NIH Biographical Sketch Common Form

Name: Dick, Thomas

Persistent Identifier (PID) of the Senior/Key Person: https://orcid.org/0000-0002-9604-9452

Position Title: Professor

Organization and Location:Hackensack Meridian Health, Center for Discovery and Innovation, Nutley, New Jersey, United States

PROFESSIONAL PREPARATION

INSTITUTION AND LOCATION	DEGREE	Start Date	Completion Date	FIELD OF STUDY
Institute of Molecular and Cell Biology, Astar, Singapore, Not Applicable, N/A, SG	Postdoc	09/1990	08/1996	Developmental biology
Heidelberg University, Heidelberg, Not Applicable, N/A, DE	PhD	05/1987	06/1990	Molecular bacteriology
Heidelberg University, Heidelberg, Not Applicable, N/A, DE	MSc	10/1981	04/1987	Biochemistry, genetics, microbiology

Appointments and Positions

2019 - present	Professor, Hackensack Meridian Health, Center for Discovery and Innovation, Nutley, New Jersey, United States
2017 - 2019	Associate Professor & Director Antimicrobial Drug Discovery, Rutgers University Newark, Public Health Research Institute, Newark, New Jersey, United States
2011 - 2017	Associate Prof & Director BSL3 core , National University of Singapore, Department of Microbiology and Immunology, Singapore, Not Applicable, N/A, SG
2003 - 2011	Head, Novartis Institute for Tropical Diseases, Tuberculosis , Singapore, Not Applicable, N/A, SG
1996 - 2003	Assistant/Associate Professor, Institute of Molecular and Cell Biology, Astar, Singapore, Not Applicable, N/A, SG

Products

Products Closely Related to the Proposed Project

1. Dartois V, Lan T, Ganapathy US, Wong CF, Sarathy JP, Jimenez 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 CC, Dick T. Next-generation rifamycins for the treatment of mycobacterial infections. Proc Natl Acad Sci U S A. 2025 May 6;122(18):e2423842122. PubMed Central PMCID: PMC12067261.
2. Sarathy JP, Xie M, Wong CF, Negatu DA, Rodriguez S, Zimmerman MD, Jimenez DC, Alshiraihi IM, Gonzalez-Juarrero M, Dartois V, Dick T. Toward a Bactericidal Oral Drug Combination for the Treatment of Mycobacterium abscessus Lung Disease. ACS Infect Dis. 2025 Apr 11;11(4):929-939. PubMed Central PMCID: PMC11997990.
3. Lan T, Ganapathy US, Sharma S, Ahn YM, Zimmerman M, Molodtsov V, Hegde P, Gengenbacher M, Ebright RH, Dartois V, Freundlich JS, Dick T, Aldrich CC. Redesign of Rifamycin Antibiotics to Overcome ADP-Ribosylation-Mediated Resistance. Angew Chem Int Ed Engl. 2022 Nov 7;61(45):e202211498. PubMed Central PMCID: PMC9633546.
4. Dartois V, Dick T. Toward better cures for Mycobacterium abscessus lung disease. Clin Microbiol Rev. 2024 Dec 10;37(4):e0008023. PubMed Central PMCID: PMC11629636.
5. Dartois V, Dick T. Drug development challenges in nontuberculous mycobacterial lung disease: TB to the rescue. J Exp Med. 2022 Jun 6;219(6) PubMed Central PMCID: PMC9098649.

Other Significant Products, Whether or Not Related to the Proposed Project

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 Apr 3;11(1):1661. PubMed Central PMCID: PMC7125159.
2. 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 Aug 24;1(5):57. PubMed Central PMCID: PMC3220188.

3. 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 Dec;7(12):845-55. PubMed Central PMCID: PMC4144869.
4. Dartois V, Dick T. Therapeutic developments for tuberculosis and nontuberculous mycobacterial lung disease. Nat Rev Drug Discov. 2024 May;23(5):381-403. PubMed Central PMCID: PMC11078618.
5. Boon C, Dick T. Mycobacterium bovis BCG response regulator essential for hypoxic dormancy. J Bacteriol. 2002 Dec;184(24):6760-7. PubMed Central PMCID: PMC135468.

