BIOGRAPHICAL SKETCH

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NAME: DICK, Thomas

eRA COMMONS USER NAME: TDICK367

POSITION TITLE: Professor

EDUCATION/TRAINING

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
Agency for Science Technology and Research, Singapore	Postdoc	08/1996	Developmental Biology

A. Personal Statement

I have over 20 years of experience in **mycobacteriology** and **antimycobacterial drug discovery**, as evidenced by my 200+ publications, h-index of 64, i10-index of 170, and D-index of 59. I currently hold positions as a Member at the Center for Discovery and Innovation, Hackensack Meridian Health (CDI, Nutley, NJ), and Professor at the Hackensack Meridian School of Medicine (Nutley, NJ) and Georgetown University (Washington, DC). Prior to my current roles, I served as Associate Professor at the National University of Singapore (NUS), Executive Director Tuberculosis (TB) at Novartis, and Principal Investigator at the Singapore Agency for Science Technology and Research (A*STAR).

Since relocating to the United States in 2017, I have secured NIH funding to support my research. This has led to the identification of a series of advanced antimycobacterial leads, characterized by their demonstrated exposure, tolerability, and efficacy in mouse infection models. Furthermore, I have advanced one compound to preclinical development and identified several promising repurposing candidates. This work, coupled with investigations into mechanisms of action and resistance, has resulted in ~100 publications and one patent.

Before my move to the U.S., I exclusively focused on discovering novel antibiotics for TB treatment. In recent years, I have increasingly shifted my attention to the neglected lung disease caused by Non-Tuberculous Mycobacteria (NTM), particularly *M. abscessus* infections.

My research aims to populate the NTM drug pipeline through a two-pronged approach: **de novo drug discovery**, identifying new target-lead couples, and **drug re-engineering**, optimizing approved drugs for improved efficacy. Furthermore, we actively seek to **repurpose drugs** in clinical use or development for other diseases to rapidly address the unmet needs of NTM patients.

At CDI, I have established a comprehensive NTM drug discovery platform, equipped with state-of-the-art in vitro bacteriology and in vivo pharmacology tools. Collaborating with medicinal chemistry partners from industry and academia, I have developed a promising portfolio that lays the foundation for accelerating the discovery of all-oral curative regimens for NTM lung disease. Given my extensive experience in mycobacteriology, antibiotic discovery, and leading multidisciplinary teams, I am well-positioned to spearhead programs and projects focused on the discovery of novel anti-mycobacterial agents.

Ongoing projects that I would like to highlight:

R01AI184502
Dick, PI
01/21/2025-12/31/*2029*
Shorter and more effective oral regimens for *M. abscessus* pulmonary disease
2R01AI132374-07A1

Dick, PI
02/01/2018-04/30/*2029*
Discovery of novel lead-target pairs and identification of all-oral bactericidal drug regimens for *Mycobacterium abscessus* lung disease
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
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
U19 AI142731
Perlin, PI, Role: project PI
05/01/2019-04/30/*2025* (in NCE)
Centre to develop innovative therapeutics to multidrug resistant high-threat bacterial agents
Project: Repositioning oxazolidinones and rifamycins for NTM lung disease

Citations (selected recent reviews):
1.Dartois V, **Dick T.** Drug development challenges in nontuberculous mycobacterial lung disease: TB to the rescue. J Exp Med. **2022**; 219(6). PMID: 35543723.
2.Dartois V, **Dick T.** Toward better cures for Mycobacterium abscessus lung disease. Clin Microbiol Rev. **2024**; e0008023. PMID: 39360834.
3.Dartois V, **Dick T.** Therapeutic developments for tuberculosis and nontuberculous mycobacterial lung disease. Nat Rev Drug Discov. **2024**; 23(5):381-403. PMID: 38418662.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2022-Present	Member of NIH study sections (TB / NTM, antibacterial drug discovery)
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 Singapore National Medical Research Council study sections
2012-2013	TB drug discovery consultant for Agency for Science Technology and Research (A*STAR) Singapore
2003-2011	Unit Head (Executive Director) Tuberculosis (2007 Senior Unit Head), 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 (IMCB), A*STAR
1996-2003	Principal Investigator, Mycobacterium Laboratory, IMCB, A*STAR

Honors

1987	PhD 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 Novel Leads for *M. abscessus*: A De Novo Drug Discovery Approach

In the following, four recent projects (I-IV) from my 2018-2025 NIH-funded portfolio are described. V highlights significant contributions prior to 2018. For a comprehensive publication list, please refer to "Thomas Dick, PhD" on Google Scholar.

