BIOGRAPHICAL SKETCH

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NAME: DICK, Thomas

eRA COMMONS USER NAME: TDICK367

POSITION TITLE: Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
University of Heidelberg, Germany	MSc	04/1987	Microbiology
University of Heidelberg, Germany	PhD	06/1990	Molecular Bacteriology
Institute of Molecular and Cell Biology, Singapore	Postdoc	08/1996	Developmental Biology

A. Personal Statement

I have 20 years of experience in mycobacteriology and anti-mycobacterial drug discovery. Prior to my current appointments as Member at the Center for Discovery and Innovation, Hackensack Meridian Health (CDI) and Professor at Hackensack Meridian School of Medicine and Georgetown University, I was Tuberculosis (TB) disease area head at Novartis and served as Associate Professor at Rutgers University and the National University of Singapore. My research focuses on the discovery of new antibiotics for the treatment of TB and lung disease caused by Non-Tuberculous Mycobacteria (NTM). At CDI I established a fully enabled TB and NTM drug discovery platform for the discovery of target-lead couples and the delivery of preclinical development candidates. The platform includes mycobacterial strain collections, a range of in vitro potency assays, and in vivo (mouse) pharmacology and efficacy models. Target deconvolution and resistance analyses complement our compound profiling capabilities. With medicinal chemistry partners from industry and academia I developed a portfolio of de novo and repositioning drug discovery projects. I published over 150 papers in the field of discovery, mechanism of action & resistance of antibacterials with an h-index of 45. Below I list recent reviews and a book I edited, illustrating my area of expertise:

1 Wu ML, Aziz DB, Dartois V, **Dick T. (2018)** NTM drug discovery: status, gaps and the way forward. *Drug Discov Today*. 23(8):1502-1519. PMCID: PMC6078814.

2 Ganapathy US, Dartois V, **Dick T (2019)** Repositioning rifamycins for Mycobacterium abscessus lung disease. *Expert Opinion Drug Discov* 14 (9), 867-878. PMCID: PMC6663560

3 Gopal P, Grüber G, Dartois V, **Dick T (2019)** Pharmacological and Molecular Mechanisms Behind the Sterilizing Activity of Pyrazinamide. *Trends Pharmacol Sciences* 40, 930-940. PMCID: PMC6884696

4 Dartois, V., Sizemore, C., **Dick, T., eds. (2019)**. NTM – The New Uber-Bugs. *Frontiers Media, Lausanne.* PMCID: PMC6582698

B. Positions and Honors

Positions and Employment

1996-2003	PI, Mycobacterium Laboratory, Institute of Molecular and Cell Biology, Singapore (IMCB)
1999/2002	Assistant/Associate Professor, IMCB
2003-2011	Unit Head (Executive Director) Tuberculosis, Novartis Institute for Tropical Diseases, Singapore (NITD)
2007	Senior Unit Head, NITD
2003-2011	Adjunct Associate Professor, Dept. of Microbiology and Immunology, School of Medicine, National University of Singapore (NUS)
2011-2017	Associate Professor & Director, Biosafety Level 3 Core Facility, NUS
2017-2020	Toh Chin Chye Visiting Professor, NUS
2017-2019	Associate Professor & Director Antimicrobial Drug Discovery, Dept. of Medicine & Public Health Research Institute, New Jersey Medical School, Rutgers University, Newark, NJ
2019-date	Member, Center for Discovery and Innovation, Hackensack Meridian Health, Nutley, NJ

2019-date Professor, Dept. of Medical Sciences, Hackensack Meridian School of Medicine, Nutley, NJ
2020-date Professor, Dept. of Microbiology and Immunology, Georgetown University, Washington, DC

Other experiences and Professional Memberships

2005-2011 Organized 10 TB conferences in endemic countries (including Tanzania, Mozambique, Cameroon and Indonesia), and the 2009 TB meeting at Keystone, CO
2007-2011 Developed a clinical research site for TB in Makassar, Sulawesi, Indonesia
2012-date Member of the Working Group on New TB Drugs, Stop TB Partnership
2012-2013 TB drug discovery consultant for Agency for Science, Technology and Research Singapore
2012-2017 Member of the Singapore's National Medical Research Council's study section
2017-date Member, American Society for Microbiology
2017-date Associate Editor, Frontiers in Microbiology – Antimicrobials, Resistance and Chemotherapy

