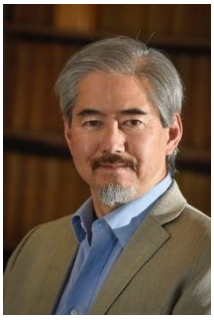
TRUDEAU INSTITUTE
Transforming Medicine Together

Greetings from Trudeau Institute!



It is my distinct pleasure to welcome you to Trudeau Institute this autumn to participate in *From Rabbit Island to Reporter Strains: A symposium celebrating over 125 years of tuberculosis research in Saranac Lake*. Scientific organizers Dr. Brian Weinrick of the Trudeau Institute, Dr. William Jacobs, Jr. of the Albert Einstein College of Medicine, and Dr. Keith Derbyshire of the Wadsworth Center (NYS Department of Health) have assembled an exciting program highlighting both new approaches to understanding tuberculosis and its causative organism, as well as emerging consensus from over a century of research.

More than 135 years ago, Dr. Edward L. Trudeau travelled to the Adirondacks to cure from tuberculosis because the climate was an acceptable treatment plan. His initial intentions were to return to New York City, however, he persuaded his family to stay. And, E.L. Trudeau built the laboratory that we commemorate today. Groundbreaking research in TB began in the Adirondack Mountains and continues today with Trudeau Institute.

In today's biomedical research our immunologists are constantly reminded of the millions of people around the world who struggle with TB and infectious diseases. Multi-drug-resistant strains of TB, outbreaks of deadly pathogens, and the globe-spanning mobility add to the overarching global threat. TB research and development at Trudeau will form a central platform within our overall Institute global health research portfolio, as we expand with top caliber partners.

With our prestigious partners committed to the nucleus of the Trudeau Research Network, developed in 2016 as the capstone of Trudeau 3.0, we move forward with groundbreaking research for the benefit of all, in order to continue ***transforming medicine together***. Many leaders have recognized that we must work together on bold and creative translational science, to achieve medical impact more quickly. The Trudeau Institute leverages its signature strengths in such mission-directed joint pursuits.

On behalf of Trudeau Institute, I am profoundly grateful to the American Society of Microbiology for recognizing Dr. Trudeau's Laboratory as a Milestones in Microbiology Site! Now the home to our wonderful partner in history, Historic Saranac Lake. And, a special recognition to OppenheimerFunds for their generous support of this event, enabling us to celebrate the momentous advances in microbiology from 1894 to today.

Sincerely,

Atsuo Kuki, Ph.D.
President and Director

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Agenda

From Rabbit Island to Reporter Strains: Celebrating over 125 years of TB research in Saranac Lake

Friday, October 11, 2019

7:30 a.m. Shuttle service from Hotel Saranac to Trudeau Institute

7:40 Continental Breakfast, Trudeau Institute

8:15 Welcome and opening remarks
Brian Weinrick, Ph.D., Trudeau Institute
William Jacobs, Jr., Ph.D., Albert Einstein College of Medicine
Keith Derbyshire, Ph.D., Wadsworth Center, New York State Department of Health

Morning session

8:30 **Dr. Marcel Behr**, McGill University, Montreal, Canada
Latent TB: 200 years of confusion

9:00 **Dr. Katrin Mayer-Barber**, NIAID, NIH, Washington, DC
Innate effector cells and cytokines in host resistance to *Mycobacterium tuberculosis*

9:30 **Dr. Heran Darwin**, New York University, NYC, NY
Proteasomal Regulation of Hormone Signaling in *M. tuberculosis* (and did we learn something interesting?)