Background The preclinical drug pipeline for Non-Tuberculous Mycobacteria (NTM) remains notably underdeveloped. Our goal is to enrich this pipeline with novel leads and deliver preclinical development compounds. Our previous research has shown that collections of TB-actives offer a rich source for identifying anti-NTM hits. Building on this insight, we hypothesized that screening chemical matter generated for TB could accelerate NTM drug discovery.

Key Findings In collaboration with GSK (1,2), Evotec (3), and Merck (4), we screened anti-TB compound collections against NTM. This approach yielded high value hit series that could be rapidly advanced to lead compounds with demonstrated in vivo efficacy against NTM. Parallel target deconvolution efforts elucidated the mechanism of action of the leads.

Impact This work has significantly enriched the NTM drug pipeline by providing lead compounds. Importantly, these results validate our strategy of leveraging chemical matter from TB drug discovery to accelerate NTM drug discovery. Furthermore, our findings suggest the feasibility of developing broad-spectrum anti-mycobacterials that can target both NTM and TB.

Role Principal Investigator

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. PMID: 33558292.

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. PMID: 33558292.

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. PMID: 34723632.

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. PMID: 36005813**.**

II. Identification of a Rifamycin Preclinical Development Candidate (PDC) Overcoming Intrinsic Resistance in *M. abscessus* (Drug Re-engineering) and development of an all-oral, sterilizing regimen

Background Rifamycins, key sterilizing drugs in TB treatment, are poorly active against *M. abscessus* due to intrinsic resistance mediated by bacterial ADP-ribosylation. Furthermore, rifamycins suffer from a drug-drug interaction (DDI) liability (CYP3A4 induction). Thus, the drug is not clinically used against *M. abscessus* infections. Incorporating a potent and DDI-free rifamycin into NTM treatment regimens is expected to significantly improve clinical outcomes.

Key Findings In a hit-to-lead project with the Aldrich lab (University of Minnesota), we modified rifabutin to block ADP-ribosylation, generating analogs with nM potency (1). In a lead optimization project, we eliminated the DDI liability and improved pharmacokinetic properties & efficacy in a mouse model of *M. abscessus* lung disease (2,3). In parallel we have generated a flowchart and a drug combination backbone for the development of an all-oral regimen containing a rifamycin as cornerstone (4).

Impact This work has yielded a rifamycin Preclinical Development Candidate (PDC) for *M. abscessus* and other rapid-growing NTM and is currently advancing towards IND-enabling studies. The work on drug combinations is expected to deliver an all-oral, sterilizing regimen ready for entering clinical trials.

Role Principal Investigator

1.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. PMID: 36222275.

2.Aldrich CC, Lan T, **Dick T**, Ganapathy U, Dartois V, Zimmerman M, Gengenbacher M. Rifamycins for nontuberculous mycobacteria. Publication No. WO/2024/076693, Publication Date 11.04.**2024**. International

Application No. PCT/US2023/034573, International Filing Date 05.10.2023. Priority Data 63/413,472, 05.10.2022, US. Available: https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2024076693
3.Dartois V, Lan T, Ganapathy US, Wong CF, Sarathy JP, Gimenez DC, Alshiraihi IM, Lam H, Rodriguez S, Xie M, Soto-Ojeda M, Jackson M, Wheat W, Dillman NC, Kostenkova K, Schmitt J, Mann L, Richter A, Imming P, Sarathy J, Kaya F, Paruchuri S, Tatek B, Folvar C, Proietto J, Zimmerman M, Gonzalez-Juarrero M, Aldrich CA, and **Dick T**. Next generation rifamycins for the treatment of mycobacterial infections. Under review.
4.Sarathy JP, Xie M, Wong CF, Negatu DA, Rodriguez S, Zimmerman MD, Jimenez DC, Alshiraihi IM, Gonzalez-Juarrero M, Dartois V and **Dick T**. Towards a bactericidal oral drug combination for the treatment of Mycobacterium abscessus lung disease. *ACS Infect Dis* **2025**, in press.