Honors

2017 Award for Scientific Excellence, Experimental Therapeutics Centre, Singapore

C. Contributions to Science

I am contributing to the field of mycobacterial drug resistance, mechanisms of action of anti-mycobacterials, and the discovery of new anti-mycobacterials since I became principal investigator in 1996. I started with a focus on tuberculosis (TB, *M. tuberculosis*) and expanded more recently into lung diseases caused by non-TB mycobacteria (NTM, *M. abscessus*, *M. avium*). The overarching goal of my research is to understand the mechanisms of action of -and resistance to- antimicrobials and to exploit this knowledge for the delivery of anti-mycobacterial target-lead couples and preclinical development compounds with demonstrated exposure, tolerability and efficacy. This objective is driven by medical needs in mycobacterial lung disease and an underdeveloped anti-mycobacterial drug pipeline. I populate the preclinical pipeline employing a two-pronged approach: **de novo drug discovery** (new targets and/or new chemotypes) and **repositioning** (improvement of approved drugs). In a third approach I am pioneering bacterial **membrane integrity** as a new chemotherapeutic intervention level. Further to populating the mycobacterial antibiotic pipeline with novel compounds and targets I also developed new drug discovery approaches, thus impacting the field of anti-bacterial drug discovery in terms of concepts. Examples include mechanism based-whole cell screens, whole cell screening of focused and 'specialized' libraries, lead optimization by addressing bacterial cell pharmacokinetics and target degradation as novel on-target anti-bacterial mechanism. In the following I discuss my main contributions to the field of anti-mycobacterial drug-discovery **over the past 5 years**. In all the described projects my role was **principal investigator** as reflected by the **senior authorship** of the corresponding **50 publications**. Selected senior authorship publications are mentioned below. A complete list of my published work can be found in My Bibliography at https://www.ncbi.nlm.nih.gov/myncbi/thomas.dick.2/bibliography/public/.

TB and NTM de novo drug discovery: new target-lead couples

Caseinolytic protease/bortezomib. Whole cell and target based approaches for discovery of new chemical starting points have both advantages and disadvantages. We developed a novel screening method that combines the advantages of target based and whole cell screening, a mechanism-based whole cell screen, and identify with caseinolytic protease and the human proteasome inhibitor bortezomib a new target-lead couple **(1)**. In a lead optimization project, we reduced mechanism-based toxicity of the hit 1000-fold **(2)**. **Dihydrofolate reductase/novel DHFR inhibitor.** To date no potent and selective antimycobacterial DHFR inhibitor has been developed. We applied a whole cell screening approach of focused DHFR inhibitor libraries to identify a novel, highly potent and selective DHFR inhibitor **(3)**. **Tryptophan biosynthesis TrpE/IPA**. Fragment-sized (Rule-of-3-compliant) compounds are attractive chemical starting points due to their physicochemical properties. However, fragment-sized libraries have not been subjected to whole cell screens. Screening fragment-sized compound libraries with follow-up target deconvolution identified with indole propionic acid (IPA) an in vivo active allosteric inhibitor of TrpE required for tryptophan biosynthesis **(4, 5)**. Interestingly, IPA is a metabolite produced by our gut microbiota, suggesting a possible gut–lung axis for mycobacterial lung diseases. **TB actives for NTM hit generation.** We demonstrated that collections of TB actives present a rich source of chemical starting point for NTM drug discovery **(6)**. Based on that finding we screened collections of TB actives resulting in identification of several TB-NTM double actives targeting clinically validated as well as novel targets: **Gyrase/non-fluoroquinolone gyrase inhibitors**. Gyrase-inhibiting fluoroquinolones (moxifloxacin) are used clinically against mycobacteria but suffer from intrinsic and acquired resistance. We identified two different novel bacterial

topoisomerase II inhibitors and demonstrated activity in vivo and against moxifloxacin resistant NTM strains (unpublished). **tRNA synthetase inhibitor**. We identified an inhibitor targeting an aminoacyl tRNA synthetase as novel TB-NTM double active and provided proof of concept in vivo (unpublished). Taken together, we added 6 novel target-lead couples to the mycobacterial / NTM drug pipeline in the past 5 years. For 3 advanced leads in vivo proof of concept in an animal model was provided.

