## 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 am Professor of Microbiology with more than 20 years of experience in **mycobacteriology** and **antimycobacterial drug discovery** (>150 papers, h-index: 52; i10-index: 129). 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 9 advanced antimycobacterial leads**, defined as compounds with demonstrated **exposure, tolerability and efficacy** in mouse infection models. **Mechanisms of action and resistance were elucidated for 12 leads**. My work since 2018 resulted total number of **~60 peer reviewed publications.**

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

The goal of my research is to determine the mechanism of action/resistance of antimycobacterials, and to exploit this knowledge for the delivery of **novel lead-target couples** with demonstrated *in vivo* efficacy and **preclinical development compounds**. I populate the preclinical NTM drug pipeline employing a two-pronged approach: **de novo drug discovery** (new targets and / or new chemotypes) and **drug repositioning** (improving approved drugs by chemical optimization).

Due to my experience in antibiotic discovery and management of multidisciplinary teams, I am well suited to lead the proposed project on the discovery of novel anti-*M. abscessus* agents and combinations. At CDI, I established a **fully enabled and productive NTM drug discovery platform**. The platform includes strain collections, *in vitro* potency assays, and *in vivo* (mouse) pharmacology and efficacy models. Target deconvolution and resistance analysis complement our compound profiling capabilities. With proven **medicinal chemistry partners** from industry (including GSK, Novartis, Evotec, Merck), not-for-profit organizations (TB Alliance, Medicines for Malaria Venture/MMV), and academia, I developed a substantial and attractive **anti-*M. abscessus* project portfolio** which provides an excellent foundation for the proposed work which will accelerate the discovery and development of all-oral curative regimens against this dreadful disease.

Ongoing projects that I would like to highlight:
R01 AI132374
Dick, PI

02/01/2018-01/31/2023
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

R01 AI106398
Dick-Dartois, MPI
06/01/2018-05/31/2023
Target-based discovery of next generation pyrazinamide

Citations (selected recent 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 | Member of NIH study section 'Drug Discovery and Mechanisms of Antimicrobial Resistance' |
| 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-Present | Associate Editor, Frontiers in Microbiology – Antimicrobials, Resistance and Chemotherapy |
| 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 section |
| 2012-2013 | TB drug discovery consultant for Agency for Science, Technology and Research Singapore |
| 2003-2011 | Unit Head Tuberculosis (from 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, 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 advanced leads with demonstrated exposure, tolerability and *in vivo* efficacy against non-tuberculous mycobacteria (NTM)**

In the following, four selected projects (**I-IV**) from my 2018/22 (i.e., NIH-funded) portfolio are described. **V** highlights some major contributions before 2018. Selected primary & senior-author research 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 this pipeline with novel advanced leads. 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, Evotec, Merck and Calibr we screened several anti-TB compound collections 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 (DNA gyrase (1), an aminoacyl-tRNA synthetase (2,3) and the DNA sliding clamp (4)).
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 in work: 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.Ganapathy US, Gengenbacher M, **Dick T.** Epetraborole is active against *Mycobacterium abscessus*. **Antimicrob Agents Chemother. 2021**; 65:e0115621. PMC8448144.

4.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.

**II Determination of intrinsic resistance mechanisms against rifamycins in *M. abscessus* and identification of rifabutin as repurposing and repositioning candidate**

Historical background of scientific problem: Rifampicin is a key sterilizing drug in the treatment of TB. However, this rifamycin is poorly active against the NTM *M. abscessus in vitro* and not used clinically. We hypothesize that inclusion of a rifamycin in the poorly performing anti-*M. abscessus* regimens could result in improvement of clinical outcomes. Thus, our goal is to identify a potent rifamycin to enable effective treatment of *M. abscessus* lung disease.
Main finding(s): A screen of FDA approved drugs identified the rifampicin analog rifabutin as reasonably active *in vitro* and in a mouse model of *M. abscessus* lung infection, thus presenting a repurposing candidate (1). Importantly, we found that this RNA polymerase inhibitor suppresses induction of macrolide resistance, a major issue in the treatment of *M. abscessus* lung disease (2). Bacterial cell pharmacokinetic analyses identified the mechanism why rifabutin is more active than rifampicin (rifampicin is substrate of bacterial oxidases) and revealed that both rifampicin and rifabutin are inactivated by ADP-ribosylation (explaining the general intrinsic 'resistance' of *M. abscessus* to rifamycins) (3). Importantly, we demonstrated that chemical blocking of the ADP-ribosylation site in rifabutin is possible without losing target engagement (3).

