BIOGRAPHICAL SKETCH

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NAME: DICK, Thomas

eRA COMMONS USER NAME: TDICK367

POSITION TITLE: Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	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 am Professor of Microbiology with more than 20 years of experience in **mycobacteriology** and **antimycobacterial drug discovery** (>200 publications; h-index: 58; i10-index: 148, D-index: 58). I am Member at the Center for Discovery and Innovation, Hackensack Meridian Health (CDI; Nutley NJ, where I am based) and Professor at the Hackensack Meridian School of Medicine (Nutley NJ) and Georgetown University (Washington DC). Prior appointments include Associate Professor at the National University of Singapore, and Executive Director of the Tuberculosis (TB) Unit at Novartis.

After moving to the United States from Singapore in 2017, I started NIH-funded research in 2018. Since the beginning of my NIH funded work, I identified a **total of 10 advanced antimycobacterial leads** (defined as compounds with demonstrated exposure, tolerability and efficacy in mouse infection models) and **several repurposing candidates**. **Mechanisms of action and resistance were elucidated for 13 leads**. My work since 2018 resulted in ~90 publications.

Until 2017, I focused exclusively on the discovery of new antibiotics for the treatment of Tuberculosis (*Mycobacterium tuberculosis*), a disease area for which a robust preclinical pipeline has now been established. Over the past years, I increasingly shifted activities towards the neglected lung disease caused by '**Non-Tuberculous Mycobacteria**' (NTM), with a focus on incurable ***Mycobacterium abscessus*** infections.

The goal of my research is to populate the NTM drug pipeline. We determine the mechanism of action/resistance of whole cell actives and exploit this knowledge for the delivery of **novel lead-target couples** and **preclinical development compounds**. We populate the preclinical space via a two-pronged approach: **de novo drug discovery** (new targets and/or new chemotypes) and **drug re-engineering** (improving approved drugs by chemical optimization). Furthermore, we populate the clinical NTM pipeline by identifying drugs in clinical use (or development) for other disease indications for **repurposing**.

Due to my experience in antibiotic discovery and multidisciplinary program management, I am well suited to lead the project **'De novo drug discovery and repurposing approaches towards better regimens for *M. abscessus* pulmonary disease'** disease to advance our portfolio of single anti-NTM drugs and combinations. At CDI, I established a **fully enabled NTM drug discovery platform**. The platform includes strain collections, *in vitro* potency assays, and *in vivo* (mouse) pharmacology models. Target deconvolution and resistance analysis complement our compound profiling capabilities. With **proven medicinal chemistry partners** from industry (including GSK, Merck, Evotec), and academia (e.g., Aldrich lab U Minnesota; Drug Discovery Unit Dundee U, Richter/Imming labs U Halle), I developed an attractive anti-NTM project portfolio which provides an excellent foundation for accelerating the discovery and development of **all-oral curative regimens** against NTM lung disease.

Ongoing projects that I would like to highlight:

Cystic Fibrosis Foundation DICK24XX0
Dick, PI
03/01/2024-02/28/2027
Advancing discovery compounds and prioritizing drug regimens for Mycobacterium abscessus lung disease in CF patients: two complementary mouse models
R01 AI177342
Dick (contact), Aldrich; MPI
06/06/2023-05/31/2028
Optimization of rifamycins to overcome intrinsic resistance of nontuberculous mycobacteria to improve treatment of NTM lung disease
R01 AI132374
Dick, PI
02/01/2018-01/31/2024 (NCE)
Combatting natural resistance and persistence in non-TB mycobacteria (NTM)
U19 AI142731
Perlin, PI, Role: project PI
05/01/2019-04/30/2024
Centre to develop innovative therapeutics to multidrug resistant high-threat bacterial agents
Project: Repositioning oxazolidinones and rifamycins for NTM lung disease