1 Moreira W, Ngan GJ, Low JL, Poulsen A, Chia BC, Ang MJ, Yap A, Fulwood J, Lakshmanan U, Lim J, Khoo AY, Flotow H, Hill J, Raju RM, Rubin EJ, **Dick T. (2015)** Target mechanism-based whole-cell screening identifies bortezomib as an inhibitor of caseinolytic protease in mycobacteria. *mBio.* 6(3):e00253-15. PMCID: PMC4436076.
2 Moreira W, Santhanakrishnan S, Ngan GJY, Low CB, Sangthongpitag K, Poulsen A, Dymock BW, **Dick T. (2017)** Towards Selective Mycobacterial ClpP1P2 Inhibitors with Reduced Activity against the Human Proteasome. *Antimicrob Agents Chemother.* 61(5):e02307-16. PMCID: PMC5404560.
3 Yang X, Wedajo W, Yamada Y, Dahlroth SL, Neo JJL, **Dick T**, Chui WK **(2018)** 1,3,5-triazaspiro[5.5]undeca-2,4-dienes as selective Mycobacterium tuberculosis dihydrofolate reductase inhibitors with potent whole cell activity. *Euro J Med Chem* 144, 262-276. PMID: 29274493
4 Negatu DA, Liu JJJ, Zimmerman M, Kaya F, Dartois V, Aldrich CC, Gengenbacher M, **Dick T. (2018)** Whole-Cell Screen of Fragment Library Identifies Gut Microbiota Metabolite Indole Propionic Acid as Antitubercular. *Antimicrob Agents Chemother.* 62(3):e01571-17. PMCID: PMC5826148.
5 Negatu DA, Yamada Y, Xi Y, Go ML, Zimmerman M, Ganapathy U, Dartois V, Gengenbacher M, **Dick T. (2019)** Gut Microbiota Metabolite Indole Propionic Acid Targets Tryptophan Biosynthesis in Mycobacterium tuberculosis. *mBio.* 10(2):e02781-18. PMCID: PMC6437058.
6 Low JL, Wu ML, Aziz DB, Laleu B, **Dick T. (2017)** Screening of TB Actives for Activity against Nontuberculous Mycobacteria Delivers High Hit Rates. *Front Microbiol.* 8:1539. PMCID: PMC5559473.