10:00 **Dr. Brian VanderVen**, Cornell University, Ithaca, NY
Current understanding of lipid import by *M. tuberculosis*

10:30 Break

10:45 **Dr. Keith Derbyshire**, Wadsworth Center, NYS Department of Health, Albany, NY
Pervasive translation and the abundant small proteome of *Mycobacterium tuberculosis*

11:15 **Dr. Nancy Woychik**, Rutgers University, Piscataway, NJ
Toxins, tRNAs and tuberculosis

11:45 **Dr. Bree Aldridge**, Tufts University, Boston, MA
Systematic phenotypic profiling to engineer combination therapy for TB

12:15 p.m. Lunch, Trudeau Institute
Optional tours of the research center and Little Red will be available

Afternoon Session

1:15 p.m. **Dr. Daniel Barber**, NIAID, NIH, Washington, DC
The role of PD-1 during *M. tuberculosis* infection of mice, macaques and humans

1:45 **Dr. Catherine Vilcheze**, Albert Einstein College of Medicine, Bronx, NY
Surprising results from generating BSL2-Safe *Mycobacterium tuberculosis* strains

2:15 **Dr. Faramarz Valafar**, San Diego State University, San Diego, CA
Comparative genomics of early *Mycobacterium tuberculosis* isolates with third-generation sequencing reveals evolution driven by small and large variations

2:45 Break

3:00 **Dr. Brian Weinrick**, Trudeau Institute, Saranac Lake, NY
A Novel Mouse Model of Tuberculosis Generates Necrotic Hypoxic Granulomas Harboring Persister Cells

3:30 **Dr. Anil Ojha**, Wadsworth Center, NYS Department of Health, Albany, NY
Molecular insights into mycobacterial persistence

4:00 **Dr. William Jacobs, Jr.**, Albert Einstein College of Medicine, Bronx, NY
Reflecting on Edward Livingston Trudeau: The Path to Tuberculosis Eradication

4:30 Group photos, Trudeau Institute

5:00 Shuttle to Historic Saranac Laboratory

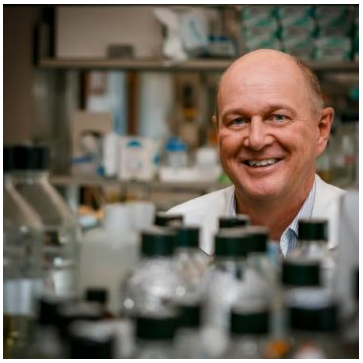
5:15 Historic Saranac Laboratory: American Society for Microbiology (ASM) Milestones in Microbiology Site Designation

6:00 Hotel Saranac Reception (including dinner style hors d'oeuvres) **and Closing Remarks**
Dr. Atsuo Kuki, President and Director of Trudeau Institute

Science Organizers

Brian Weinrick, Ph.D. is the Tuberculosis R&D Center Lead Investigator at the Trudeau Institute and an Associate at the Albert Einstein College of Medicine. His research focuses on survival mechanisms of tuberculosis bacilli. Combining genomic, transcriptomic, and metabolomic tools, Dr. Weinrick has characterized the unique physiological state of *Mycobacterium tuberculosis* persister cells in a search for their vulnerabilities. His efforts to alleviate the burden of tuberculosis include coordinating the creation a national tuberculosis reference laboratory for Eritrea. After attaining a B.S. in biochemistry at the University of Michigan, Dr. Weinrick earned his Ph.D. in microbiology from New York University School of Medicine, studying the regulation of gene expression in *Staphylococcus aureus* with Dr. Richard P. Novick. He was a postdoctoral fellow and research associate in the laboratory of Dr. William R. Jacobs, Jr. at the Albert Einstein College of Medicine prior to joining the Trudeau Institute in 2017.

