BIOGRAPHICAL SKETCH

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NAME	POSITION TITLE
Dartois, Véronique Anne	Associate Professor, NJ Medical School, Rutgers Biomedical and Health Sciences Faculty Member, Public Health Research Institute
eRA COMMONS USER NAME (credential, e.g., agency login) DARTOIS	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	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	Post-doct.	1997-1998	Microbial genetics

A. Personal Statement

I joined the PHRI in 2012 and assembled a research team which focuses on the pharmacology and imaging of anti-infective drugs. Prior to this appointment, 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 PHRI, the research interests of our group include the fate of anti-mycobacterial drugs from plasma to tissues, lung and CNS lesions and single cells, including the spatial distribution of drugs at high resolution, and how this affects drug efficacy in various animal models and in patients. Our group has access to a large animal biosafety level-3 facility within the institute (the regional biocontainment lab at the Public Health Research Institute of Rutgers University), where we routinely conduct PK and efficacy studies in various mouse and rabbit models of TB infection and chronic TB disease, including infections caused by drug resistant strains. We have established a fully integrated analytical platform for the quantification of drugs, lipids and other small molecules in various biological matrices. In the biosafety level 3 facility, we have a state-of-the-art MALDI mass spectrometry imaging suite, enabling the visualization of therapeutic agents and endogenous metabolites in tissues/organs infected with tuberculosis, NTM and other high-threat pathogens. This unique set-up offers ideal pharmacological, analytical and imaging support for mechanistic studies and translational drug development programs.

B. Positions and Honors

Positions

1993-1996	Postdoctoral Fellow, Division of Cell Biology, Scripps Research Institute, La Jolla, CA.
1996-1997	Postdoctoral Fellow, Dept. of Microbial Biochemistry, Pasteur Institute, Paris.
1997-2003	Principal Scientist, Embiosis Pharmaceuticals, Inc., Carlsbad, CA.
2004	Principal Scientist, Adaptive Therapeutics Inc., San Diego, CA
2005-2012	Executive Director, Pharmacology, Novartis Institute for Tropical Diseases, Singapore
2012-2014	Assistant Professor, New Jersey Medical School, Public Health Research Institute of UMDNJ
2014-	Associate Professor, New Jersey Medical School, Rutgers, The State University of New Jersey
2007-2012	Adjunct Assistant Professor, Department of Biological Science, Natl University of Singapore
2008-2012	Scientific Steering Committee member, International TB Research Institute, South Korea
2013-	Scientific Advisory Committee member, Drug Discovery Unit, University of Dundee

Honors

2012	Member of the scientific committee of the 5th and 6th International Workshop on the Pharmacology of TB Drugs (San Francisco, 2012 and Denver, 2013)
2013	Co-Chair of the Gordon Research Conference on TB Drug Development (Lucca, July 2013)

C. Contribution to Science

1. As head of the Pharmacology Unit at the Novartis Institute for Tropical diseases, I supervised and contributed to 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 and pharmacodynamics to guide medicinal chemistry programs. We also provided modeling support and allometric scaling to select doses and dose ranges for efficacy studies and early drug development programs. The team contributed to the discovery and development of antimalarial clinical candidate NITD-609, now in Phase II (http://www.malariajournal.com/content/11/1/316/table/T4) .

1. Yeung BK, Zou B, Rottmann M, Lakshminarayana SB, Ang SH, Leong SY, Tan J, Wong J, Keller-Maerki S, Fischli C, Goh A, Schmitt EK, Krastel P, Francotte E, Kuhen K, Plouffe D, Henson K, Wagner T, Winzeler EA, Petersen F, Brun R, **Dartois V,** Diagana TT, Keller TH. 2010. Tetrahydro beta-carbolines (spiroindolones): a new class of potent and orally efficacious compounds for the treatment of malaria. **J Med Chem**. 53:5155-5164
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.
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
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.

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.
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
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
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

3. Recently, 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
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
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
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.

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. In the past few years, 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.
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
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)
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.

