UCLA Health

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BIO

Dr. Horwitz is Distinguished Professor of Medicine and Microbiology, Immunology, & Molecular Genetics. He received his M.D. degree from Columbia U. College of Physicians and Surgeons and subsequently trained in Internal Medicine and Infectious Diseases at the Albert Einstein College of Medicine. He served for two years as an Epidemic Intelligence Officer at the CDC and then trained in cellular physiology and immunology at The Rockefeller University. From 1980-85, he was on the faculty of The Rockefeller University as an Assistant Professor and Associate Physician. In 1985, he joined the faculty of UCLA as Professor of Medicine and of Microbiology, Immunology & Molecular Genetics and as Chief of the Division of Infectious Diseases, a position he held until 1992.

Dr. Horwitz is a fellow in the Infectious Diseases Society of America and a member of the American Society for Clinical Investigation. His awards include the Oswald Avery (formerly Squibb) Award from the Infectious Diseases Society of America and election to Fellowship in the American Association for the Advancement of Science.

His research has focused on intracellular parasitism, especially the immunobiology of the etiologic agents of Legionnaires' disease, leprosy, tuberculosis, and tularemia.

CURRENT RESEARCH PROJECTS

Atomic Model and Mutational Analysis of the *Francisella tularensis* Type VI Secretion System (T6SS)
F. tularensis subsp. *tularensis (F. tularensis)*, the causative agent of tularemia, is an intracellular pathogen and Tier I Select Agent of bioterrorism. The Horwitz laboratory has described the life cycle of *F. tularensis* in human macrophages including its ingestion by a novel mechanism – looping phagocytosis; its entry into a unique

fibrillar-coated phagosome that resists fusion with lysosomes and exhibits limited acquisition of lysosomal markers; its subsequent escape from the phagosome via a unique Type VI Secretion System (T6SS); and its intracytoplasmic replication. T6SSs, multi-protein nano-machines that inject bacterial effector molecules into target prokaryotic and eukaryotic cells, are important virulence determinants found in one-quarter of Gram-negative bacteria including many that cause serious human diseases. The Horwitz laboratory, in collaboration with the Hong Zhou laboratory, first described the atomic structure of the T6SS contracted sheath and more recently that of the central spike complex. Current projects center on determining the atomic structure of the *F. tularensis* precontraction sheath, the composition and structure of the T6SS baseplate and membrane complex, and further delineating the composition and protein interactions of the secreted tube and spike complex.

Characterization of a Novel Mycobacterial Heme Acquisition System
Iron is an essential nutrient for all pathogens, and intracellular pathogens must acquire it under the iron-limiting conditions within the host. It has long been known that *Mycobacterium tuberculosis* (Mtb), the agent of TB, has a siderophore-mediated iron acquisition (SMIA) system. In previous studies, the Horwitz laboratory determined the structure of the extracellular siderophores of Mtb known as exochelins (or exomycobactins). Subsequently, the Horwitz laboratory made the unexpected discovery that Mtb additionally has a heme-iron acquisition (HIA) system, and in collaboration with the Celia Goulding laboratory at UCI, characterized several genes involved in this system. Recently, the Horwitz laboratory identified *ppe37,* an iron-regulated PPE family gene, and demonstrated that it is essential for HIA. We also showed that a mutation in this gene explains the profound defect in HIA of the BCG vaccine. Current projects seek to further understand the role of key molecular participants in the HIA pathway.

Vaccines against Tuberculosis and Leprosy
TB kills ~1.8 million people per year globally and a better vaccine is needed. The Horwitz laboratory developed the first vaccine against tuberculosis more potent than BCG, the currently used vaccine. This live recombinant vaccine, called rBCG30, was the first replacement vaccine for BCG to enter human clinical trials. rBCG30 also induces superior protection than BCG against *Mycobacterium bovis*, the agent of bovine tuberculosis, and *Mycobacterium leprae*, the agent of leprosy. The Horwitz laboratory also developed the first replication-limited recombinant BCG vaccine [rBCG(*mbtB*)30], a vaccine that is both safer and more potent than BCG and designed specifically for HIV-positive infants and adults in whom conventional BCG can disseminate and cause serious disease. In addition, the Horwitz laboratory developed the first defined heterologous booster vaccine demonstrated to augment the level of protective immunity induced by BCG. Current laboratory projects seek to develop even more potent recombinant prime and booster vaccines against tuberculosis including a live attenuated recombinant Listeria-vectored booster vaccine.

