BIOGRAPHICAL SKETCH

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NAME: Jansy Passiflora Sarathy

eRA COMMONS USER NAME (credential, e.g., agency login): SARATHJA

POSITION TITLE: Assistant Member; Center for Discovery and Innovation, Hackensack Meridian Health

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
National University of Singapore; Singapore	BSc (Hons)	05/2008	Biomedical Science
Yong Loo Lin School of Medicine, National University of Singapore; Singapore	PhD	02/2014	Microbiology, Pharmacology
Novartis Institute for Tropical Diseases; Singapore			
Public Health Research Institute, Rutgers University; New Jersey	Postdoctoral	01/2016	Microbiology, Pharmacology

A. Personal Statement

I have been working in the field of tuberculosis (TB) research for almost 15 years. The bulk of my research efforts have been focused on enabling TB drug discovery via the study of pharmacokinetic and pharmacodynamics (PK-PD) properties of drugs. I have spent years investigating the distribution of TB drugs in specific in vivo sites of infection and unravelling mechanisms of phenotypic drug resistance in *Mycobacterium tuberculosis*. My experience working in both academic institutions and in the pharmaceutical sector gives me a unique perspective of translational research. I have co-authored 45 relevant scientific publications and have over 1,800 citations. I also have over 16 years of experience working on the pathogen *M. tuberculosis* (Mtb) in 4 different biosafety level 3 (BSL-3) facilities.

My current position as an Asst. Member at the HMH Center for Discovery and Innovation (CDI) requires me to manage a variety projects and services associated with TB drug discovery. Recently, I have been most invested in characterizing the metabolic state and drug susceptibility of Mtb that resides in caseous granulomas and cavities. I also manage the testing of drug discovery compounds from various collaborators in our *in vitro* PK and potency assays. Previously, I had spent six years at the Public Health Research Institute (PHRI) at Rutgers, a regional hub for TB research, gathering valuable knowledge, skills and experience. The impact of my collective post-grad work has helped [1] our understanding of drug efficacy, or lack thereof, in patients and animal models of TB infection and [2] inform the design of more efficacious and safer TB drug regimens by combining agents with complementary PK/PD properties. The bulk of my graduate work was conducted at the Novartis Institute for Tropical Diseases in Singapore, which blended ‘big pharma’ resources with basic scientific research to improve treatment options for neglected infectious diseases.

In the last few years, I have worked and interacted with numerous microbiologists, pharmacologists, PK modelers and medicinal chemists from various pharmaceutical companies and academic institutions. My personal work continues to provide invaluable support to two major tuberculosis research consortia and the TB drug discovery field overall.

Ongoing and recently completed projects that I would like to highlight include:

1UM1AI179699-01 (Savic PI, University of California SF) 03/2024 – 02/2029
Role: Co-Investigator
National Institutes of Health (NIH)
Preclinical design and clinical translation of TB regimens (PreDiCTR) consortium

INV-055894 (Schnappinger PI, Weill Cornell Medicine) 11/2023 – 10/2026
Role: Co-Investigator
Bill & Melinda Gates Foundation
Partial gene inactivation and pharmacological modulation of Mtb targets: Gene inactivation of Mtb targets in caseum and rabbits

INV-080650 (Robertson PI, Colorado State U) 12/2024 – 02/2026
Role: Co-Investigator
Bill & Melinda Gates Foundation
TB Drug Accelerator: TB Mouse in vivo Models

B. Positions and Employment

Employment

2023 – Current	Assistant Professor Hackensack Meridian School of Medicine, Nutley, NJ
2023 – Current	Assistant Member Hackensack Meridian Health, Center for Discovery and Innovation, Nutley, NJ
2020 – 2022	Sup. Research Assistant Member Hackensack Meridian Health, Center for Discovery and Innovation, Nutley, NJ
2019 – 2020	Research Associate / Project Manager Hackensack Meridian Health, Center for Discovery and Innovation, Nutley, NJ
2016 – 2019	Research Associate Public Health Research Institute, Rutgers University, Newark, NJ
2013 – 2015	Post-doctoral Research Fellow Public Health Research Institute, Rutgers University, Newark, NJ

Honors

2025	Member of the Tuberculosis Drug Accelerator, Gates Foundation
2023	New Jersey Health Foundation award

C. Contributions to Science

C.i. Dormancy and drug tolerance of Mtb in caseous granulomas and cavities

The caseous foci of TB lung granulomas and cavities are reservoirs of extracellular bacilli that are recalcitrant to antibiotic treatment, as proven by clinical observations and efficacy studies in various animal models of TB infection. My primary goal these last few years has been the novel study of intra-caseum Mtb, with specific focus on the replication state and drug susceptibility of this subpopulation. I leveraged access to excised caseum from the rabbit model of TB infection to develop an *in vitro* assay that measures drug potency against intra-caseum Mtb. I proved that this subpopulation exhibits extreme drug tolerance to many 1st- and 2nd-line TB drugs. The caseum minimum bactericidal concentration (casMBC) assay has also enabled us to compare TB drugs within the same class in an effort to help clinicians and public health officials select the most efficacious class member. We currently use this assay to profile the potency of preclinical compounds and lead compounds in various stages of the TB drug discovery pipeline. It has proven to be an effective tool at predicting treatment efficacy.