Certification:

I certify that the information provided is current, accurate, and complete. This includes but is not limited to information related to domestic and foreign appointments and positions.

I also certify that, at the time of submission, I am not a party to a malign foreign talent recruitment program.

Misrepresentations and/or omissions may be subject to prosecution and liability pursuant to, but not limited to, 18 U.S.C. §§ 287, 1001, 1031 and 31 U.S.C. §§ 3729-3733 and 3802.

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NIH BIOGRAPHICAL SKETCH SUPPLEMENT

Name: Dick, Thomas

Persistent Identifier (PID) of the Senior/Key Person: https://orcid.org/0000-0002-9604-9452

Position Title: Professor

Organization and Location: Hackensack Meridian Health, Center for Discovery and Innovation, Nutley, New Jersey, United States

Personal Statement

I have over 20 years of experience in mycobacteriology and antimycobacterial drug discovery, as evidenced by my 200+ publications (h-index of 69). I currently hold positions as a Member at the Center for Discovery and Innovation, Hackensack Meridian Health (CDI, Nutley, NJ), 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 US 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 models, including rifamycins in preclinical development. This work, coupled with investigations into mechanisms of action and resistance, has resulted in over 100 publications and one patent. Until 2017, 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. Our team follows a two-pronged approach to populate the NTM drug pipeline: de novo drug discovery, identifying new target-lead couples, and drug re-engineering approved drugs for improved efficacy. We also 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 bacteriology and in vivo pharmacology tools. Collaborating with medicinal chemists 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. Below is a list of active grant support: 1. C-Path TRxA#12357 Dick, PI; 04/01/2025-03/31/2026 Novel rifamycins to improve cure rates and shorten treatment of M. abscessus lung disease (RIF4Mab) 2. R01AI184502 Dick, PI; 01/21/2025-12/31/2029 Shorter and more effective oral regimens for M. abscessus pulmonary disease 3. R01AI132374 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 4. R01AI177342 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 5. 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 6. U19AI189168-01 Perlin, PI, Role: project #1 PI; 06/01/2025-05/31/2030 Centre to develop innovative therapeutics to multidrug resistant high-threat bacterial agents Project: Optimization of rifamycins to improve cure rates and shorten treatment of M. abscessus lung disease

Honors

2017 - 2020	Toh Chin Chye Visiting Professor, National University of Singapore
2017 - 2017	Award for Scientific Excellence , Experimental Therapeutics Centre, Singapore
1987 - 1987	PhD Scholarship award, German Academic Scholarship Foundation

Contribution to Science

1. Identification of a rifamycin Preclinical Development Candidate (PDC) overcoming intrinsic resistance in M. abscessus (Mab) and devoid of drug-drug interaction Background: Rifamycins, key sterilizing drugs in TB treatment, are poorly active against Mab 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 Mab infections. Incorporating a potent and DDI-free rifamycin into NTM treatment regimens is expected to significantly improve clinical outcomes. (Dartois V, Drug development challenges in nontuberculous mycobacterial lung disease: TB to the rescue. J Exp Med. 2022; Dartois V, Toward better cures for Mycobacterium abscessus lung disease. Clin Microbiol Rev. 2024) Key Findings: In a hit-to-lead project with the Aldrich lab (UMinn), we modified rifabutin to block ADP-ribosylation. In a lead optimization project, we

eliminated the DDI liability and improved pharmacokinetic properties & efficacy in a mouse model of Mab lung disease. 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. (Lan T, Redesign of Rifamycin Antibiotics to Overcome ADP-Ribosylation-Mediated Resistance. Angew Chem. 2022; Dartois V, Next-generation rifamycins for the treatment of mycobacterial infections. PNAS 2025; Sarathy JP, Toward a Bactericidal Oral Drug Combination for the Treatment of Mycobacterium abscessus Lung Disease. ACS ID 2025) Impact: This work has yielded a rifamycin Preclinical Development Candidate (PDC) for Mab and is currently advancing towards IND-enabling studies. The work on drug combinations is expected to deliver an all-oral regimen ready for entering clinical trials. Role: Principal Investigator

