Motors Company: From Scientific Discovery to Pharmaceutical Drug Targeting and Development

Vladimir Marshansky and Mhairi Skinner, Neuro-Horizon Pharma Inc., Sharon, MA, 02067, USA

Neuro-Horizon Pharma Inc. (NHP Inc.) is a USA-based drug development company that capitalizes on the advances in the molecular and cell biology of ATP-driven rotary nano-motors: i) human V-ATPase and ii) pathogenic *Mycobacterial* F-ATPsynthase as important therapeutic targets for innovative drug design and development. Our main goal is to generate innovative therapeutic peptides, antibodies and small molecule drugs specifically targeting these cellular pathways for the treatment of cancer, neurodegenerative and infectious diseases.

NHP Inc. has partnered with Nanyang Technological University and EDDC, Singapore to develop drugs targeting the F-ATPsynthase of *Mycobacterium tuberculosis* for use in the treatment of pulmonary tuberculosis (TB). These novel chemical scaffold compounds were discovered by teams of TOPNet in Singapore and specifically target pathogenic *Mycobacterial* F-ATPsynthase by binding to a unique loop within the γ-subunit. NHP Inc. is advancing the preclinical development of the lead compound, NHP-101, for treatment of MDR, XDR and BDQR drug-resistant TB.