William Jacobs, Jr., Ph.D. was trained as mathematician and received his bachelor's degree from Edinboro University in 1977. He then attended graduate school at the University of Alabama, Birmingham where he obtained a Ph.D. in molecular cell biology. For his thesis work, Dr. Jacobs constructed the first genomic libraries of the *Mycobacterium leprae* working with Drs. Roy Curtiss and Josephine Clark-Curtiss as co-mentors. For his post-doctoral fellowship, he worked with Dr. Barry Bloom towards the goal of developing gene transfer systems for BCG to be used as a recombinant vaccine vector. By using mycobacteria phages, Dr. Jacobs introduced foreign DNA into mycobacteria for the first time in 1987. He became an assistant professor at Albert Einstein College of Medicine and a Howard Hughes Medical Institute Investigator for the next 29 years. Using the original shuttle phasmid vector, Dr. Jacobs and his team developed the first plasmid transformable mutants of *Mycobacterium smegatis*, mc^2155, efficient transposon mutagenesis, and specialized transduction. Using these genetic tools, Dr. Jacobs' lab discovered the previously unknown: 1) target of Isoniazid (INH), 2) the primary attenuating mutation of BCG affected cell lysis and host cell membrane modification, 3) the signal transduction regulation of acid fast staining, and 4) the molecular genetic definition of INH persistent cells. To date, Dr. Jacobs has published over 350 manuscripts and has trained a generation of mycobacterial genetics researchers. He has also initiated studies on herpes viruses using a special herpes mutant to engender protective antibody responses that use Fc function. He was elected to the National Academy of Sciences in 2013, the National Academy of Inventors in 2018, and is currently the Leo and Julia Forchheimer Chair of Microbiology and Immunology at the Albert Einstein College of Medicine.



Keith M. Derbyshire, Ph.D. completed his doctoral research at the University of Edinburgh working on DNA replication and conjugation of plasmids in *E. coli*, under the mentorship of Dr. Neil Willetts. As a post-doctoral fellow at Yale University, he studied the molecular mechanisms of site-specific recombination and transposition, under the mentorship of Dr. N. Grindley. Since 1992, Dr Derbyshire has worked as a Research Scientist at the Wadsworth Center, the New York State Department of Health's public health laboratory, in Albany, NY. He has been the Director of the Division of Genetics at the Center since 2008, and also is a Professor in the Department of Biomedical Sciences in the U Albany's School of Public Health. Dr. Derbyshire's laboratory studies the molecular genetics and biology of mycobacteria utilizing both basic molecular genetic techniques and state-of-the-art genome-wide approaches to determine the genetic architecture, expression and functions of mycobacterial genes.

Presenters

Bree Aldridge, Ph.D. is an Assistant Professor in the Department of Molecular Biology and Microbiology and Department of Biomedical Engineering t Tufts University. Her lab specializes in developing quantitative tools to interrogate and interpret the complexity of tuberculosis drug response and virulence. She earned double B.S. degrees in computer engineering and molecular and cellular biology at the University of Arizona as a Flinn Scholar. She completed her Ph.D. in Biological Engineering at MIT with Douglas Lauffenburger and Peter Sorger with the support of a DOE Computational Science Graduate Fellowship. She brought her interdisciplinary perspective to tuberculosis during her postdoctoral training at the Harvard School of Public Health with Sarah Fortune. She is an Alfred P. Sloan Research Fellow and is the recipient of an NIH Director's New Innovator Award. Her lab website is: https://sites.tufts.edu/aldridgelab/

Daniel Barber, Ph.D. obtained his B.S. from Rider University and his Ph.D. from Emory University in the Department of Microbiology and Immunology. In 2006, he joined the Laboratory of Parasitic Diseases as a postdoctoral fellow in the Immunobiology Section. In 2012, Dr. Barber was awarded a position as an Earl Stadtman Tenure-Track Investigator in the Laboratory of Parasitic Diseases. Dr. Barber's lab performs mouse, non-human primate and human studies to investigate the mechanisms of CD4 T cell-mediated protection against *Mycobacterium tuberculosis* infection, as well as the mechanisms of immune regulation that limit CD4 T cell mediated immunopathology.

Marcel Behr, Ph.D. is a clinician-scientist with appointments of Full Professor in the Department of Medicine and Associate member in the departments of Epidemiology and Biostatistics as well as Microbiology and Immunology. He is the founding Director of the McGill International TB Centre and led it from 2012 to 2018. He is the Associate Program Leader of the Infectious Diseases and Immunity in Global Health Program at the Research Institute of the McGill University Health Centre since 2016, and in 2017 he became the co-Director the McGill Interdisciplinary Initiative in Infection and Immunity (McGill-i4). He is the interim director of McGill Infectious Diseases Division. Dr. Behr trained at the University of Toronto, Queen's, McGill and Stanford. His work has been recognized by election into the Canadian Academy of Health Sciences, the Royal Society of Canada, the American Society for Clinical Investigation and the American Academy of Microbiology. Dr. Behr's lab uses bacterial genomic methodologies to study the epidemiology and pathogenesis of tuberculosis and other mycobacterial diseases.