1. A Novel Tool to Identify Bactericidal Compounds against Vulnerable Targets in Drug-Tolerant M. tuberculosis found in Caseum. **Sarathy JP**, Xie M, Jones RM, Chang A, Osiecki P, Weiner D, Tsao WS,

Dougher M, Blanc L, Fotouhi N, Via LE, Barry CE 3rd, De Vlaminck I, Sherman DR, Dartois VA. mBio. 2023 Apr 25;14(2):e0059823.

2. Molecular and microbiological methods for the identification of nonreplicating Mycobacterium tuberculosis. **Sarathy JP**. PLoS Pathog. 2024 Oct 9;20(10):e1012595.
3. Caseum: a Niche for Mycobacterium tuberculosis Drug-Tolerant Persisters. **Sarathy JP,** Dartois V. Clin Microbiol Rev. 2020 Apr 1;33(3):e00159-19.
4. Extreme Drug Tolerance of Mycobacterium tuberculosis in Caseum. **Sarathy JP**, Via LE, Weiner D, Blanc L, Boshoff H, Eugenin EA, Barry CE 3rd, Dartois VA. Antimicrob Agents Chemother. 2018 Jan 25; 62(2).A Novel Tool to Identify Bactericidal Compounds against Vulnerable Targets in Drug-Tolerant M. tuberculosis found in Caseum. Sarathy JP, Xie M, Jones RM, Chang A, Osiecki P, Weiner D, Tsao WS, Dougher M, Blanc L, Fotouhi N, Via LE, Barry CE 3rd, De Vlaminck I, Sherman DR, Dartois VA. mBio. 2023 Apr 25;14(2):e0059823.

C.ii. Lesion-centric drug distribution studies in multiple animal models of TB infection

For the past several years, I have also supported the study of drug distribution and efficacy in the rabbit and mouse models of TB lung infection. Our group has demonstrated that different anti-TB agents exhibit very different patterns of distribution from blood to distinct and complex sites of infection. Specifically, our rabbit infection model has enabled the study of self-sterilization and drug-mediated sterilization of different kinds of TB lesion types. We use a combination of laser capture microdissection and mass spectrometry analytical methods to study drug penetration in C3HeB/FeJ mouse lesions too. We work with PK modelers to develop *in silico* models that extrapolate from our measures of drug efficacy and distribution to predict TB drug performance in different clinical dosing regimens. Our results are paving the way to informed design of new drug regimens that combine agents with complementary distribution into lesions and sublesional areas, a significant departure from current – mostly empirical – approaches.

1. Spectinamide MBX-4888A exhibits favorable lesion and tissue distribution and promotes treatment shortening in advanced murine models of tuberculosis. Bauman AA, **Sarathy JP**, Kaya F, Massoudi LM, Scherman MS, Hastings C, Liu J, Xie M, Brooks EJ, Ramey ME, Jones IL, Benedict ND, Maclaughlin MR, Miller-Dawson JA, Waidyarachchi SL, Butler MM, Bowlin TL, Zimmerman MD, Lenaerts AJ, Meibohm B, Gonzalez-Juarrero M, Lyons MA, Dartois V, Lee RE, Robertson GT. Antimicrob Agents Chemother. 2024 Sep 30:e0071624.
2. Drug distribution and efficacy of the DprE1 inhibitor BTZ-043 in the C3HeB/FeJ mouse tuberculosis model. Ramey ME, Kaya F, Bauman AA, Massoudi LM, **Sarathy JP**, Zimmerman MD, Scott DWL, Job AM, Miller-Dawson JA, Podell BK, Lyons MA, Dartois V, Lenaerts AJ, Robertson GT. Antimicrob Agents Chemother. 2023 Nov 15;67(11):e0059723.
3. Fluoroquinolone Efficacy against Tuberculosis Is Driven by Penetration into Lesions and Activity against Resident Bacterial Populations. **Sarathy J**, Blanc L, Alvarez N, O'Brien P, Dias-Freedman I, Mina M, Zimmerman M, Kaya F, Liang HP, Prideaux B, Dietzold J, Salgame P, Savic R, Linderman J, Kirschner D, Pienaar E, Dartois V. 2018. Antimicrob Agents Chemother. 2019 Feb; 63(5).
4. Lesion Penetration and Activity Limit the Utility of Second-Line Injectable Agents in Pulmonary Tuberculosis. Ernest JP, **Sarathy J**, Wang N, Kaya F, Zimmerman MD, Strydom N, Wang H, Xie M, Gengenbacher M, Via LE, Barry CE 3rd, Carter CL, Savic RM, Dartois V. Antimicrob Agents Chemother. 2021 Sep 17; 65(10).

