BIOGRAPHICAL SKETCH

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NAME: DICK, Thomas

eRA COMMONS USER NAME: TDICK367

POSITION TITLE: Member, Centre for Discovery and Innovation, Hackensack Meridian Health.

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
University of Heidelberg, Germany	MSc	08/1987	Biology
University of Heidelberg, Germany	PhD	08/1990	Bacteriology
Institute of Molecular and Cell Biology, Singapore	Postdoc	08/1996	Developmental biology

A. Personal Statement I have 20 years of experience in antibacterial drug discovery and R&D program management. Prior to my current appointment as Member at the Center for Discovery and Innovation, Hackensack Meridian Health (CDI-HMH), I was Tuberculosis (TB) disease area head at Novartis and served as professor at the National University of Singapore and at Rutgers, Newark. My research focuses on the discovery of new medicines for the treatment of TB and lung disease caused by Non-Tuberculous Mycobacteria (NTM). At CDI-HMH I i) established a fully enabled drug discovery platform, and ii) developed an attractive portfolio of repositioning and de novo drug discovery projects with partners from industry and academia. Publications on antibiotic resistance and discovery: >100; h-index = 43.

B. Positions and Honors

Positions and Employment

1996-2003 Head, Mycobacterium Biology Laboratory, Institute of Molecular and Cell Biology, Singapore
1999-2002 Assistant Professor, Institute of Molecular and Cell Biology, Singapore
2002-2003 Associate Professor, Institute of Molecular and Cell Biology, Singapore
2003-2007 Unit Head – Tuberculosis, Novartis Institute for Tropical Diseases, Singapore
2007-2011 Senior Unit Head – Tuberculosis, Novartis Institute for Tropical Diseases, Singapore
2011-2017 Associate Professor, Department of Microbiology and Immunology, School of Medicine, National University of Singapore
2012-2017 Director, Biosafety Level 3 Core Facility, School of Medicine, National University of Singapore
2017-date Visiting Toh Chin Chye Professor, Department of Microbiology and Immunology, School of Medicine, National University of Singapore
2017-2019 Associate Professor & Director, Antimicrobial Drug Discovery, Public Health Research Institute, New Jersey Medical School, Rutgers University
2019-date Member, Center for Discovery and Innovation, Hackensack Meridian Health

Other Experience and Honors

2009 Organizer of TB Keystone Conference 'Tuberculosis: Biology, pathology and Therapy', Keystone
2012-date Member of the Working Group on New TB Drugs, Stop TB Partnership
2012-2013 TB drug discovery consultant for Agency of Science and Technology, Singapore
2014-2017 Member of the Singapore's National Medical Research Council's study section
2017 Award for Scientific Excellence, Experimental Therapeutics Centre, Singapore

C. Contributions to Science

1. As head of the Mycobacterium Biology lab at the Institute of Molecular and Cell Biology (1996-2003): Discovery that mycobacteria have a genetic dormancy program

Historical background that frames the scientific problem: Persistence of TB infection despite extensive chemotherapy is a major issue in current TB treatments. What is the cause of persistence of disease? Evidence had emerged suggesting that mycobacteria may enter a non-replicating drug tolerant state. Central finding(s): We established an in vitro model for non-replicating persistence, carried out a proteomic analysis of the temporal changes in protein levels during the shift down from growth to quiescence, and subjected upregulated proteins to a genetic analysis (a). This resulted in the discovery that a dormancy induced transcription factor was essential for survival of quiescent bacilli and the identification of a regulon controlled by this transcription factor. Based on these findings we named the transcription factor Dormancy survival regulator DosR. Influence of the finding(s) on the progress of science or the application of those finding(s) to health or technology: The discovery of DosR and its regulon had wide implications for TB drug discovery, vaccine development and diagnostics (b). Scientifically it paved the way for the dissection of the molecular mechanisms of a critical aspect of mycobacterial pathophysiology (b). A Google scholar search 'dosR regulon mycobacterium' shows 15,000 publications. My specific role in the described work: Principal Investigator

a. Boon C. and **Dick T. (2002)** *Mycobacterium bovis* BCG response regulator essential for hypoxic dormancy. J. Bacteriol. 184, 6760-6767.

b. Boon C. and **Dick T. (2012)** How *Mycobacterium tuberculosis* goes to sleep: the DosR dormancy survival regulator a decade later. Future Microbiology 7, 513-518.

