UCLA Health

UCLA Division of Infectious Diseases

Marcus Horwitz MD

Title
Professor of Medicine and Microbiology, Immunology & Molecular Genetics

Gender
Male

Affiliation
Ronald Reagan UCLA Medical Center
David Geffen School of Medicine at UCLA, Division of Infectious Diseases

EDUCATION

- MD, Columbia U Colleg of Physicians ans Surgeons
- Internal Medicine and Infectious Diseases, Albert Einstein College of Medicine
- Cellular Physiology and Immunology, Rockerfeller University

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

Vaccines against Tuberculosis and Leprosy
TB kills ~1.8 million people per year globally and a better vaccine is needed. Dr. Horwitz's 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.

Vaccines against Tularemia and other Category A Bioterrorism Agents
Francisella tularensis, the agent of tularemia, is a potential agent of bioterrorism, and no vaccine is currently available. The Horwitz laboratory has developed novel live recombinant prime and booster vaccines expressing selected F. tularensis proteins that protect against highly virulent aerosolized F. tularensis subspecies tularensis. Current projects seek to develop more potent recombinant prime and booster vaccines against F. tularensis as well as other Category A agents of bioterrorism including anthrax and plague. In addition, current studies seek to understand molecular and functional correlates of immune protection against tularemia.

Characterization of the Mycobacterium tuberculosis Phagosome
Dr. Horwitz's laboratory has demonstrated that M. tuberculosis enters a phagosome in human macrophages that interacts with the host cell endolysosomal pathway but arrests the normal maturation of that pathway. Current studies use cryosection immunogold electron microscopy and proteomics approaches to understand the molecular basis for the arrested maturation of the M. tuberculosis phagosome.

Characterization of the Francisella tularensis Phagosome
Dr. Horwitz's laboratory has demonstrated that F. tularensis enters human mononuclear phagocytes by a novel process termed looping phagocytosis and subsequently resides in a unique phagosome that is coated with a fibrillar structure. The pathogen then arrests the maturation of the phagosome, inhibits its acidification, and finally lyses the phagosome to escape and multiply free in the cytoplasm. Current projects seek to delineate the mechanism underlying looping phagocytosis, identify the molecular composition of the fibrillar coat on the F. tularensis phagosome, to understand the mechanism by which the organism escapes the phagosome, and to identify pharmacologic inhibitors of F. tularensis intracellular trafficking as drugs against tularemia.

Characterization of a Novel Mycobacterial Heme Acquisition System
Dr. Horwitz's laboratory, in collaboration with the Celia Goulding laboratory at UCI, recently described a novel heme acquisition system in mycobacteria including Mycobacterium tuberculosis, the agent of TB. Current projects seek to further understand the role of key molecular participants in this pathway and the basis for the attenuation of this pathway in BCG.

Targeted Drug Treatment of Tuberculosis using Functionalized Nanoparticles
Dr. Horwitz's laboratory, in collaboration with the Jeffrey Zink and Andre Nel laboratories at UCLA, has demonstrated the utility of functionalized mesoporous silica nanoparticles (MSNP) in delivering drugs intracellularly to Mycobacterium tuberculosis in human macrophages. Studies have demonstrated that MSNP equipped with pH-operated valves and loaded with isoniazid or equipped with polyethyleneimine coating and loaded with rifampin are internalized efficiently by human macrophages, traffic to acidified endosomes, release high concentrations of anti-tuberculosis drugs intracellularly, and kill M. tuberculosis more effectively than an equivalent amount of free drug. Current studies seek to develop improved MSNP for the treatment of TB.