Citations (selected reviews):
1. Wu ML, Aziz DB, Dartois V, **Dick T.** NTM drug discovery: status, gaps and the way forward. **Drug Discov Today. 2018**; 23:1502-1519. PMC6078814.
2. Ganapathy US, Dartois V, **Dick T.** Repositioning rifamycins for *Mycobacterium abscessus* lung disease. **Expert Opin Drug Discov. 2019**; 14:867-878. PMC6663560.
3. Gopal P, Grüber G, Dartois V, **Dick T.** Pharmacological and Molecular Mechanisms Behind the Sterilizing Activity of Pyrazinamide. **Trends Pharmacol Sci. 2019**; 40:930-940. PMC6884696.
4. Dartois V, **Dick T.** Drug development challenges in nontuberculous mycobacterial lung disease: TB to the rescue. **J Exp Med. 2022**; 219(6):e20220445. PMC9098649.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2022-Present	Member of NIH study sections (antibacterial drug discovery, tuberculosis)
2020-Present	Professor, Dept. of Microbiology and Immunology, Georgetown University, Washington, DC
2019-Present	Professor, Dept. of Medical Sciences, Hackensack Meridian School of Medicine, Nutley, NJ
2019-Present	Member, Center for Discovery and Innovation, Hackensack Meridian Health, Nutley, NJ
2017-Present	Member, American Society for Microbiology
2017-2020	Toh Chin Chye Visiting Professor, Dept. of Microbiology and Immunology, School of Medicine, National University of Singapore (NUS)
2017-2019	Associate Professor, Public Health Research Institute, New Jersey Medical School, Rutgers University, Newark, NJ
2011-2017	Associate Professor, Dept. of Microbiology and Immunology, School of Medicine, NUS
2012-2017	Director, Biosafety Level 3 Core Facility, School of Medicine, NUS
2012-Present	Member of the Working Group on New TB Drugs, Stop TB Partnership
2012-2017	Member of the Singapore National Medical Research Council's study sections
2012-2013	TB drug discovery consultant for Agency for Science, Technology and Research Singapore
2003-2011	Unit Head Tuberculosis (from 2007 Senior Unit Head / Executive Director), Novartis Institute for Tropical Diseases, Singapore
2003-2011	Adjunct Associate Professor, Dept. of Microbiology and Immunology, School of Medicine, NUS
1999/2002	Assistant/Associate Professor, Institute of Molecular and Cell Biology, Singapore (IMCB)
1996-2003	PI, Mycobacterium Laboratory, IMCB

Honors

1987 Scholarship award from the German Academic Scholarship Foundation (Studienstiftung)
1990 Summa cum laude award for PhD work (University of Heidelberg)
2017 Award for Scientific Excellence (Experimental Therapeutics Centre, Singapore)

C. Contributions to Science

I Discovery of a series of novel leads with demonstrated exposure, tolerability and *in vivo* efficacy against *M. abscessus* (de novo drug discovery)

In the following, four selected projects (**I-IV**) from my 2018/24 (NIH-funded) portfolio are described. **V** highlights some significant contributions before 2018. Only selected publications are mentioned. For a full publication list see 'Thomas Dick, PhD' at Google Scholar.

Historical background of scientific problem: The preclinical drug pipeline for NTM is thinly populated. Our goal is to populate the pipeline with novel advanced leads and to deliver preclinical development compounds. We showed that collections of TB active compounds provide a rich source for the identification of novel anti-NTM hits. Thus, we hypothesized that screening chemical matter generated for TB could fast-track NTM drug discovery.

Main finding(s): In collaboration with GSK (1,2), Evotec (3), and Merck (4) we screened anti-TB compound collections and series against NTM and were indeed able to identify high value hits that could be rapidly progressed to advanced leads with demonstrated *in vivo* efficacy against NTM. Parallel target deconvolution identified the mechanism of action of the leads.

Impact of finding(s) on science/health or technology: This work enriched the NTM pipeline with advanced lead compounds. Importantly, the results support our strategy to exploit chemical matter generated in TB drug discovery efforts for fast-tracking NTM drug discovery. Furthermore, our results suggest that broad spectrum antimycobacterials (covering both NTM and TB disease) are feasible.