2. As head of the Tuberculosis Unit at the Novartis Institute for Tropical Diseases (2003-2011): Development of a new approach and new target selection criteria for antibacterial drug discovery

Historical background that frames the scientific problem: After a long pause in de novo antibacterial drug discovery, the genome revolution triggered renewed activities. Transposon mutagenesis together with genomic analyses delivered 'essential' targets which were screened for inhibitors in biochemical assays. Being in charge of the newly established TB disease area at Novartis I adopted this approach. After initial excitement, I changed strategy and developed new target selection criteria. Central finding(s): Biochemical target based approaches to TB drug discovery do rarely deliver whole cell active lead compounds, phenotypic screens do. For compound optimization it is critical to employ not only in vitro genetically but also chemically (pharmacologically) validated targets. This strategic shift resulted in the discovery of a series of lead and development compounds (a). Influence of the finding(s) on the progress of science or the application of those finding(s) to health or technology: We contributed to the general paradigm shift towards 'compound first approaches' in antibacterial drug discovery. At the same time, we identified major issues with this empirical phenotypic approach: a disconnect between in vitro potency and in vivo efficacy (b) which I addressed next (see below, 3). My specific role in the described work: Disease area head/Program leader.

a. Barry C.E., Boshoff H., Dartois V., **Dick T.**, Ehrt S., Flynn J., Schnappinger D., Wilkinson R.J., and Young D. **(2009)** The spectrum of latent tuberculosis: rethinking the biology and intervention strategies. Nat Rev Microbiol 7, 845-855.

b. Pethe K., ,.. and **Dick T. (2010)** A chemical genetic screen in *M. tuberculosis* identifies carbon-source dependent growth inhibitors devoid of in vivo efficacy. Nature Commun 1, 57 doi 10.1038/ncomms1060

3. As Associate Professor at the National University of Singapore (2011-2017):

A Development of a novel antibacterial screening strategy combining the advantages of biochemical target based approaches with the advantages of whole cell screens

Historical background that frames the scientific problem: Biochemical target based approaches to antibacterial drug discovery had failed. We and others moved back to whole cell screens, which in principal work, but do so only very inefficiently with high attrition rates (because of for instance in vitro – in vivo disconnect issues I discovered during my work at Novartis, see above (2b)). Can antibacterial drug discovery be reconnected to modern genome based biology? Can we bring back the target into whole cell screens? Central finding(s): We developed a novel, a target mechanism based, whole cell strategy that allows to assay a molecular target that resides inside intact bacilli. The target employed was the caseinolytic protease ClpP, which had been genetically validated in vivo via silencing to ensure we do not encounter another case of in vitro – in vivo disconnect. A screen was carried out and bortezomib, an anti-cancer drug acting on the human proteasome, was identified as the first whole cell active inhibitor of mycobacterial ClpP (a). Influence of the finding(s) on the progress of science or the application of those finding(s) to health or technology: This work provided proof of concept that this novel screening approach indeed works: we can 'go back' to productive target based screening when we screen the

target inside the bacterium. The identification of bortezomib as inhibitor of ClpP validated the protease chemically as target for TB (b). My specific role in the described work: Principal Investigator

a. Moreira W., … **Dick T. (2015)** A target mechanism-based whole cell screen identifies Bortezomib as an inhibitor of caseinolytic protease in mycobacteria. mBio 6, (3):e00253-15.

b. Moreira W, … **Dick T. (2017)** Towards selective mycobacterial ClpP1P2 inhibitors with reduced activity against the human proteasome. Antimicrobial Agents Chemotherapy. doi:10.1128/AAC.02307-16.