Single Vector Platform Vaccines against Tier 1 Select Agents and Emerging Pathogens
The most practical way to protect against Tier 1 Select Agents of bioterrorism (especially, the bacterial agents of tularemia, anthrax, plague, and melioidosis) is a safe and effective vaccine. Currently, no licensed vaccines exist against tularemia, plague, and melioidosis, and the licensed vaccine against anthrax is poorly effective and cumbersome to administer. Practically speaking, a single platform vaccine against multiple Tier 1 Select Agents of bioterrorism is highly desirable, as it would simplify manufacture, regulatory approval, and clinical evaluation; allow administration of multiple vaccines simultaneously and hence be more acceptable; and lower costs. The Horwitz laboratory has developed a novel safe and highly immunogenic plug-and-play Single Vector Platform for expressing key immunoprotective antigens of Tier 1 Select Agents based upon its novel vector LVS Δ*capB*, derived from *F. tularensis subsp. holarctica*, and demonstrated exceptionally potent vaccines against all four of the aforementioned Tier 1 Select Agent diseases. Current projects seek to further develop these vaccines for FDA approval and to expand the number of target pathogens, including most recently SARS-CoV-2, the agent of Covid-19. In addition, current studies seek to understand molecular and functional correlates of immune protection against tularemia and melioidosis.

Identification of Novel Synergistic Ultra-Short Universal Tuberculosis Drug Regimens
Current treatments for TB require exceedingly prolonged administration of multiple antibiotics, often resulting in poor adherence and consequently drug resistance. Identifying synergistic drug combinations among TB drugs has been stymied by the impossibility of studying billions of possible drug-dose combinations. To deal with this problem, the Horwitz laboratory has collaborated with the Chih-Ming Ho laboratory to employ an artificial intelligence-enabled Parabolic Response Surface (PRS) platform in concert with an *in vitro M. tuberculosis*-infected human macrophage cell culture assay amenable to high throughput screening; the approach dramatically reduces the number of tests required to identify highly effective TB drug regimens. We then used the PRS approach to optimize drug doses of select TB drug regimens *in vivo*. Using this approach, we have identified novel regimens that are far superior to the Standard Regimen used to treat pulmonary TB, reducing

the treatment time required to achieve relapse-free cure in mice by 80-85% compared with the Standard Regimen. Several PRS regimens comprising approved drugs are universal regimens suitable for treating both drug-sensitive and drug-resistant TB. Two PRS regimens are now in clinical trials and a clinical trial of a third regimen is planned.

Targeted Controlled-Release Nanotherapeutics against Infectious Diseases
Nanoparticles for delivery of antibiotics are especially promising for the treatment of infectious diseases caused by intracellular pathogens, such as *M. tuberculosis* and *F. tularensis*, because macrophages, the primary host cells for these etiologic agents, are professional phagocytes that avidly ingest nanoparticles. By targeting nanoparticle drug-delivery systems to the site of infection and to the host cells at that site, and by releasing the drugs only intracellularly in host cells, nanotherapeutics have the potential to increase the therapeutic index of the drugs by orders of magnitude. The Horwitz laboratory, In collaboration with the laboratory of Jeffrey Zink at UCLA, has been developing and optimizing multifunctional stimulus-responsive mesoporous silica nanoparticles (MSNs) for delivery of antibiotics to treat tuberculosis and tularemia using *in vitro* and *in vivo* models. These MSNs contain internal pores that are loaded with antibiotic, after which the pores are capped by a stimulus responsive molecule. When administered to the host, these MSNs are rapidly and selectively ingested by host macrophages, and they subsequently release the drug contained within their pores in response to an intramacrophage signal - e.g. a lowering of the pH or a change in redox potential - that displaces or changes the configuration of the capping molecule such that the drug escapes from the pores and kills intracellular bacteria including *M. tuberculosis* and *F. tularensis*. These drug-loaded nanoparticles are substantially more effective than an equivalent amount of free drug in treating TB in a mouse model of pulmonary tuberculosis and in treating tularemia in a mouse model of pneumonic tularemia. Current studies are aimed at optimizing PRS drug regimens for inhalation delivery so as to further reduce the time needed to treat TB.

High Throughput Screening for Inhibitors of the *F. tularensis* Type VI Secretion System
T6SSs are found in over one-quarter of Gram-negative bacteria and are critical to the virulence of many pathogens of major clinical significance. As such, it presents an attractive and novel target for drug development. The Horwitz laboratory has recently developed novel assays for identifying specific inhibitors of the *Francisella* T6SS that are amenable to high throughput screening, and in collaboration with Robert Damoiseaux, Director of the UCLA Molecular Screening Shared Resource (MSSR) facility, is screening libraries of small molecules to identify lead compounds that block T6SS assembly and secretion.

High Throughput Screening for Inhibitors of the *M. tuberculosis* Type VII Secretion System (T7SS)
Better drugs are needed to combat the global emergence of drug resistant strains of *M. tuberculosis*. Attractive and novel targets not previously exploited for drug development are the newly identified T7SSs that transport proteins essential to virulence through the *M. tuberculosis* hydrophobic cell wall. The Horwitz laboratory has developed a highly specific ELISA assay for T7SS function suitable for high-throughput screening of small molecules that block T7SS secretion.

AWARDS

- Oswald Avery (formerly Squibb) Award from the Infectious Diseases Society of America
- Fellowship in the American Association for the Advancement of Science

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