BIOGRAPHICAL SKETCH

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NAME: Véronique A Dartois

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

POSITION TITLE: Professor, Hackensack School of Medicine at Seton Hall; Member, Center for Discovery and Innovation, Hackensack Meridian Health; Adjunct Professor, NJ Medical School, Rutgers University

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 Louvain-la-Neuve, Belgium	B.Sc.	1986	Biology
University of Louvain-la-Neuve, Belgium	PhD	1992	Microbiology
Scripps Research Institute, La Jolla, CA	Post-doct.	1993-1996	Microbial genetics
Pasteur Institute, Paris	Post-doct.	1997-1998	Microbial genetics

A. Personal Statement

I recently joined the new HMH Center for Discovery and Innovation (CDI) following six years at the Public Health Research Institute of Rutgers New Jersey Medical School where I assembled a research team focused on the pharmacology and imaging of anti-infective drugs at the site of disease. Previously, I spent 7 years in the pharmaceutical industry in the field of pharmacokinetics and pharmacodynamics (PK-PD) of new drugs for neglected diseases. As Executive Director and Pharmacology Unit Head, I managed a team of Research Associates, Post-doc Fellows and Principal Scientists to carry out in vitro and in vivo pharmacokinetics and efficacy studies supporting hit-to-lead, lead optimization and preclinical stages of drug discovery programs in Tuberculosis, Dengue fever and Malaria. At CDI, the research interests of our group include the fate of anti-mycobacterial drugs from plasma to tissues, pulmonary and CNS lesions, and single cells, including the spatial distribution of drugs at high resolution, and how this affects drug efficacy in animal models and in patients. Our group has access to a large, dedicated animal biosafety level-3 (BSL3) facility, as well as to the Rutgers Regional Biocontainment Lab, where we conduct PK and efficacy studies in animal models of mycobacterial infection and chronic TB disease, with a variety of inhalation systems to deliver aerosolized Mycobacteria and other high-threat pathogens to the lungs. We have a fully integrated analytical platform for the quantification of drugs, lipids and other small molecules in various biological matrices. This unique set-up offers ideal pharmacological and animal model support for the proposed project focusing on the metabolism, pharmacokinetics and pharmacodynamics of SQ109 in TB lesions, and the efficacy of SQ109-containing regimens in different mouse models. As highlighted below, I have published and/or am collaborating with the five MPIs and co-investigators on this grant application (two manuscripts with Dr Carol Nacy are currently in review at AAC and ACS ID). Our group has long-standing working relationships with Dr. Schnappinger, Aldridge, Savic and Nuermberger. Some of our co-funded grants and co-authored articles are listed below. Dr. Aldridge, Schnappinger and I are members of the BMGF-funded TB Drug accelerator, where we interact during monthly teleconferences and at two semiannual meetings.

Active funded projects that I would like to highlight:

R01 AI150684-01 (Aldridge-Dartois-Kirschner MPI) 04/01/20 - 3/31/25
NIH-NIAID
Lesion-centric optimization of multidrug therapies for tuberculosis
The major goal of this project is to prioritize new TB drug regimens by developing a data-driven pipeline that combines in vitro and in vivo measurements of drug action with mathematical modeling.

R01 AI145436-01A1 (Dartois-Wilkinson MPI) 04/01/20 - 3/31/25
NIH-NIAID
Translational approaches to improve understanding and outcome in Tuberculous meningitis
Our goal is to develop and validate tools to quantifying drug penetration at the site of disease, characterize disease progression, and model response therapy.

R01 AI106398 (Dartois-Dick, MPI) 06/01/18-05/31/23
Target-based discovery of next generation pyrazinamide
Goal: Identify pyrazinamide-derived anti-TB lead compounds with improved potency employing a target-based approach combined with novel ex vivo lesion penetration and sterilization assays

INV-004704 (Dartois PI) 12/01/12 – 11/30/22
Bill & Melinda Gates Foundation
Lesion PK/PD to design new drugs and drug combinations for TB
The major goal of this project is to prioritize new drug regimens for testing in TB clinical trials based on pharmacokinetics and pharmacodynamics in lesions.

INV002483 (Savic-Dartois) 08/28/19 – 9/30/22
Bill and Melinda Gates Foundation
TB Drug Lesion Penetration and Translational Modeling
Project goal: to build a translational rabbit-to-human pharmacokinetic-pharmacodynamic model to rationally prioritize drug regimens with the best potential to shorten TB therapy duration.