K. Heran Darwin, Ph.D. earned her Bachelor's (1992) and Ph.D. (1999) degrees in Microbiology and Molecular Genetics at the University of California, Los Angeles with Dr. Virginia Miller, PhD characterizing virulence gene regulation in *Salmonella typhimurium*. She continued her work in microbial pathogenesis in Dr. Carl Nathan's lab at Weill Medical College of Cornell University in New York. After her completion of her post-doctoral studies, she moved to New York University School of Medicine in the Department of Microbiology where she is now a Professor. Among her honors, she received an Interscience Conference on Antimicrobial Agents and Chemotherapy Young Investigator Award (2006), a Burroughs Wellcome Fund Investigators in the Pathogenesis of Infectious Disease Award (2009), and an Irma T. Hirschl Charitable Trust Award (2010). She is a Kavli Fellow (2012) and a Fellow of the American Academy of Microbiology (2016). She has been a member of the American Society for Microbiology since 1996. Postdoctoral training: Yale University.

Katrin Mayer-Barber, Ph.D. received her diploma in Biology from the University of Würzburg, Germany in 2002. In 2003 she came to the United States for her Ph.D. thesis-work in the laboratory of Dr. Markus Mohrs at the Trudeau Institute in Saranac Lake, NY. There she specialized on multi-parameter flow-cytometry analysis of pulmonary CD4 effector T cells after viral and parasitic infections and studied immune cell derived interferon responses in vivo. She obtained her Ph.D. degree (Dr. rer. nat.) in 2006 from the University of Würzburg, Germany and joined NIH/NIAID in 2007 as a post-doctoral fellow in the Laboratory of Parasitic Diseases in Alan Sher's group. .There she studied pulmonary innate effector cells, such as inflammatory monocytes and dendritic cells, and delineated the role of inflammatory mediators like IL-1, type I Interferons and prostaglandins in host resistance to tuberculosis. .Dr. Mayer-Barber was awarded the Earl Stadtman Tenure-Track Investigator position in the Laboratory of Clinical Infectious Diseases in NIAID in 2015 where she is Chief of the Inflammation and Innate Immunity Unit. .Research in her laboratory focuses on how innate cellular immune responses modulate inflammation and the outcome of pulmonary infections and how insights into these pathways can be translated into novel immuno-therapeutic approaches for tuberculosis.

Anil K. Ojha, Ph.D. studies the molecular basis of persistence of one of the deadliest bacterial pathogens, *Mycobacterium tuberculosis* (Mtb), which kills over a million people every year. Mtb is the causative agent of human tuberculosis (TB), which has inflicted mankind since the prehistoric era. But even in the age of modern medicine, the only possible treatment of TB is a 6-9 month regimen of at least three specialized anti-TB antibiotics. This lengthy and complicated regimen is in sharp contrast to the week-long, mono-drug treatment for most other bacterial infections. We are focused on addressing unmet challenges in TB therapy. Our investigations are addressing questions like; a) What makes *M. tuberculosis* the toughest of all bacterial species, with an ability to tolerate virtually all kinds of stress? and b) How we can shorten the TB treatment? We are testing a hypothesis that the extraordinary persistence of *M. tuberculosis* against antibiotics is facilitated by the pathogen's ability to grow in organized multicellular structures, called biofilms. Using biofilm as the growth model we are specifically investigating the contribution of ribosome hibernation in mycobacteria, and identifying the mechanisms underlying the inactivation of ribosomes. In the course of our investigations, we are also developing molecular tools to visualize drug tolerant persisters within biofilms. Using these tools, we are asking as to how localization and frequency of these types of bacilli are perturbed in biofilms *in vitro* and in animal models.