Role: PI

1. Ganapathy US, del Río RG, Cacho-Izquierdo M, Ortega F, Lelièvre J, Barros-Aguirre D, Aragaw WW, Zimmerman MD, Lindman M, Dartois V, Gengenbacher M, **Dick T.** A *Mycobacterium tuberculosis* NBTI DNA gyrase inhibitor is active against *Mycobacterium abscessus*. **Antimicrob Agents Chemother. 2021**; 65(12):e0151421. PMC8597734.
2. Ganapathy US, del Rio RG, Cacho-Izquierdo M, Ortega F, Lelièvre J, Barros-Aguirre D, Lindman M, Dartois V, Gengenbacher M, **Dick T.** A Leucyl-tRNA Synthetase Inhibitor with Broad-Spectrum Anti-Mycobacterial Activity. **Antimicrob Agents Chemother. 2021**; 65:e02420-20. PMC8092876.
3. Aragaw WW, Roubert C, Fontaine E, Lagrange S, Zimmerman MD, Dartois V, Gengenbacher M, **Dick T.** Cyclohexyl-griselimycin is active against *Mycobacterium abscessus* in mice. **Antimicrob Agents Chemother. 2022**; 66:e0140021. PMC8765428.
4. Madani A, Negatu DA, El Marrouni A, Miller RR, Boyce CW, Murgolo N, Bungard CJ, Zimmerman MD, Dartois V, Gengenbacher M, Olsen DB, **Dick T.** Activity of Tricyclic Pyrrolopyrimidine Gyrase B Inhibitor against *Mycobacterium abscessus*. **Antimicrob Agents Chemother. 2022;** 25:e0066922. PMC9487482**.**

II Determination of the intrinsic resistance mechanisms of *M. abscessus* against rifamycins and identification of rifabutin-derived leads overcoming intrinsic resistance (drug re-engineering)

Historical background of scientific problem: Rifampicin is a key sterilizing drug in the treatment of TB. However, this rifamycin is inactive against the NTM *M. abscessus* in vitro and not used clinically. Inclusion of a potent rifamycin in the poorly performing anti-*M. abscessus* regimens is expected to improve clinical outcomes.

Main finding(s): A screen of FDA approved drugs identified the rifampicin analog rifabutin as reasonably (**μM**) active *in vitro* and efficacious in a mouse model of *M. abscessus* lung infection, thus suggesting rifabutin as an attractive lead compound (1). We found that this RNA polymerase inhibitor suppresses inducible macrolide resistance, a major issue in the treatment of *M. abscessus* lung disease. Bacterial cell pharmacokinetic analyses revealed the mechanism why rifabutin is more active than rifampicin (rifampicin is substrate of bacterial monooxygenases) and showed that both rifampicin and rifabutin are inactivated by ADP-ribosylation, explaining the general intrinsic resistance of *M. abscessus* to rifamycins (2). In a proof-of-concept study we demonstrated that chemical blocking of the ADP-ribosylation site in rifabutin is possible without affecting target engagement (2). In collaboration with the Aldrich lab (U Minnesota) we are using a structure-based approach to redesign rifamycins through modifications of the ansa-chain to block ADP-ribosylation. Validated by a combination of biochemical, structural, microbiological, and *in vivo* studies, the most potent analogs overcome

ADP-ribosylation, and restore their intrinsic **nM** activity, efficacy (3) and bactericidal activity against drug tolerant persister bacteria in caseum (4). The lead compounds also display improved activity against other ADP-ribosylase positive rapid-growing (e.g. *M. chelonae*, *M. fortuitum*) and some slow-growing NTM (e.g. *M. simiae*).
Impact of finding(s) on science/health or technology: This work provides advanced lead compounds and a rational path for the generation of a potent rifamycin drug candidate for the treatment *M. abscessus* and other NTM lung diseases.
Role: PI

1. **Dick T**, Shin SJ, Koh WJ, Dartois V, Gengenbacher M. Rifabutin Is Active against *Mycobacterium abscessus* in Mice. **Antimicrob Agents Chemother. 2020**; 64:e01943-19. PMC6985736.
2. Ganapathy US, Lan T, Krastel P, Lindman M, Zimmerman MD, Sarathy JP, Evans JC, Dartois V, Aldrich CC, **Dick T.** Blocking bacterial naphthohydroquinone oxidation and ADP-ribosylation improves activity of rifamycins against *Mycobacterium abscessus*. **Antimicrob Agents Chemother. 2021**; 65:e0097821. PMC8370238.
3. Lan T, Ganapathy US, Sharma S, Ahn Y-M, Zimmerman MD, Molodtsov V, Hegde P, Gengenbacher M, Ebright RE, Dartois V, Freundlich JS, **Dick T***, Aldrich CC*. Redesign of Rifamycin Antibiotics to Overcome ADP-Ribosylation-Mediated Resistance. **Angew Chem Int Ed Engl**. **2022**; 61(45):e202211498. *corresponding authors. PMC9633546
4. Xie M, Ganapathy US, Lan T, Osiecki P, Sarathy JP, Dartois V, Aldrich CC, **Dick T**. ADP-ribosylation-resistant rifabutin analogs show improved bactericidal activity against drug-tolerant *M. abscessus* in caseum surrogate. **Antimicrob Agents Chemother. 2023**; 26:e0038123. PMC10508146.