INV-004761 (Schnappinger) 11/01/20 – 10/31/23
Bill and Melinda Gates Foundation
Conditional M. tuberculosis knockdown mutants for TB drug discovery: Isolation of Mtb mutants resistant to TBDA compounds
The major goals of this project are to rank Mycobacterium tuberculosis proteins as targets for tuberculosis (TB) drug development and to identify strategies to shorten TB chemotherapy.
Role: co-investigator

INV-004764 (Schnappinger) 11/01/20 – 10/31/23
Bill & Melinda Gates Foundation
Partial gene inactivation and pharmacological modulation of Mtb targets: Gene inactivation of Mtb targets in caseum and rabbits
The major goal of this project is to accelerate target identification and in vitro pharmacological profiling of new compounds with anti-tuberculosis activity.
Role: co-investigator

Citations that highlight my experience, qualifications and interactions with other investigators involved in this project:

1. Strydom N, Gupta SV, Fox WS, Via LE, Bang H, Lee M, Eum S, Shim T, Barry CE 3rd, Zimmerman M, **Dartois V**, Savic RM. 2019. Tuberculosis drugs' distribution and emergence of resistance in patient's lung lesions: A mechanistic model and tool for regimen and dose optimization. **PLoS Med**. 2019 Apr 2;16(4):e1002773. PMCID: PMC6445413
2. Beites T, O'Brien K, Tiwari D, Engelhart CA, Walters S, Andrews J, Yang HJ, Sutphen ML, Weiner DM, Dayao EK, Zimmerman M, Prideaux B, Desai PV, Masquelin T, Via LE, **Dartois V**, Boshoff HI, Barry CE 3rd, Ehrt S, Schnappinger D. Plasticity of the Mycobacterium tuberculosis respiratory chain and its impact on tuberculosis drug development. **Nat Commun**. 2019 Oct 31;10(1):4970. PMCID: PMC6823465
3. Sarathy JP, **Dartois V**. Caseum: a Niche for *Mycobacterium tuberculosis* Drug-Tolerant Persisters. **Clin Microbiol Rev.** 2020 Apr 1;33(3). pii: e00159-19. PMCID: PMC7117546
4. Ernest JP, Strydom N, Wang Q, Zhang N, Nuermberger E, **Dartois V**, Savic RM. Development of New Tuberculosis Drugs: Translation to Regimen Composition for Drug-Sensitive and Multidrug-Resistant Tuberculosis. **Annu Rev Pharmacol Toxicol**. 2021 Jan 6;61:495-516. PMCID: PMC7790895

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2021	Professor (in waiting), Dept. of Microbiol & Immunol, Georgetown Univ SOM, Washington, D.C.
2019-	Member, Hackensack Meridian Health Center for Discovery and Innovation, Nutley,NJ
2019-	Professor, Dept. of Medical Sciences, Hackensack Meridian Health School of Medicine at Seton Hall
2014-	Associate Professor, New Jersey Medical School, Rutgers, The State University of New Jersey
2013-2019	Scientific Advisory Committee member, Drug Discovery Unit, University of Dundee
2012-2014	Assistant Professor, New Jersey Medical School, Public Health Research Institute of UMDNJ
2008-2012	Scientific Steering Committee member, International TB Research Institute, South Korea
2007-2012	Adjunct Assistant Professor, Department of Biological Science, Natl University of Singapore
2005-2012	Executive Director, Pharmacology, Novartis Institute for Tropical Diseases, Singapore
2004	Principal Scientist, Adaptive Therapeutics Inc., San Diego, CA
1997-2003	Principal Scientist, Embiosis Pharmaceuticals, Inc., Carlsbad, CA.
1996-1997	Postdoctoral Fellow, Dept. of Microbial Biochemistry, Pasteur Institute, Paris.
1993-1996	Postdoctoral Fellow, Division of Cell Biology, Scripps Research Institute, La Jolla, CA.