B Identification of targets of clinically used Tuberculosis drugs for target based drug optimization

Historical background that frames the scientific problem: The identification of the mechanism of action of clinically proven drugs provides the basis for the rational optimization of first-in-class drugs to best-in-class. The mechanism of action of the old key sterilizing TB drug pyrazinamide is poorly understood. The mechanism of action of the new TB drug bedaquiline was thought to be understood. Central finding(s): Employing in vitro and in vivo genetics combined with metabolomics and biophysical analyses we identified the mechanism of action of pyrazinamide: pyrazinamide blocks coenzyme A biosynthesis by inhibiting aspartate decarboxylase PanD (a,b,c,d). Employing a site directed genome mutagenesis approach, we showed that Bedaquiline inhibits ATP synthase via binding the epsilon -in addition to the previously known- c subunit (e). Influence of the finding(s) on the progress of science or the application of those finding(s) to health or technology: These works provide the basis for target based optimization of clinically proven drugs. My specific role in the described work: Principal Investigator

a. Gopal P., … **Dick T. (2016)** Pyrazinamide resistance is caused by two distinct mechanisms: prevention of Coenzyme A depletion and loss of virulence factor synthesis. ACS Infectious Diseases, doi: 10.1021/acsinfecdis.6b00070.

b. Yee M., Gopal P., **Dick T. (2017)** Missense mutations in the unfoldase ClpC1 of the caseinolytic protease complex are associated with pyrazinamide resistance in *Mycobacterium tuberculosis*. Antimicrobial Agents Chemotherapy 61:e02342-16. https://doi.org/10.1128/AAC.02342-16

c. Gopal P., … **Dick T. (2017)** In vivo selected pyrazinoic acid resistant M. tuberculosis strains harbour missense mutations in the aspartate decarboxylase PanD and unfoldase ClpC1. ACS Infectious Diseases. doi: 10.1021/acsinfecdis.7b00017.

d. Gopal P., … **Dick T. (2017)** Pyrazinoic acid inhibits mycobacterial coenzyme A biosynthesis by binding to aspartate decarboxylase PanD. ACS Infectious Disease. DOI: 10.1021/acsinfecdis.7b00079.

e. Kundu S., … **Dick T. (2016)** Bedaquiline targets the ε subunit of mycobacterial F-ATP synthase. Antimicrobial Agents Chemotherapy, 60, 6977-6979.

C Proof-of-concept for a novel chemotherapeutic strategy addressing resistance and persistence in mycobacteria

Historical background that frames the scientific problem: Persistence of infection due to phenotypically drug tolerant non-replicating persister bacilli and development of genetic drug resistant due to mutations in drug targets represent key issues in TB as well as in infections due to non-tuberculous mycobacteria (NTM). The membrane as target has not been explored for the development of antimycobacterials. We hypothesized that targeting the membrane (as opposed to targeting specific proteins or rRNAs) prevents the emergence of resistance and kills persister bacteria. Central finding(s): Using a natural product, boromycin (a), and a semisynthetic natural product, AM-0016 (b), as well as synthetic small molecular weight indole-based amphiphiles (c), we showed that targeting the mycobacterial membrane eradicates persister bacilli and has a low propensity for the development of genetic drug resistance. Importantly, we showed recently that we can generate small molecular weight membrane disruptors that are well tolerated and show efficacy in a TB mouse model. Influence of the finding(s) on the progress of science or the application of those finding(s) to health or technology: These proof of concept works opens the mycobacterial membrane as a novel chemotherapeutic intervention level that is ‘anti-resistance’ and ‘anti-persistence’. My specific role in the described work: Principal Investigator

a. Moreira W., Aziz D.B. and **Dick T. (2016)** Boromycin kills mycobacterial persisters without detectable resistance. Frontiers in Microbiology, doi.org/10.3389/fmicb.2016.00199.

b. Mukherjee D., … **Dick T. (2016)** Membrane-targeting AM-0016 kills mycobacterial persisters and shows low propensity for resistance development. Future Microbiology doi: 10.2217/fmb-2015-0015.

c. Yang T., … **Dick T. (2017)** Amphiphilic indole derivatives as anti-mycobacterial agents: structure-activity relationships and membrane targeting properties. Journal Medicinal Chemistry, Doi: 10.1021acs.jmedchem.6b01530.