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

D. Veronique DARTOIS – Research Support

ACTIVE

1R01 AI111967-01 (Dartois-Alland MPI) 04/01/14 - 03/31/19
NIH/NIAID
Rutgers, The State University of New Jersey
Lesion-centric imaging and PK-PD of pyrazinamide for TB/HIV co-infection
The major goal of this project is to study the pharmacokinetics, tissue distribution, metabolism and activity of pyrazinamide in the rabbit model of latent and chronic cavitary TB

U19 AI109713-01 (Perlin PI) 04/01/14 - 03/31/19
NIH-NIAID
Rutgers, The State University of New Jersey
Center to develop therapeutic countermeasures to high-threat bacterial agents

Project goals: our role in this program is to coordinate in vitro pharmacokinetic profiling of hits and leads, conduct in vivo pharmacokinetic studies in rodents and characterize intracellular uptake of discovery compounds.
Role: Pharmacology Core Leader
U19 AI111143-01 (Nathan PI) 07/01/14 - 06/30/21
NIH-NIAID
Weill Cornell Medical College
Tri-Institutional TBRU: Persistence and Latency (Merged TBRU-CETR)
Project goals: our group will evaluate the pharmacokinetic, tolerability, efficacy and lesion penetration properties of compounds to assist in hit triage, hit-to-lead progression and lead selection efforts, and reduce attrition rates related to poor pharmacokinetic, toxicity and unfavorable tissue distribution characteristics
Role: Pharmacology Core Leader
U19 AI111276-01 (Ellner PI) 08/01/15 – 07/31/21
NIH-NIAID
Boston University
Biomarkers and Mechanisms of Paucibacillary and Latent Tuberculosis
Project goals: our group will characterize and optimize the rabbit model of paucibacillary and latent TB to study microbial to study the biology of the pathogen, evaluate biomarkers of disease progression and drug response, and test new vaccine candidates and drug combinations.
Role: Project Leader
1R01AI124217– 01 (Ellner PI) 09/01/2015 – 08/31/2020
NIH-NIAID
Boston University
Impact of Pregnancy on Tuberculosis
Project goals: our group provides pharmacokinetics and pharmacodynamic support
1UH2AI122309-01 (Karakousis PI) 12/1/2015 – 11/30/2020
NIH-NIAID
Johns Hopkins University
Statins as Adjunctive, Host-Directed Therapy for TB
Project goals: our group provides pharmacokinetics and pharmacodynamic support
U01 HL131072-01 (Kirschner PI) 09/01/2016 – 08/31/2020
NIH-NIAID
University of Michigan
A Multi-scale systems pharmacology approach to TB therapy
Project goals: our group generates in vivo data of pharmacokinetics, pharmacodynamics and tissue distribution to support multi-scale modeling.
OPP1154895 (Dartois PI) 11/01/2016 – 10/30/2019
Bill & Melinda Gates Foundation
A dynamic drug delivery system to accelerate the profiling of early discovery compounds
Project goal: to accelerate target identification and in vitro pharmacological profiling of new compounds with anti-tuberculosis activity
Role: principal investigator
OPP1174780 (Dartois PI) 09/01/2017 – 10/30/2019
Bill & Melinda Gates Foundation
Rutgers, The State University of New Jersey
Integrated pharmacokinetics to rationally design new drug combinations for TB
Project goal: To characterize the penetration and distribution of new TB drug candidates in the lung to guide the selection of optimal regimens for the treatment of TB
Role: principal investigator
OPP1182859 (Schnappinger PI) 12/01/2017 - 11/30/2019
Bill & Melinda Gates Foundation
Rutgers, The State University of New Jersey
Conditional M. tuberculosis knockdown mutants for TB drug development
Role: Co-investigator
OPP1180610 (Rubin, PI) 01/01/2016 - 12/31/2020
Bill & Melinda Gates Foundation

Rutgers, The State University of New Jersey
Controlled Human Infection Model: detection of vaccine effect in NHPs
Role: Co-investigator

1R01 AI132374-01 (Dick PI) 04/01/2018 – 3/31/2023
NIH/NIAID
Rutgers, The State University of NJ
Combatting natural resistance and persistence in non-TB mycobacterial disease
Project goal: to discover, develop or repurpose new antibiotics for non-tuberculous mycobacterial disease
Role: Co-Principal Investigator