Honors

2019	Co-Chair of the Keystone Symposium on Tuberculosis: Mechanisms, Pathogenesis and Treatment (Banff, Canada)
2013	Co-Chair of the Gordon Research Conference on TB Drug Development (Lucca, July 2013)
2012-	Member of the scientific committee of the Intl Workshop on the Pharmacology of TB Drugs
2002-	Member, American Society for Microbiology

C. Contributions to Science

1. As head of the Pharmacology Unit at the Novartis Institute for Tropical diseases from 2005 to 2012, I managed the pharmacological profiling of early drug discovery compounds active against malaria, tuberculosis, and the Dengue fever. Our group was responsible for conducting in vitro and in vivo studies of pharmacokinetics, tissue distribution and pharmacodynamics to guide medicinal chemistry programs both at Novartis and within a large consortium funded by the Bill and Melinda Gates Foundation: The Grand Challenges for Global Health. We also provided modeling support and allometric scaling to select doses and dose ranges for efficacy studies and early drug and preclinical development. The team contributed to the discovery and development of antimalarial clinical candidates KAF156 and KAE609, now in Phase II and III trials

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(12):845-55. PMCID: PMC4144869.
2. Rottmann M, McNamara C, Yeung BKS, Lee MCS, Bin Zou, Russell B, Seitz P, Plouffe DM, Dharia NV, Tan J, Cohen SB, Spencer KR, González-Páez GE, Lakshminarayana SB, Goh A, Suwanarusk R, Jegla T, Schmitt EK, Beck H-P, Brun R, Nosten F, Renia L, **Dartois V,** Keller TH, Fidock D, Winzeler E, and Diagana TT. 2010. Spiroindolones, a new and potent chemotype for the treatment of malaria. **Science**, 329:1175-80. PMCID: PMC3050001
3. 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. 2010. A chemical genetic screen in *Mycobacterium tuberculosis* identifies carbon-source dependent growth inhibitors deprived of in vivo efficacy. **Nat. Comm.** 1:1-8. PMCID: PMC3220188
4. Lakshminarayana SB, Huat TB, Ho PC, Manjunatha UH, **Dartois V**, Dick T, Rao SP. 2015. Comprehensive physicochemical, pharmacokinetic and activity profiling of anti-TB agents. **J Antimicrob Chemother.** 70(3):857-67. PMID: 25587994

2. After working for 7 years in the pharmaceutical industry in the field of neglected diseases, I decided to focus entirely on studying the pharmacological mechanisms contributing to the very long therapy duration required to cure tuberculosis (TB) and nontuberculous mycobacterial (NTM) disease. These factors essentially fall under two categories: the presence of multiple bacterial subpopulations exhibiting differential (and reduced) susceptibility to most drugs, and the complexity of the lung pathology leading to sequestration of the pathogen in remote niches where drugs may fail to distribute efficiently. While the phenotypic tolerance of *Mycobacterium tuberculosis* to most antibiotics has been the focus of extensive research, the pharmacological question of drug penetration at the site of infection has largely been neglected so far. Using both quantitative and imaging methods, our group has demonstrated that different anti-TB agents exhibit very different patterns of distribution from blood to the sites of infection. Our results have paved to way to guiding the selection of new drug regimens that combine agents with *complementary* distribution into lesions and sublesional areas, a significant departure from current – mostly empirical – approaches.

1. Prideaux B, Via LE, Zimmerman MD, Eum S, Sarathy J, O'Brien P, Chen C, Kaya F, Weiner DM, Chen PY, Song T, Lee M, Shim TS, Cho JS, Kim W, Cho SN, Olivier KN, Barry CE 3rd, **Dartois V**. 2015. The association between sterilizing activity and drug distribution into tuberculosis lesions. **Nat Med**. 21(10):1223-7. PMCID: PMC4598290
2. Jansy P. Sarathy, Fabio Zuccotto, Ho Hsinpin, Lars Sandberg, Laura E. Via, Gwendolyn A. Marriner, Thierry Masquelin, Paul Wyatt, Peter Ray, and **V. Dartois**. 2016. Prediction of Drug Penetration in Tuberculosis Lesions. **ACS Infect. Dis**., 2 (8), pp 552–563. PMCID: PMC5028112
3. Sarathy JP, Via LE, Weiner D, Blanc L, Boshoff H, Eugenin EA, Barry CE 3rd, **Dartois VA**. 2017. Extreme drug tolerance of Mycobacterium tuberculosis in caseum. **Antimicrob Agents Chemother**. Jan 25;62(2). pii: e02266-17. PMCID: PMC5786764
4. Blanc L, Daudelin IB, Podell BK, Chen PY, Zimmerman M, Martinot AJ, Savic RM, Prideaux B, **Dartois V**. 2018. High-resolution mapping of fluoroquinolones in TB rabbit lesions reveals specific distribution in immune cell types. **Elife.** 2018 Nov 14;7. pii: e41115. PMCID: PMC6249001

3. We have applied quantitative and analytical methodologies to identify and image markers of disease progression, study host-induced drug tolerance, validate host targets, and characterize the response to host directed therapy.