2. Identification of Pyrazinamide as 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. 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, we expanded our investigation to M. abscessus PanD, providing the foundation for structure-based lead optimization against both TB and NTM. (Gopal P, Pyrazinamide triggers degradation of its target aspartate decarboxylase. Nat Commun. 2020) Impact: Targeted protein degradation (TPD) is a drug discovery paradigm exploited largely 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. Role: Principal Investigator
3. Identification of a major pitfall in whole cell screens for antimycobacterial drug discovery Background: After a major failure of target based (biochemical) approaches to hit finding, the TB drug discovery field moved to whole cell screens in the late 2000s. Key findings: At Novartis we were one of the first to implement this approach. We identified a highly active hit and optimized potency and PK to generate a lead compound with excellent in vitro activity and favorable pharmacological properties. Surprisingly, the optimized lead showed no efficacy in a mouse model of TB lung disease. To determine the cause of this fatal disconnect we engaged in a major program. We identified glycerol - used in standard mycobacterium media as a carbon source - as the culprit. The lead activity was glycerol dependent - and there is not much glycerol in mouse lungs (Pethe K, A chemical genetic screen in Mycobacterium tuberculosis identifies carbon-source-dependent growth inhibitors devoid of in vivo efficacy. Nat Commun. 2010). Impact: This work had multiple impacts on the TB drug discovery field. Several companies and researcher checked their hits for glycerol dependence (before optimization) and found similar artifacts. This work triggered activities to test hits in more in vivo like media and / or to demonstrate medium independent activity before moving into medicinal chemistry activities. Role: Principal Investigator
4. Identification of the master regulator dosR of hypoxia-induced dormancy in mycobacteria Background: In vitro and in vivo evidence suggested that the obligate aerobe M. tuberculosis shifts to a state of non-replicating persistence (dormancy) when exposed to hypoxia. Importantly, these dormant bacilli are tolerant to killing by antibiotics and thus appear to contribute to the long treatment times. The genetic basis for this response was unknow. Key findings: We employed an in vitro culture model and proteomics to identify a candidate dormancy response regulator. Genetic studies demonstrated the essential role for this regulator (named dormancy survival regulator, dosR) for the execution of the response and maintaining viability of the bacilli under hypoxic conditions (Boon C, Dick T. Mycobacterium bovis BCG response regulator essential for hypoxic dormancy. J Bacteriol. 2002). Impact: This work identified the master regulator of the mycobacterial dormancy response. This finding triggered a huge activity in the field to dissect the mechanistic details, define the regulon and to provide in vivo evidence for the role of dormancy and dosR. In these works new, dormancy-specific targets, leads and vaccine candidates were identified. Role: Principal Investigator
5. Providing forward-looking reviews to guide the anti-TB and anti-NTM drug discovery and development field Background: The TB drug discovery and development landscape underwent a revolution over the past 20 years and is still evolving. The NTM drug discovery field is still in its infancy. Thus, there was and is a need for critical and forward looking reviews. Key findings: A landmark review on TB research, drug discovery and development in 2009 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 (Barry CE 3rd, The spectrum of latent tuberculosis: rethinking the biology and intervention strategies. Nat Rev Microbiol. 2009). Recently a 'follow-up review' on the field, extended to NTM research, was provided (Dartois V, Therapeutic developments for tuberculosis and nontuberculous mycobacterial lung disease. Nat Rev Drug Discov. 2024). Impact: These reviews helped to shape TB research activities and to move the field forward Role: Principal Investigator 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/

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