2R01 AI090810-06 (Lee PI) 04/01/2018 – 3/31/2023
NIH/NIAID
Development of Novel Proteins Synthesis Inhibitors for MDR Tuberculosis.
Project goals: our group generates in vivo data of pharmacokinetics and tissue distribution to support medicinal chemistry nd drug discovery efforts
Role: Co-Investigator

1R01 AI106398 (Dartois-Dick MPI) 07/01/18 - 06/30/23
NIH/NIAID
Rutgers, The State University of New Jersey
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
Role: Co-Principal Investigator

R01 AI136445 (Aldrich) 12/01/2017–11/30/2022
NIH/NIAID
Siderophore Inhibitors for Tuberculosis that Block Mycobactin Biosynthesis
The major goals of this project are to develop a new class of antibiotics for tuberculosis that target iron acquisition.
Role: Co-Investigator

R01 AI143784 (Aldrich)
NIH-NIAID 12/01/2018–11/30/2023
Targeting Biotin Metabolism in *Mycobacterium Tuberculosis*
The major goal of this project is to develop a new class of antibiotics for tuberculosis that target biotin metabolism. Our group provides pharmacological support.
Role: Co-Investigator

COMPLETED

OPP1024050 (Dartois) 11/01/2015 – 10/31/2018
Rutgers, The State University of New Jersey
Bill & Melinda Gates Foundation
Metabolomics-based approaches to TB drug development
Project goals: to enable early and integrated pharmacokinetic profiling of the structure-activity relationships around progressible hit compound series that emerge from existing TBDA screening centers

1UH2AI122295 (Flynn-Sassetti PI) 9/1/2015 – 8/31/2017
NIH-NIAID
University of Pittsburgh
Rational design of combination regimens targeting both host and pathogen
Project goals: our group provides pharmacokinetics support to quantify oxazolidinones and biomarkers of inflammation in plasma and tissues of mice and non-human primates

1R01 AI106398 (Dartois) 08/01/13 - 07/31/18
NIH/NIAID
Rutgers, The State University of New Jersey
Lesion-centric imaging and PK-PD of pyrazinamide for TB/HIV co-infection
The major goal of this project is to study the pharmacokinetics, tissue distribution, metabolism and activity of pyrazinamide in the rabbit model of latent and chronic cavitary TB

1S10OD023524-01 (Dartois PI) 04/01/2017 – 03/31/2018
Rutgers, The State University of NJ
NIH – NIAID
A QTRAP 6500 LC-MS/MS System from SCIEX for high accuracy drug content analysis
OPP1140482 (Rakesh JAIN PI) 12/01/2015 – 11/30/2017
Mass General Hospital
Bill & Melinda Gates Foundation
Normalizing Tuberculosis Granuloma Vasculature and Matrix to Improve Drug Delivery and Efficacy
Project goals: to measure and image the distribution of TB drugs in animals receiving anti-angiogenic and antifibrotic therapy
OPP1119065 (Abramovitch PI) 11/01/14 - 10/31/17
Bill & Melinda Gates Foundation
Michigan State University
Development of tuberculosis therapeutics that inhibit persistence and antibiotic tolerance
Project goals: our group provides pharmacokinetics and pharmacodynamic support
OPP1066499 (Dartois) 11/01/12-10/31/16
Rutgers, The State University of New Jersey
Bill & Melinda Gates Foundation
Integrated pharmacokinetics to rationally design new drug combinations for TB
Project goals: the objectives of this program were (1) to bridge the gap in translational pharmacology by providing PK support to the BMGF-funded TB Drug Accelerator screening centers, and (2) inform the selection of drug combinations in upcoming clinical trials by measuring drug distribution in the different TB lesions and lesion compartments.
1S10OD018072-01 (V Dartois) 05/01/2015 - 04/30/2016
NIH-NIAID
Title: A MALDI LTQ Orbitrap XL Mass Spectrometer for BioImaging
Shared Instrumentation Grant
1034408 (Flynn) 11/14/11-11/13/15
University of Pittsburgh
Bill & Melinda Gates Foundation
Application of clinical imaging modalities to tuberculosis treatment and transmission
Project goals: Our role was to provide pharmacokinetic analysis of small molecule drugs and PET probes in the various animal models.