TB and NTM repositioning: new leads with improved properties

Less hydrophobic diarylquinolines free of cardiotoxicity. The diarylquinoline bedaquiline (BDQ) is a F-ATP synthase inhibitor used for the treatment of drug resistant TB and NTM disease. However, the drug suffers from high lipophilicity and hERG inhibition. We discovered that BDQ has a dual on-target mechanisms of action against ATP synthase: the drug targets the coupling epsilon subunit, in addition to the rotating c-subunit shown previously. This presents a critical finding for target-based generation of next generation BDQ **(1,2,3)**. We demonstrated that the next generation BDQ development compound TBAJ-876 with improved physicochemical properties and reduced hERG activity retained BDQ's dual mechanism of action and is active against NTM in vivo **(4)**. **Metabolism resistant rifamycins.** Rifampicin suffers from poor potency against *M. abscessus* and is thus not used clinically. Considering the critical role of this RNA polymerase inhibitor in the treatment for other mycobacterial diseases, the lack of a rifamycin in the *M. abscessus* regimen may contribute to poor treatment outcomes. We identified an approved rifampicin analog, rifabutin, to be active in vivo against *M. absessus* and showed that rifabutin suppresses inducible macrolide resistance commonly found in *M. abscessus* strains **(5,6)**. These findings suggest that ribfabutin should be explored as a repurposing candidate. We found that the poor potency of rifampicin is due to oxidation of its hydroquinone moiety -not present in rifabutin- by the bacterium. In a lead optimization project, we are currently blocking a second metabolic mechanism affecting bacterial cell PK of rifamycins (ADP-ribosylation) to deliver next generation rifabutin showing even higher potency. **Oxazolidinones free of mitochondrial toxicity**. The ribosome-inhibiting oxazolidinone linezolid is used against TB and NTM but causes side effects including cytopenias and neuropathies due to inhibition of mitochondrial protein synthesis. We currently carry out a lead optimization project to remove the mechanism-based toxicity of this drug class and provided in vivo proof of concept for this approach for NTM (unpublished). **Resistance resistant macrolides.** The ribosome-inhibiting macrolide clarithromycin presents a corner stone in NTM therapy. Acquired resistance due to mutations in the drug's rRNA binding site as well as intrinsic resistance due to binding site methylation present major issues in the clinic. We are identifying macrolides that are active against macrolide resistant strains. **Beta-lactamase resistant beta-lactams**. Imipenem and cefoxitin are use clinically against *M. abscessus*. However, potency is modest and variable due to expression of beta-lactamases. We are identifying beta-lactamase resistant beta-lactams and identified a cephalosporin as an attractive lead (unpublished)**. Novel synergies for repurposing.** As part of our 'repositioning' program we identified novel combinations of drugs used clinically for non-mycobacterial infections to be active against NTM **(7)**. We also uncovered clinically relevant antagonistic effects of approved drugs **(8)**. Taken together, we added 5 repositioning leads and 2 novel drug combinations for potential repurposing to the mycobacterial / NTM drug pipeline since 2016. For 2 advanced leads in vivo proof of concept in an animal model was provided.

1 Kundu S, Biukovic G, Grüber G, **Dick T. (2016)** Bedaquiline Targets the ε Subunit of Mycobacterial F-ATP Synthase. *Antimicrob Agents Chemother.* 60(11):6977-6979. PMCID: PMC5075122.
2 Sarathy JP, Ragunathan P, Shin J, Cooper CB, Upton AM, Grüber G, **Dick T. (2019)** TBAJ-876 Retains Bedaquiline's Activity against Subunits c and ε of Mycobacterium tuberculosis F-ATP Synthase. *Antimicrob Agents Chemother.* 63(10):e01191-19. PMCID: PMC6761534.
3 Sarathy JP, Ragunathan P, Cooper CB, Upton AM, Grüber G, **Dick T. (2020)** TBAJ-876 Displays Bedaquiline-Like Mycobactericidal Potency without Retaining the Parental Drug's Uncoupler Activity. *Antimicrob Agents Chemother.* 64(2):e01540-19. PMCID: PMC6985740.
4 Sarathy JP, Ganapathy US, Zimmerman MD, Dartois V, Gengenbacher M, **Dick T. (2020)** TBAJ-876, a 3,5-Dialkoxypyridine Analogue of Bedaquiline, Is Active against Mycobacterium abscessus. *Antimicrob Agents Chemother.* 64(4):e02404-19. PMCID: PMC7179298.
5 Aziz DB, Low JL, Wu ML, Gengenbacher M, Teo JWP, Dartois V, **Dick T. (2017)** Rifabutin Is Active against Mycobacterium abscessus Complex. *Antimicrob Agents Chemother.* 61(6):e00155-17. PMCID: PMC5444174.
6 Dick T, Shin SJ, Koh WJ, Dartois V, Gengenbacher M **(2020)** Rifabutin Is Active against Mycobacterium abscessus in Mice. *Antimicrob Agents Chemother.* 64(2):e01943-19. PMCID: PMC6985736.
7 Mukherjee D, Wu ML, Teo JWP, **Dick T. (2017)** Vancomycin and Clarithromycin Show Synergy against Mycobacterium abscessus In Vitro. *Antimicrob Agents Chemother.* 61(12):e01298-17. PMCID: PMC5700366.
8 Lindman M, **Dick T. (2019)** Bedaquiline Eliminates Bactericidal Activity of β-Lactams against Mycobacterium abscessus. *Antimicrob Agents Chemother.* 63(8):e00827-19. PMCID: PMC6658768.

