Infectious Diseases Labs

A*STAR IDL

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Wednesday 5th February 2025
9:30 AM to 10:30 AM (SGT)

Registration required.
Please click here or scan QR code to register for the webinar.

How mycobacteria cross the blood-brain barrier

The Madigan Lab seeks to understand how bacteria interact with the nervous system during infection. Several medically relevant diseases are characterized by infection of the nervous system, including TB meningitis and leprosy, which are caused by *Mycobacterium tuberculosis* and *M. leprae*, respectively. After invasion of neurological tissue, mycobacteria are thought to incite neuroinflammation, causing damage to neurons. The mechanisms at play are largely unknown. To understand the key pathological events in infections like TB meningitis and leprosy, we use an unusual model host: zebrafish larvae. The similarities between these transparent vertebrates and humans outweigh their differences: over 70% of human genes have known zebrafish orthologs. Zebrafish are amenable to infection by M. marinum, a model mycobacterial pathogen from fish. Using these resources, we track bacteria as they interact with neuroglia and cells of the immune system in the zebrafish brain in real-time. This approach revealed the mechanism by which mycobacteria cross the blood-brain barrier, which protects the brain from infection. Whereas elsewhere in the body, mycobacteria use phagocytes for dissemination, we found that only extracellular mycobacteria reach the brain microvasculature. There, they adhere to the microvascular endothelium and grow into microcolonies. These microcolonies induce endothelial cell tight junction reorganization, creating transient gaps through which bacteria enter the brain. This reorganization is induced by the mycobacterial surface glycolipid trehalose dimycolate. Strikingly, M. tuberculosis, its pathogenic relative *M. marinum* and the saprophyte *M. smegmatis* all use this same pathway for brain invasion. Thus, the zebrafish model revealed that *M. tuberculosis* initiates meningitis, the deadliest form of tuberculosis, using an ancestral determinant that evolved for environmental survival.

Dr Cressida Madigan grew up in Michigan and attended the University of Michigan for college. There, she was an undergraduate researcher in Michele Swanson's lab, where she contributed to research on how L. pneumophila flagella engage TLR5. For graduate school, Cressida attended Harvard University as an NSF GRFP fellow, where she studied the antigenic lipids of *M. tuberculosis* in Branch Moody's lab. As a post doc at the University of California, Los Angeles and in the Ramakrishnan lab at the University of Washington, she established a zebrafish model of leprosy and used it to define a mechanism of immune-mediated demyelination of nerves. Further, her work modeling TB meningitis in zebrafish revealed the mechanism by which mycobacteria cross the blood-brain barrier. In 2018, Cressida became an Assistant Professor at the University of California, San Diego. There, as a Pew fellow and NIH New Innovator awardee, she uses zebrafish technology to study neurological infections.

Hosted by: Dr Stefan Oehlers

Seminar is open to all. Registration is required.

Questions? Contact us at **seminars@idlabs.a-star.edu.sg**

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