III Discovery of potent *oral* β-lactams and β-lactam combinations against *M. abscessus* (drug repurposing)
Historical background of scientific problem: Imipenem and cefoxitin are in clinical use for the treatment of *M. abscessus* lung disease. However, these two β-lactams show poor activity in vitro and are injectables, severely limiting their clinical utility. Potent and oral β-lactams are expected to improve clinical outcomes. A significant number of oral β-lactams and oral β-lactamase inhibitors are in clinical use or clinical development for other disease indications. However, these drugs and their combinations have not been systematically evaluated for activity against *M. abscessus*.
Main finding(s): Bioactive forms of oral β-lactams were screened in vitro against *M. abscessus* with and without the bioactive form of the oral β-lactamase inhibitor avibactam ARX1796. Sulopenem was equally active without avibactam, while tebipenem, cefuroxime, and amoxicillin required avibactam for optimal activity. Systematic pairwise combination of the four β-lactams revealed strong bactericidal synergy for each of sulopenem, tebipenem, and cefuroxime combined with amoxicillin in the presence of avibactam (1). For oral tebipenem-avibactam efficacy was demonstrated in a mouse model of *M. abscessus* lung Infection (2).
Impacts of finding(s) on science/health or technology: These all-oral β-lactam combinations warrant clinical evaluation. Positive results may have a major impact on *M. abscessus* treatments.
Role: PI

1. Negatu DA, Zimmerman MD, Dartois V, **Dick T.** Strongly Bactericidal All-Oral β-Lactam Combinations for the Treatment of *Mycobacterium abscessus* Lung Disease. **Antimicrob Agents Chemother. 2022**; 66(9):e0079022. PMC9487536.
2. Negatu DA, González Del Río R, Cacho-Izquierdo M, Barros-Aguirre D, Lelievre J, Rullas J, Casado P, Ganapathy US, Zimmerman MD, Gengenbacher M, Dartois V, **Dick T.** Activity of Oral Tebipenem-Avibactam in a Mouse Model of Mycobacterium abscessus Lung Infection. **Antimicrob Agents Chemother. 2023**; 23:e0145922. PMC9933631.

IV Identification of the first antibacterial acting as a target degrader (TB drug discovery)
Historical background of scientific problem: Pyrazinamide (PZA) is a key sterilizing drug for the treatment of TB. However, *in vitro* potency against *M. tuberculosis* is poor. A more potent PZA is expected to shorten therapy of TB. To enable a rational, target-based optimization for the delivery of a next generation PZA, the mechanism of action needed to be determined.
Main finding(s): We found that PZA inhibits coenzyme A biosynthesis in *M. tuberculosis* by blocking the aspartate decarboxylase (PanD) catalyzed step. Surprisingly, we discovered that the drug acts by triggering degradation of its target (rather than only inhibiting PanD's catalytic activity). Binding of the drug induces

conformational changes in PanD, triggering proteolytic degradation of the enzyme by the bacterial caseinolytic protease complex (1). Thus, PZA kills the tubercle bacillus by inducing a suicidal response in which the bacterium 'eats-up' one of its essential enzymes.
Impact of finding(s) on science/health or technology: Targeted protein degradation (TPD) is a novel concept in drug discovery for human diseases. With PZA, the first antibiotic was identified that exerts its antimicrobial activity via TPD, providing proof of concept that this approach can also employed for antibiotics. Our discovery stimulated interest in the antibacterial field to explore PROTAC-like approaches. We are exploiting our mechanistic insights for the discovery of next generation PZA (2,3,4).
Role: PI