C.iii. *in vitro* assay development for the study of drug PK-PD properties at the site-of-action

The penetration of antibiotics in necrotic tuberculosis lesions is heterogeneous and drug-specific, but the factors underlying such differential partitioning were unknown. This motivated my development of an *in vitro* assay that uses rapid equilibrium dialysis to measure drug binding in *ex vivo* caseum. We have shown that the unbound fraction in caseum correlates well with drug penetration in the caseous core of granulomas. I worked with chemists and modelers to develop an *in silico* model that predicts how physicochemical properties affect the partitioning of antibiotics into necrotic granulomas *in vivo*. I currently oversee the testing of drug candidates from the Bill and Melinda Gates Foundation –funded Tuberculosis Drug Accelerator (TBDA) in this caseum

binding assay and a macrophage drug uptake assay. We also developed a foamy macrophage infection model, from which we can extrapolate drug potency against intracellular Mtb in pulmonary granulomas. Another *in vitro* assay that I validated measures intracellular drug accumulation in Mtb bacilli. It has since helped decipher the mechanisms of antibiotic metabolism and resistance in Mtb.

1. Adaptation to the intracellular environment of primary human macrophages influences drug susceptibility of Mycobacterium tuberculosis. Lanni F, Wijnant GJ, Xie M, Osiecki P, Dartois V, **Sarathy JP**. Tuberculosis (Edinb). 2023 Mar; 139:102318.
2. Prediction of Drug Penetration in Tuberculosis Lesions. **Sarathy JP**, Zuccotto F, Hsinpin H, Sandberg L, Via LE, Marriner GA, Masquelin T, Wyatt P, Ray P, Dartois V. ACS Infect Dis. 2016 Aug 12;2(8):552-63.
3. An In Vitro Caseum Binding Assay that Predicts Drug Penetration in Tuberculosis Lesions. **Sarathy JP**, Liang HH, Weiner D, Gonzales J, Via LE, Dartois V. J Vis Exp. 2017 May 8;(123).
4. Reduced drug uptake in phenotypically resistant nutrient-starved nonreplicating Mycobacterium tuberculosis. **Sarathy J**, Dartois V, Dick T, Gengenbacher M. Antimicrob Agents Chemother. 2013 Apr;57(4):1648-53.

C. v. Identification of novel TB drug candidates with unique mechanisms of action

The increasing incidence rates of multidrug resistant (MDR) TB worldwide highlights the pressing need for new antibiotics with novel drug targets. An overarching goal of my work is to assist the identification of such agents through collaborative work with medicinal chemists and other microbiologists. As a member of the TB Drug Accelerator, our lab works closely with pharmaceutical companies and other research institutions to profile the PK-PD properties of drug candidates, develop translational models, and prioritize candidates for clinical trials. Most of this work, with the exception of the few projects below, involves proprietary information that we are not yet permitted to publish.

1. Targeting de novo purine biosynthesis for tuberculosis treatment. Lamprecht DA, Wall RJ, Leemans A, Truebody B, Sprangers J, Fiogbe P, Davies C, Wetzel J, Daems S, Pearson W, Pillay V, Saylock S, Ricketts MD, Davis E, Huff A, Grell T, Lin S, Gerber M, Vos A, Dallow J, Willcocks SJ, Roubert C, Sans S, Desorme A, Chappat N, Ray A, Pereira Moraes M, Washington T, D'Erasmo H, Sancheti P, Everaerts M, Monshouwer M, Esquivias J, Larrouy-Maumus G, Draghia Akli R, Fletcher H, Pym AS, Aldridge BB, **Sarathy JP**, Clancy KW, Stoops B, Dhar N, Steyn AJC, Jackson P, Aguilar-Pérez C, Koul A. Nature. 2025 Jun 18.
2. Next-generation rifamycins for the treatment of mycobacterial infections. 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. Proc Natl Acad Sci U S A. 2025 May 6;122(18):e2423842122.
3. Investigation into the Mechanism of Action of the Tuberculosis Drug Candidate SQ109 and Its Metabolites and Analogues in Mycobacteria. Malwal SR, Mazurek B, Ko J, Xie P, Barnes C, Varvitsiotis C, Zimmerman MD, Olatunji S, Lee J, Xie M, **Sarathy J**, Caffrey M, Strynadka NCJ, Dartois V, Dick T, Lee BNR, Russell DG, Oldfield E. J Med Chem. 2023 Jun 8;66(11):7553-7569.
4. Synergistic Lethality of a Binary Inhibitor of Mycobacterium tuberculosis KasA. Kumar P, Capodagli GC, Awasthi D, Shrestha R, Maharaja K, Sukheja P, Li SG, Inoyama D, Zimmerman M, Ho Liang HP, **Sarathy J**, Mina M, Rasic G, Russo R, Perryman AL, Richmann T, Gupta A, Singleton E, Verma S, Husain S, Soteropoulos P, Wang Z, Morris R, Porter G, Agnihotri G, Salgame P, Ekins S, Rhee KY, Connell N, Dartois V, Neiditch MB, Freundlich JS, Alland D. mBio. 2018 Dec 18;9(6):e02101-17.

Complete List of Published Work in MyBibliography:
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