III. Discovery of Synergistic Bactericidal Dual β-Lactam Combinations Against NTM and TB (Drug Repurposing)

Background β-lactams are typically not employed in the treatment of NTM or TB infections. While imipenem and cefoxitin are used clinically for *M. abscessus* lung disease, their poor in vitro activity and parenteral administration limit their utility. Potent, orally available β-lactams could significantly improve clinical outcomes. Numerous oral β-lactams and β-lactamase inhibitors are currently in clinical use or development for other diseases, but their activity against NTM and TB, particularly in combination, remains largely unexplored.
Key Findings In collaboration with GSK and Iterum Therapeutics, we screened oral β-lactams against *M. abscessus* (1,2), MAC (3), and TB (4), both alone and in combination with oral β-lactamase inhibitors. A systematic pairwise combination of active β-lactams revealed potent bactericidal synergy between specific β-lactams from different classes (carbapenem, cephalosporin, penicillin) at clinically achievable concentrations.
Impact Our research has identified FDA-approved drugs as potential repurposing candidates, including the Sulopenem + Cefuroxime combination for *M. abscessus* and MAC infections. These all-oral dual β-lactam combinations may offer treatment options for patients with recalcitrant infections, especially when standard therapies are ineffective or contraindicated.
Role Principal Investigator
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. PMID: 36047786.
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. PMID: 36688684.
3.Negatu DA, Shin SJ, Kim SY, Jhun BW, Dartois V, **Dick T**. Oral β-lactam pairs for the treatment of Mycobacterium avium complex pulmonary disease. J Infect Dis. **2024**; 230(2):e241-e246. PMID: 38150401.
4.Negatu DA, Aragaw WW, Dartois V, **Dick T.** A pairwise approach to revitalize β-lactams for the treatment of TB. Antimicrob Agents Chemother. **2024** 1:e0003424. PMID: 38690896.

IV. Identification of the First Antibacterial Acting as a Target Degrader

Background Pyrazinamide (PZA) is a crucial sterilizing agent in TB treatment. Despite its clinical efficacy, PZA exhibits poor in vitro potency against *M. tuberculosis*. A more potent PZA analog could potentially shorten TB therapy. To enable rational, target-based optimization of PZA, elucidating its mechanism of action was needed.
Key Findings We discovered that PZA inhibits coenzyme A biosynthesis in TB by targeting aspartate decarboxylase (PanD). Surprisingly, PZA does not inhibit PanD's catalytic activity but instead induces its degradation. Binding of PZA to PanD triggers conformational changes, leading to the enzyme's proteolytic degradation by the bacterial ClpP protease complex (1). Thus, PZA kills the tubercle bacillus by eliciting a suicidal response, where the bacterium self-destructs by degrading an essential enzyme. After detailed structure-function studies of TB PanD and structure-activity relationship (SAR) analyses (2), we expanded our investigation to *M. abscessus* PanD (3), providing the foundation for structure-based lead optimization against both TB and NTM.
Impact Targeted protein degradation (TPD) is a novel drug discovery paradigm for human diseases. The identification of PZA as the first antibiotic utilizing TPD as its mechanism of action provides proof-of-concept for this approach in antimicrobial drug development. Our discovery has stimulated interest in exploring PROTAC-like strategies within the antibacterial field (4).
Role Principal Investigator

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. PMID: 32245967.
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. ACS Chem Biol. **2021**; 16:1030–1039. PMID: 33984234.
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. ACS Infect Dis. **2022**; 8:1324-1335. PMID: 35731701.
4.Sarathy JP, Aldrich CC, Go ML, **Dick T.** PROTAC antibiotics: the time is now. Expert Opin Drug Discov. **2023**; 18(4):363-370. PMID: 37027333.

V. Selected Contributions to Mycobacteriology and Drug Discovery Before NIH Funding

As Principal Investigator at A*STAR and National University, and as Executive Director TB at Novartis in Singapore from 1996 to 2017, I led numerous impactful research projects funded by A*STAR, the National Medical Research Council, Novartis and the Bill & Melinda Gates Foundation. Some of my most significant contributions include:
- A landmark review on TB research, drug discovery, and development in 2009 (1) as part of the 'Grand Challenges in Global Health 11' program (led by D. Young, Imperial College). This influential document, cited over 1,700 times, shaped the research landscape in the field, advocating for instance for a shift away from simplistic, genome-driven target-based drug discovery approaches (prevalent in the 2000s) towards whole-cell approaches coupled with target deconvolution.
- Pioneering research on the genetic basis of the mycobacterial dormancy response (*dosR* regulon) (2), providing insights into the molecular mechanisms underlying the formation of drug-tolerant mycobacteria.
- Development of in vitro models for cultivating drug-tolerant mycobacteria (3), enabling a deeper understanding of their biology and potential treatment strategies.
- Identification of pitfalls associated with whole-cell approaches and solutions to overcome these challenges (4). These contributions had a lasting impact on the field of mycobacteriology and drug discovery, advancing our understanding of these complex diseases and informing the development of novel therapeutic strategies.

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. PMID: 19855401.
2.Boon C, **Dick T.** Mycobacterium bovis BCG response regulator essential for hypoxic dormancy. J Bacteriol. **2002**; 184:6760-7. PMID: 12446625.
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,..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. PMID: 20975714.

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/