Impact of finding(s) on science/health or technology: This work identified a repurposing candidate (rifabutin) and provides a rational path for the generation of more potent rifabutins by blocking bacterial metabolism. The work also highlights the critical importance of bacterial cell pharmacokinetics in antibacterial drug discovery.
Role in work: 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.Aziz DB, Go ML, **Dick T.** Rifabutin Suppresses Inducible Clarithromycin Resistance in *Mycobacterium abscessus* by Blocking Induction of *whiB7* and *erm41*. **Antibiotics (Basel). 2020**; 9:72. PMC7168051

3.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.

**III Discovery of a novel, potent and selective triaza-coumarin inhibitor against TB dihydrofolate reductase (DHFR) and a novel 'bioaugmentation' approach to antibiotic discovery.**

Historical background of scientific problem: The folate pathway in *M. tuberculosis* is a validated drug target. However, we do not have a potent and selective DHFR inhibitor for the treatment of TB.
Main finding(s): In a target-based approach we identified a triaza-coumarin as a novel, potent and selective lead. Interestingly, the µM enzyme inhibitor displayed nM whole cell activity. Detailed mechanism of action studies revealed that the µM DHFR is converted to a nM DHFR inhibitor by bacterial metabolism (1). Thus, the bacterium commits suicide by converting a moderately potent enzyme inhibitor into a highly potent inhibitor. Triaza-coumarin is the first antimycobacterial prodrug that has baseline on-target activity before bio-activation.
Impact of finding(s) on science/health or technology: The novel selective anti-DHFR lead provides the substrate for a lead optimization campaign. Importantly, this work uncovered a novel 'bio-augmentation' approach which exploits bacterial metabolism to improve whole cell potency of biochemical hits.
Role in work: PI

1.Aragaw WW, Lee BM, Yang X, Zimmerman MD, Gengenbacher M, Dartois V, Chui WK, Jackson CJ, **Dick T.** Potency boost of a *Mycobacterium tuberculosis* dihydrofolate reductase inhibitor by multi-enzyme $F_{420}H_2$ dependent reduction. **Proc Natl Acad Sci USA. 2021**; 118e2025172118. PMC8237569.

**IV Determination of the mechanism of action of the anti-TB first line drug pyrazinamide and its exploitation for the discovery of next generation pyrazinamide**

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 as a target degrader (rather than an inhibitor of PanD's catalytic activity). Binding of the drug induces conformational changes in PanD, triggering proteolytic degradation of the enzyme by the caseinolytic protease complex of the bacterium (1). Thus, PZA kills the tubercle bacillus by inducing a suicidal molecular response in the proteome homeostatic network of the bacterium.
Impact of finding(s) on science/health or technology: With PZA, the first antibiotic was identified that exerts its antimicrobial activity via targeted protein degradation (TPD). The mechanistic insights are now being exploited for the discovery of more potent PanD degraders (2). Furthermore, this finding stimulated interest in the antibiotic field to explore PROTAC-like approached for the discovery of novel antibacterials.
Role in work: 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 C*, **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.

**V Selected contributions to mycobacteriology and drug discovery before NIH funding (i.e., before 2018)** (work carried out as PI and 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 >1,400 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 > 250 times) on mycobacteriology and drug discovery: I discovered the genetic basis of the mycobacterial dormancy response (*dosR* regulon), and thus identified the 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/