4. As Associate Professor at Rutgers University (2017-2019): Identification of new hits, leads and repurposing candidates for NTM lung disease

Historical background that frames the scientific problem: Non-tuberculous mycobacteria (NTM), such as *Mycobacterium abscessus* and *Mycobacterium avium*, have emerged as major health threat for vulnerable patient populations, including cystic fibrosis and COPD patients. 'New drugs for NTM' represents an urgent medical need. The hit rate against intrinsically resistant NTM in whole cell screens is extremely low, hindering the identification of lead compounds. Repurposing and repositioning efforts are limited (a). Central finding(s): We hypothesized and confirmed that screening libraries of hits active against TB generates a high hit rate against NTM (b,c). Screening of FDA drug libraries identified repurposing candidates, including rifabutin (d,e,f). Influence of the finding(s) on the progress of science or the application of those finding(s) to health or technology: The finding that that high NTM hit rates can be achieved when libraries of TB actives are screened enables efficient early drug discovery for NTM pathogens. The identification of repurposing candidates enables rapid translation into clinical practice. My specific role in the described work: Principal Investigator

a. Wu M.L., … **Dick T. (2018)** NTM drug discovery: status, gaps and the way forward. Drug Discovery Today. doi.org/10.1016/j.drudis.2018.04.001.

b. Moreira W., … **Dick T. (2016)** Fragment-based whole cell screen delivers hits against *M. tuberculosis* and non-tuberculous mycobacteria. Frontiers in Microbiology, doi: 10.3389/fmicb.2016.01392.

c. Low J.L., … **Dick T. (2017)** Screening of TB actives for activity against nontuberculous mycobacteria delivers high hit rates. Frontiers in Microbiology. doi: 10.3389/fmicb.2017.01539

d. Aziz D.B., … **Dick T. (2017)** Rifabutin is active against *Mycobacterium abscessus* complex. Antimicrobial Agents Chemotherapy. doi:10.1128/AAC.00155-17

e. Mukherjee D., … **Dick T. (2017)** In vitro combination of vancomycin and clarithromycin shows synergy against *Mycobacterium abscessus* isolates. Antimicrobial Agents Chemotherapy. doi: 10.1128/AAC.01298-17

f. Aziz D.B., … **Dick T. (2018)** Teicoplanin - tigecycline combination shows synergy against Mycobacterium abscessus. Frontiers in Microbiology. doi: 10.3389/fmicb.2018.00932.

5. As Member at Center for Discovery and Innovation, Hackensack Meridian Health (2019-date):

A Discovery that pyrazinamide is a target degrader

Historical background that frames the scientific problem: Drugs usually work by interfering with protein function. They inhibit for instance the enzymatic activity of their targets. Recently, drug-induced target degradation (PROTAC) gained momentum as a novel approach to drug discovery. Central finding(s): Characterizing the mechanism of action of the TB drug pyrazinamide (PZA), we discovered that this critical first line drug does not act as an inhibitor of its target aspartate decarboxylase PanD. Rather, binding of the drug to PanD promotes degradation of the protein via the caseinolytic protease complex. Thus, PZA acts as target degrader: the drug makes *Mycobacterium tuberculosis* 'eat up' one of its essential enzymes (a). Influence of the finding(s) on the progress of science or the application of those finding(s) to health or technology: This finding provides the basis for a mechanism-based optimization to develop more potent next generation PZA. My specific role in the described work: Principal Investigator

a. Gopal P., … and **Dick T. (2019)** Pyrazinamide triggers degradation of its target aspartate decarboxylase. Submitted.

B Discovery of a novel anti-mycobacterial antibiotic produced by gut microbiota

Historical background that frames the scientific problem: The gut microbiota is known to produce a large number of metabolites that can be detected in the blood of the host. The actual effects of gut microbiota metabolites on the human host are largely unknown. Central finding(s): We screened a library of fragment sized molecules for activity against *M. tuberculosis* and discovered that the gut microbiota metabolite indole propionic acid (IPA) shows broad anti-mycobacterial activity in vitro and in vivo (a). Determination of the anti-bacterial mechanism of action of IPA showed that the molecule blocks tryptophan synthesis by mimicking tryptophan as allosteric inhibitor of the TrpE (b). Influence of the finding(s) on the progress of science or the application of those finding(s) to health or technology: This finding suggest that there may be a gut microbiota – TB lung axis. The discovery of the target of IPA provides the basis for an optimization project. My specific role in the described work: Principal Investigator

a. Negatu DA, … **Dick T (2018)** Whole cell screen of fragment library identifies gut microbiota metabolite indole propionic acid as antitubercular. Antimicrob Agents Chemother. PMI: 29229639

b. Negatu DA, … **Dick T. (2019)** Gut microbiota metabolite indole propionic acid targets tryptophan biosynthesis in Mycobacterium tuberculosis. mBio DOI: 10.1128/mBio.02781-18.