1. Marakalala MJ, Raju RM, Sharma K, Zhang YJ, Eugenin EA, Prideaux B, Daudelin IB, Chen PY, Booty MG, Kim JH, Eum SY, Via LE, Behar SM, Barry CE 3rd, Mann M, **Dartois V**, Rubin EJ. 2016. Inflammatory signaling in human tuberculosis granulomas is spatially organized. **Nat. Med**., 22(5):531-8. PMCID: PMC4860068
2. **Dartois V**, Saito K, Warrier T, Nathan C. 2016. New Evidence for the Complexity of the Population Structure of *Mycobacterium tuberculosis* Increases the Diagnostic and Biologic Challenges. **Am J Respir Crit Care Med**. 2016 Dec 15;194(12):1448-1451. PMCID: PMC5215036
3. Mishra BB, Lovewell RR, Olive AJ, Zhang G, Wang W, Eugenin E, Smith CM, Phuah JY, Long JE, Dubuke ML, Palace SG, Goguen JD, Baker RE, Nambi S, Mishra R, Booty MG, Baer CE, Shaffer SA, **Dartois V**, McCormick BA, Chen X, Sassetti CM. Nitric oxide prevents a pathogen-permissive granulocytic inflammation during tuberculosis. **Nat Microbiol**. 2017 May 15;2:17072. PMCID: PMC5461879
4. Xu Y, Wang L, Zimmerman MD, Chen KY, Huang L, Fu DJ, Kaya F, Rakhilin N, Nazarova EV, Bu P, **Dartois V,** Russell DG, Shen X. 2018. Matrix metalloproteinase inhibitors enhance the efficacy of frontline drugs against *Mycobacterium tuberculosis*. **PLoS Pathog**. 2018 Apr 26;14(4):e1006974. PMCID: PMC5919409

4. Pyrazinamide is one of two critical treatment shortening drugs in the treatment of tuberculosis, yet its mechanism of action and pharmacology largely remain an enigma. Our group has significantly contributed to lifting the pyrazinamide mystery, by combining genetics, pharmacokinetics, and pharmacodynamics approaches.

1. Via LE, Savic R, Weiner DM, Zimmerman MD, Prideaux B, Irwin SM, Lyon E, O'Brien P, Gopal P, Eum S, Lee M, Lanoix JP, Dutta NK, Shim T, Cho JS, Kim W, Karakousis PC, Lenaerts A, Nuermberger E, Barry CE 3rd, **Dartois V**. Host-Mediated Bioactivation of Pyrazinamide: Implications for Efficacy, Resistance, and Therapeutic Alternatives. **ACS Infect Dis**. 2015 May 8;1(5):203-214. PMCID: PMC4467917

2. Irwin SM, Prideaux B, Lyon ER, Zimmerman MD, Brooks EJ, Schrupp CA, Chen C, Reichlen MJ, Asay BC, Voskuil MI, Nuermberger EL, Andries K, Lyons MA, **Dartois V**, Lenaerts AJ. 2016. Bedaquiline and Pyrazinamide Treatment Responses Are Affected by Pulmonary Lesion Heterogeneity in *Mycobacterium tuberculosis* Infected C3HeB/FeJ Mice. **ACS Infect Dis**. 2(4):251-267. PMCID: PMC4874602
3. Naftalin CM, Verma R, Gurumurthy M, Lu Q, Zimmerman M, Yeo BCM, Tan KH, Lin W, Yu B, **Dartois V,** Paton NI. Coadministration of Allopurinol To Increase Antimycobacterial Efficacy of Pyrazinamide as Evaluated in a Whole-Blood Bactericidal Activity Model. **Antimicrob Agents Chemother.** 2017 Sep 22;61(10). PMCID: PMC5610504
4. Blanc L, Sarathy JP, Alvarez Cabrera N, O'Brien P, Dias-Freedman I, Mina M, Sacchettini J, Savic RM, Gengenbacher M, Podell BK, Prideaux B, Ioerger T, Dick T, **Dartois V.** 2018. Impact of immunopathology on the antituberculous activity of pyrazinamide. **J Exp Med.** Aug 6;215(8):1975-1986. PMCID: PMC6080910
5. Gopal P, Grüber G, **Dartois V**, Dick T. Pharmacological and Molecular Mechanisms Behind the Sterilizing Activity of Pyrazinamide. **Trends Pharmacol Sci**. 2019; 40(12):930-940. PMCID: PMC6884696.

Complete List of Published Work: http://www.ncbi.nlm.nih.gov/pubmed/?term=dartois+v