Pyrazinamide, repositioning with a surprise: drug induced target degradation

Pyrazinamide is a key treatment shortening drug against tuberculosis but suffers from poor potency. Interestingly, its mechanism of action remained obscure for half a century. We showed that pyrazinamide inhibits bacterial coenzyme A biosynthesis by binding to PanD **(1,2)**. Surprisingly, pyrazinamide acts by a fundamentally novel anti-bacterial on-target mechanism. Rather than modulating the activity of the target, the drug promotes degradation of its target by the bacterium's own protease machinery **(3,4,5)**. This finding enables us to develop mechanism-based next gen pyrazinamide with improved potency. We propose induced target degradation as a novel strategy for antibacterial drug discovery **(6)**.

1 Gopal P, Yee M, Sarathy J, Low JL, Sarathy JP, Kaya F, Dartois V, Gengenbacher M, **Dick T. (2016)** Pyrazinamide Resistance Is Caused by Two Distinct Mechanisms: Prevention of Coenzyme A Depletion and Loss of Virulence Factor Synthesis. *ACS Infect Dis.* 2(9):616-626. PMCID: PMC5731467.
2 Gopal P, Nartey W, Ragunathan P, Sarathy J, Kaya F, Yee M, Setzer C, Manimekalai MSS, Dartois V, Grüber G, **Dick T. (2017)** Pyrazinoic Acid Inhibits Mycobacterial Coenzyme A Biosynthesis by Binding to Aspartate Decarboxylase PanD. *ACS Infect Dis.* 3(11):807-819. PMCID: PMC5734868.
3 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. *Antimicrob Agents Chemother.* 61(2):e02342-16. PMCID: PMC5278685.
4 Gopal P, Tasneen R, Yee M, Lanoix JP, Sarathy J, Rasic G, Li L, Dartois V, Nuermberger E, **Dick T. (2017)** In Vivo-Selected Pyrazinoic Acid-Resistant Mycobacterium tuberculosis Strains Harbor Missense Mutations in the Aspartate Decarboxylase PanD and the Unfoldase ClpC1. *ACS Infect Dis.* 3(7),492-501. PMCID: PMC5514395.
5 Gopal P, Sarathy JP, Yee M, Ragunathan P, Shin J, Bhushan S, Zhu J, Akopian T, Kandror O, Lim TK, Gengenbacher M, Lin Q, Rubin EJ, Grüber G, **Dick T. (2020)** Pyrazinamide triggers degradation of its target aspartate decarboxylase. *Nat Commun.* 11(1):1661. PMCID: PMC7125159.
6 Gopal P, **Dick T (2020)** Targeted protein degradation in antibacterial drug discovery? *Prog Biophys Mol Biol.* 152, 10-14. PMCID: PMC7145722

Membrane integrity as novel intervention level for the treatment of TB and NTM

The bacterial membrane is an under-explored intervention level in chemotherapy of mycobacterial diseases. Its attractiveness as target is based on the essentially of membrane integrity for viability independent of the physiological and metabolic state of the bacteria: an intact membrane is required for growing and drug tolerant non-growing and biofilm bacteria. Hence, membrane targeting agents should have 'anti-persister' activity and thus shorten treatment duration. Furthermore, membrane function disrupting agents should show a low propensity for the development of genetic drug resistance. First, we demonstrated extreme drug tolerance of non-growing and biofilm NTM and confirmed the hypothesis that membrane function disrupting agents are bactericidal for drug tolerant bacteria and show low resistance frequency **(1,2).** Then we developed membrane-

inserting amphiphilic indolyl Mannich bases **(4)** and optimized the class to deliver a lead with in vivo tolerability, exposure and activity **(5)**. Our work demonstrates feasibility of targeting the membrane as a novel chemotherapeutic intervention against mycobacterial diseases.