AWARDS

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

PUBLICATIONS (selected recent articles)

1. Clemens, D.L., P. Ge, B-Y Lee, **M.A. Horwitz**,*and Z. H. Zhou* (*Corresponding Authors). 2015. Atomic structure of T6SS reveals interlaced array essential to function. Cell 160:940-951. PMID: 25723168. PMCID: PMC4351867. NIHMSID: NIHMS665122
doi: 10.1016/j.cell.2015.02.005.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4351867/

2. Wu, Y-C., T-H. Wu, D. L. Clemens, B-Y. Lee, X. Wen, **M.A Horwitz**, M. A. Teitell, and P-Y. Chiou. 2015. Massively parallel delivery of large cargo into mammalian cells with light pulses. Nat Methods 12:439-444. Epub 2015-04-06. PMID: 25849636. PMCID: PMC5082232. NIHMSID: NIHMS823163 doi: 10.1038/nmeth.3357.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5082232/

3. Hwang, A., B-Y. Lee, D.L. Clemens, B.J. Dillon, J.I. Zink, and **M.A. Horwitz**. 2015. pH-responsive isoniazid-loaded nanoparticles markedly improve tuberculosis treatment in mice. Small 11(38):5065-5078. Epub 2015-07-20. PMID: 26193431. NIHMSID 723094. PMCID – PMC5628743. doi: 10.1002/smll.201500937.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5628743/

4. Li, Z., Clemens, D.L., Lee, B-Y, Dillon, B.J., **Horwitz, M.A.**, Zink, J.I. 2015. Mesoporous Silica nanoparticles with pH – sensitive nanovalves for delivery of moxifloxacin provide improved treatment of lethal pneumonic tularemia. ACS Nano. 9(11):10778-10789. Epub 2015-10-09. PMID: 26435204. PMCID-in process. doi:10.1021/acsnano.5b04306
https://pubs.acs.org/doi/10.1021/acsnano.5b04306

5. Cunningham, C., A. Champhekar, M.V. Tullius, B.J. Dillon, A. Zhen, J. de la Fuente, J. Herskovitz, H. Elsaesser, E.B. Wilson, S.G. Kitchen, **M.A. Horwitz**, S.J. Bensinger, S. Smale and D.G. Brooks. 2016. Type I and type II interferon coordinately regulate suppressive dendritic cell fate and function during viral persistence. PLOS Pathogens. Jan. 25, 2016. 12(1):e1005356. PMID: 26808628. PMCID: PMC4726812. doi: 10.1371/journal.ppat.1005356.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4726812/

6. Silva A., B-Y. Lee, D.L. Clemens, T. Kee, X. Ding, C-M Ho, and **M.A. Horwitz**. 2016. Output-driven Feedback System Control platform optimizes combinatorial therapy of tuberculosis using a macrophage cell culture model. Proc. Natl. Acad. Sci. USA. E2172-2179. Epub 2016-03-28. PMID: 27035987. PMCID: PMC4839402.
doi: 10.1073/pnas.1600812113.
http://www.pnas.org/content/pnas/113/15/E2172.full.pdf

7. Lee, B-Y., Z. Li, D.L. Clemens, B.J. Dillon, A.A. Hwang, J.I. Zink, and **M.A. Horwitz**. 2016. Redox-triggered release of moxifloxacin from mesoporous silica nanoparticles functionalized with disulfide snap-tops enhances efficacy against pneumonic tularemia in mice. Small 12 (27): 3690-3702. EPub 2016-06-01. PMID: 27412305. PMCID-in process. doi: 10.1002/smll.201600892
https://onlinelibrary.wiley.com/doi/epdf/10.1002/smll.201600892

8. Jia, Q., R. Bowen, R., B-Y. Lee, B.J. Dillon, S. Masleša-Galić, and **M.A. Horwitz**. 2016. *Francisella tularensis* Live Vaccine Strain deficient in capB and overexpressing the fusion protein of IglA, IglB, and IglC from the *bfr* promoter induces improved protection against *F. tularensis* respiratory challenge. Vaccine 34:4969-4978. PMID: 27577555. PMCID: PMC5028307. NIHMSID: NIHMS813638 doi: 10.1016/j.vaccine.2016.08.041.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5028307/