1.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.** Pyrazinamide triggers degradation of its target aspartate decarboxylase. **Nat Commun. 2020**; 11:1661. PMC7125159.
2.Ragunathan P, Cole M, Latka C, Aragaw WW, Hedge P, Shin J, Manimekalai MSS, Rishikesan S, Aldrich CC*, **Dick T***, Grüber G*. *Mycobacterium tuberculosis* PanD structure-function analysis and identification of a potent pyrazinoic acid-derived enzyme inhibitor. *corresponding authors. **ACS Chem Biol. 2021**; 16:1030–1039. PMC8217388.
3.Saw WG, Leow CY, Harikishore A, Shin J, Cole MS, Aragaw WW, Ragunathan P, Hegde P, Aldrich CC*, **Dick T***, Grüber G*. Structural and Mechanistic Insights into *Mycobacterium abscessus* Aspartate Decarboxylase PanD and a Pyrazinoic Acid-Derived Inhibitor. *corresponding authors. **ACS Infect Dis. 2022**; 8:1324-1335. PMC10517418.
4.Sarathy JP, Aldrich CC, Go ML, **Dick T.** PROTAC antibiotics: the time is now. **Expert Opin Drug Discov**. **2023**; 18(4):363-370. PMC10540314.

V Selected contributions to mycobacteriology and drug discovery before NIH funding (i.e., before 2018)
Work carried out as PI at IMCB & NUS, and as Head of TB at Novartis in **Singapore from 1996 to 2017** with funding from the Singapore Agency of Science Technology and Research, Novartis, The Bill and Melinda Gates Foundation, and the Singapore National Medical Research Council:
Examples for some impactful contributions from my work in Singapore includes a landmark review on TB research, drug discovery and development in 2009 (1) by the PIs of the Bill and Melinda Gates Foundation-funded consortium 'Grand Challenges in Global Health 11 - TB' (led by D Young, Imperial College). This road map document had a major impact on the research directions and approaches in the disease area (cited >1,600 times). Importantly, this publication contributed to the move away from the simplistic (and largely unsuccessful) genome-driven target-based drug discovery approach (industry standard in the 2000s) towards whole cell approaches coupled to target deconvolution. Noteworthy primary research publications (cited ~300 times) on mycobacteriology and drug discovery: I discovered the genetic basis of the mycobacterial dormancy response (*dosR* regulon), and thus identified a molecular framework underlying the formation of drug tolerant mycobacteria (2). I developed *in vitro* models for growing drug tolerant mycobacteria (3), and identified major pitfalls associated with whole cell approaches - and suggested solutions to overcome them (4).

1.Barry CE 3rd, Boshoff HI, Dartois V, **Dick T**, Ehrt S, Flynn J, Schnappinger D, Wilkinson RJ, Young D. The spectrum of latent tuberculosis: rethinking the biology and intervention strategies. **Nat Rev Microbiol**. **2009**; 7:845-55. PMC4144869.
2.Boon C, **Dick T.** *Mycobacterium bovis* BCG response regulator essential for hypoxic dormancy. **J Bacteriol. 2002**; 184:6760-7. PMC135468.
3.Gengenbacher M, Rao SPS, Pethe K, **Dick T.** Nutrient-starved, non-replicating *Mycobacterium tuberculosis* requires respiration, ATP synthase and isocitrate lyase for maintenance of ATP homeostasis and viability. **Microbiology**. **2010**; 156(Pt 1):81-87. PMID: 19797356.
4.Pethe K, Sequeira PC, Agarwalla S, Rhee K, Kuhen K, Phong WY, Patel V, Beer D, Walker JR, Duraiswamy J, Jiricek J, Keller TH, Chatterjee A, Tan MP, Ujjini M, Rao SP, Camacho L, Bifani P, Mak PA, Ma I, Barnes SW, Chen Z, Plouffe D, Thayalan P, Ng SH, Au M, Lee BH, Tan BH, Ravindran S, Nanjundappa M, Lin X, Goh A, Lakshminarayana SB, Shoen C, Cynamon M, Kreiswirth B, Dartois V, Peters EC, Glynne R, Brenner S, **Dick T.** A chemical genetic screen in *Mycobacterium tuberculosis* identifies carbon-source-dependent growth inhibitors devoid of in vivo efficacy. **Nat Commun**. **2010**; 1:57. PMC3220188.

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/