D. Additional Information: Research Support

Ongoing Research Support

DICK17XX00 (Dick, PI) 01/01/2018-12/31/2019

Cystic Fibrosis Foundation Therapeutics
Rutgers, The State University of New Jersey
Title: Development of preclinical persister assays for NTM drug discovery
Goal: Develop in vitro models for persistence of *M. abscessus* including non-replicator, macrophage infection, biofilm, mucus and caseum assays

R01AI132374 (Dick, PI) 02/01/2018-01/31/2023
NIH/NIAID
Rutgers, The State University of New Jersey
Title: Combatting natural resistance and persistence in non-TB mycobacteria (NTM)
Goal: Deliver preclinical development compounds employing de novo drug discovery and repositioning strategies for treatment of *M. abscessus* and *M. avium* lung disease

2R01AI106398-05 (Dick-Dartois, MPI) 07/01/2018-06/30/2023
NIH/NIAID .
Rutgers, The State University of New Jersey
Title: Target-based discovery of next generation pyrazinamide
Goal: Identify pyrazinamide-derived anti-TB lead compounds with improved potency employing a target based approach combined with novel ex vivo lesion penetration and sterilization assays.

Pending Research Support

Tracking # GRANT12596876/CETR (Perlin, PI) 04/01/2019-03/31/2024
NIH/NIAID
Rutgers, The State University of New Jersey
Title: Centre to develop innovative therapeutics to multidrug resistant high-threat bacterial agents.
Role: Project Leader (Repositioning oxazolidinones and rifamycins for non-TB mycobacterial (NTM) lung disease)
Project goals: Identify preclinical development compounds by optimizing oxazolidinones and rifamycins for NTM. Develop an immunocompetent mouse infection model for *M. abscessus* lung disease

Completed Research Support

(Note: in Singapore; 2012-2017, i.e. after moving from industry to academia, and before moving to the US)
NMRC/CBRG/022/2012 (PI Dick), 2012-2016, National Medical Research Council Singapore, National University of Singapore; *Targeting proteome homeostasis: a new approach to anti-mycobacterial drug discovery.* The goals are to develop a novel target mechanism based whole cell screen and deliver new leads for TB.
NMRC/CG/013/2013 (PI Dick), 2013-2018, National Medical Research Council Singapore, National University of Singapore; *Translational clinical research on infectious diseases caused by risk group 3 pathogens.* The goal is to launch and support translational infectious diseases programs for TB and other agents
NMRC/TCR/011-NUHS/2014 (Program PI Paton, Project PI Dick), 2014-2019, National Medical Research Council Singapore, National University of Singapore; *Singapore Programme of Research to Investigate New approaches to drug discovery and clinical translation - to deliver improved treatments for Tuberculosis-SPRINT-TB*. The goal is to deliver new preclinical development candidates and new drug combinations for TB
TDR-G002-001/H16/02/b0/001 (PI Dick), 2017-2018, Biomedical Research Council Singapore, National University of Singapore; *Therapeutics Development Review Grant Bortezomib for TB*. The goal is to deliver less toxic and more potent leads for proof of concept in TB mouse infection models
NMRC/CBRG/0037/2013 (PI Gruber PI, Co-I Dick), 2013-2017, National Medical Research Council Singapore, Nanyang Technological University; *Insights into the mechanisms and structure of the key coupling subunits ε and γ of the Mycobacterium tuberculosis F1FO ATP synthase, and their potential as novel TB drug target.* Goals include to determine the precise mechanisms of action / binding of Bedaquiline to ATP synthase.
SHF/FG538P/2013 (PI Liu, Co-I Dick), 2014-2016, SingHealth Singapore, Singapore Eye Research Institute; *Optimization of anti-tuberculosis molecules by lipid tail modification of cationic amphiphilic alpha-mangostin derivatives*. Goal is the optimization of membrane targeting lead compound AM-0016.
CNIG13nov001 (PI Ong, Co-I Dick), 2014-2017, National Medical Research Council Singapore, National University Hospital; *Doxycyline and the modulation of tissue destruction in human pulmonary tuberculosis: A pilot study.* Goal is to explore the possible use of doxycycline as add-on TB drug.