9. Lee, B-Y., D.L. Clemens, A. Silva, B.J. Dillon, S. Masleša-Galić, S. Nava, X. Ding, C-M Ho and **M.A. Horwitz**. 2017. Drug Regimens Identified and Optimized by Output-Driven Platform Markedly Reduce Tuberculosis Treatment Time. Nature Comm. 8:14183 PMID: 28117835. PMCID: PMC5287291. doi: 10.1038/ncomms14183.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5287291/

10. Ruehle, B., D.L. Clemens, B-Y. Lee, **M.A. Horwitz**, and J.I. Zink. 2017. Pathogen-specific cargo delivery platform based on mesoporous silica nanoparticles. J. Am. Chem. Soc. 139(19):6663-6668. Epub 2017 May 5. PMID: 28437093. doi: 10.1021/jacs.7b01278.

https://pubs.acs.org/doi/10.1021/jacs.7b01278

11. Stefanova, D., A. Raychev, J. Arezes, P.P. Ruchala, V.R. Gabayan, M. Skurnik, B.J. Dillon, **M.A. Horwitz**, T. Ganz, Y. Bulut, and E. Nemeth. 2017. Endogenous hepcidin and its agonist mediate resistance to selected infections by clearing non-transferrin-bound iron. Blood. 130(3):245-257. Epub 2017 May 2. PMID: 28465342. PMCID: PMC5520472. doi: 10.1182/blood-2017-03-772715. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5520472/?report=classic

12. Jia, Q., B.J. Dillon, S. Masleša-Galić, and **M.A. Horwitz**. 2017. Listeria-vectored vaccine expressing the *Mycobacterium tuberculosis* 30 kDa major secretory protein via the constitutively active prfA* regulon boosts BCG efficacy against tuberculosis. Infect. Immun. Epub 2017 June 19. PMID: 28630063. PMCID: PMC55633566. doi: 10.1128/IAI.00245-17. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5563566/?report=classic

13. Jia, Q., R. Bowen, B.J. Dillon, S. Masleša-Galić, B.T. Chang, A.C. Kaidi, and **M.A. Horwitz**. 2018. Single vector platform vaccine protects against lethal respiratory challenge with Tier 1 select agents of anthrax, plague, and tularemia. Scientific Reports 8:7009. May 3, 2018. PMID: 29725025 PMCID: PMC5934503 doi: 10.1038/s41598-018-24581-y https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5934503/?report=classic

14. Clemens, D.L., B-Y. Lee, and **M.A. Horwitz**. 2018. The Francisella Type VI Secretion System. Frontiers in Cellular and Infection Microbiology 8:121, April 23, 2018. PMID: 29740542 PMCID: PMC5924787 doi:10.3389/fcimb.2018.00121. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5924787/?report=classic

15. Jia, Q. and **M.A. Horwitz**. 2018. Live attenuated tularemia vaccines for protection against respiratory challenge with virulent *F. tularensis* subsp. *tularensis*. Frontiers in Cellular and Infection Microbiology 8:154. PMID: 29868510 PMCID: PMC5963219 doi:10.3389/fcimb.2018.00154. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5963219/

16. Chen, W., C-A Cheng, B-Y. Lee, D.L. Clemens, W-Y. Huang, **M.A. Horwitz** and J.I. Zink. 2018. A facile strategy enabling both high loading and high release amounts of water-insoluble drugs using mesoporous silica nanoparticles. ACS Applied Materials & Interfaces. Epub September 13, 2018. DOI: 10.1021/acsami.8b09069 https://pubs.acs.org/doi/10.1021/acsami.8b09069

17. Lee , B-Y., D.L. Clemens , A. Silva, B.J. Dillon, S. Masleša-Galić, S. Nava, C-M. Ho, and **M.A. Horwitz** 2018. Ultra-rapid near universal TB drug regimen identified via parabolic response surface platform cures mice of both conventional and high susceptibility. PLoS One . 2018 Nov 14;13(11):e0207469. PMID: 30427938. doi: 10.1371/journal.pone. 0207469 . eCollection 2018. https://doi.org/10.1371/journal.pone.0207469