Faramarz Valafar, Ph.D. is a Professor of Epidemiology and Biostatistics in the School of Public Health (SPH), San Diego State University (SDSU). Before joining SPH, Dr. Valafar was a Professor of Computer Science from until 2019. Before SDSU, Dr. Valafar was an Assistant Professor of Cognitive and Neural Systems at Boston University from 1999 until 2001. Dr. Valafar is a NIAID Principal Investigator leading projects on global pathogenesis and diagnosis of antibiotic resistance in tuberculosis (TB). This project involves diagnostics, prognostics, evolutionary analysis, molecular epidemiology, systems epidemiology, systems biology of TB and Drug Resistant TB (DRTB). The clinical component of the project includes diagnosis, sample collection, and treatment of TB in eight high TB burden countries from Europe, Asia, and Africa. Microbiological components of the project are conducted in the World Health Organization (WHO) Supra-National TB Reference Laboratories in Stockholm and Antwerp. All *in silico* components of the project (e.g. epidemiology, evolutionary, systems analysis) are conducted in San Diego.

Brian C. VanderVen, Ph.D. received his B.S. in Microbiology from Montana State University. He completed his Ph.D. at Colorado State University in John Belisle's lab studying *M. tuberculosis* and continued his training as a Postdoctoral Fellow in David Russell's laboratory. His lab at Cornell University uses chemical-genetics and biochemical approaches to discover and characterize novel *M. tuberculosis* pathways required during infection with an overarching goal of discovering new drugs to treat Tuberculosis.

Catherine Vilchèze, Ph.D. received her Engineering degree in chemistry and a Ph.D. in organic chemistry from the University of Haute-Alsace, France. After receiving her Ph.D., Dr. Vilcheze accepted a research associate position in the laboratory of Dr. Robert Bittman at CUNY where she synthesized synthetic sterols. Shortly after she joined Dr Bittman's lab, she was asked to lead a collaboration with Drs William R. Jacobs, Jr. and James Sacchettini to develop inhibitors of the *M. tuberculosis* enoyl-ACP reductase InhA, the target of the tuberculosis drug isoniazid. After completing her project, she spent a brief period in the Jacobs' laboratory to learn how these inhibitors were being tested. During this time, Dr. Jacobs gave Dr. Vilchèze her first microbiology project: isolate an isoniazid-resistant, temperature-sensitive *inhA Mycobacterium smegmatis* mutant. The short foray into the molecular genetics of antibiotic resistance led to a 21-year journey, with over 60 publications, uncovering novel mechanisms of isoniazid resistance, *Mycobacterium tuberculosis'* sterilization, and delving into the darkness of mycobacterial drug persistence.

Nancy Woychik, Ph.D. obtained her Ph.D. in Microbiology from the University of Wisconsin-Madison and performed her postdoctoral work at the Whitehead Institute-MIT. She started her independent career in 1991 at the former Roche Institute of Molecular Biology, an academic institute created and supported by Hoffmann La-Roche. She then moved to her current faculty position at Rutgers University-Robert Wood Johnson Medical School in 1996, where she is now a Full Professor.

American Society for Microbiology

The American Society for Microbiology is the largest single life science society, composed of more than 30,000 scientists and health professionals. ASM's mission is to promote and advance the microbial sciences. ASM advances the microbial sciences through conferences, publications, certifications and educational opportunities. It enhances laboratory capacity around the globe through training and resources. It provides a network for scientists in academia, industry and clinical settings. Additionally, ASM promotes a deeper understanding of the microbial sciences to diverse audiences. The ASM Milestones in Microbiology program, administered by the Center for the History of Microbiology/ASM Archives Committee, recognizes institutions and the scientists who worked there that have made significant contributions toward advancing microbiology. By placing explanatory plaques at these sites, ASM hopes to promote greater awareness and appreciation of microbiology.