1 Moreira W, Aziz DB, **Dick T. (2016)** Boromycin Kills Mycobacterial Persisters without Detectable Resistance. *Front Microbiol.* 7:199. PMCID: PMC4761863.
2 Yam YK, Alvarez N, Go ML, **Dick T. (2020)** Extreme Drug Tolerance of Mycobacterium abscessus Persisters. *Front Microbiol.* 11:359. PMCID: PMC7064438.
3 Yang T, Moreira W, Nyantakyi SA, Chen H, Aziz DB, Go ML, **Dick T (2017)** Amphiphilic indole derivatives as antimycobacterial agents: structure–activity relationships and membrane targeting properties. *J Med Chem* 60 (7), 2745-2763. PMID: 28290692
4 Nyantakyi SA, Li M, Gopal P, Zimmerman M, Dartois V, Gengenbacher M, **Dick T**, Go ML **(2018)**. Indolyl Azaspiroketal Mannich Bases Are Potent Antimycobacterial Agents with Selective Membrane Permeabilizing Effects and in Vivo Activity. *J Med Chem.* 61(13):5733-5750. PMCID: PMC6043372.
5 Li M, Phua ZY, Xi Y, Xu Z, Nyantakyi SA, Li W, Jackson MC, Wong MW, Lam Y, Chng SS, Go ML, **Dick T (2020)** Potency Increase of Spiroketal Analogs of Membrane Inserting Indolyl Mannich Base Antimycobacterials Is Due to Acquisition of MmpL3 Inhibition. *ACS Infect Dis.* XXXX. PMID: 32413266

D. Additional Information: Research Support

DICK17XX00 Dick, PI 01/01/2018-12/31/2020
Cystic Fibrosis Foundation Therapeutics
Title: Development of preclinical persister assays for NTM drug discovery
Goal: Develop in vitro models for persistence of *M. abscessus*

R01AI132374 Dick, PI 02/01/2018-01/31/2023
NIH/NIAID
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

R01AI106398 Dick-Dartois, MPI 06/01/2018-05/31/2023
NIH/NIAID .
Title: Target-based discovery of next generation pyrazinamide
Goal: Identify pyrazinamide-derived anti-TB lead compounds with improved potency

U19AI142731 Perlin, PI 05/01/2019-04/30/2024
NIH/NIAID
Title: Centre to develop innovative therapeutics to multidrug resistant high-threat bacterial agents
Role: Project PI - Repositioning oxazolidinones and rifamycins for NTM lung disease
Project goal: Identify oxazolidinones and rifamycin leads with improved tolerability and potency

Completed Research Support at the National University of Singapore (2011-2017), 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, Targeting proteome homeostasis: a new approach to anti-mycobacterial drug discovery. **NMRC/CG/013/2013** (PI Dick), 2013-2018, National Medical Research Council Singapore, Translational clinical research on infectious diseases caused by risk group 3 pathogens.
NMRC/CBRG/0037/2013 (PI Gruber PI, Co-I Dick), 2013-2017, National Medical Research Council Singapore, 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. **SHF/FG538P/2013** (PI Liu, Co-I Dick), 2014-2016, SingHealth, Optimization of anti-tuberculosis molecules by lipid tail modification of cationic amphiphilic alpha-mangostin *derivatives*. **CNIG13nov001** (PI Ong, Co-I Dick), 2014-2017, National Medical Research Council Singapore, Doxycyline and the modulation of tissue destruction in human pulmonary tuberculosis: A pilot study. **NMRC/TCR/011-NUHS/2014** (Program PI Paton, Project PI Dick), 2014-2020, National Medical Research Council Singapore, Singapore Programme of Research to Investigate New approaches to drug discovery and clinical translation - to deliver improved treatments for Tuberculosis-SPRINT-TB. **TDR-G002-001/H16/02/b0/001** (PI Dick), 2017-2018, Biomedical Research Council Singapore, Therapeutics Development Review Grant 'Bortezomib for TB'.
At Novartis (2003-2011): funded internally and by the Bill and Melinda Gates Foundation (**Grand Challenges #11**/ Drugs for Treatment of Latent Tuberculosis, Program PI Young, Project PI Dick, 2005-2015). At IMCB (1996-2003): funded by institutional grants from the Agency for Science, Technology, Research, Singapore.