McGill Biochemistry Department | Département de biochimie

BIOC 462/491 Internship Position in Industry

Summer or Fall 2024

Restrictions

Open only to Honours Students enrolled in BIOC 462/491 during the summer or fall 2024 semesters

Company

Ventus Therapeutics
7150 Frederick-Banting
Montreal, Quebec H4S 2A1
https://www.ventustx.com/

Title

Inflammatory markers and signalling pathways suppressed by pharmacological inhibition of cGAS

Project Description

The detection of viral nucleic acids (NA) elicits a transient type I interferon (IFN) response central to antiviral immunity. Chronic type I IFN responses, however, driven by the sensing of endogenous NA, can drive severe auto-inflammatory diseases. Indeed in humans, loss-of-function mutations in the intracellular 3'repair exonuclease 1 (TREX1) gene are linked to an accumulation of cytosolic DNA and are associated with type I IFN-driven diseases such as Aicardi-Goutières Syndrome (AGS) and systemic lupus erythematosus (SLE). Likewise, TREX1-deficient mice exhibit a chronic systemic interferonopathy. Genetic studies have demonstrated that the cytosolic DNA sensor cyclic GMP-AMP synthase (cGAS), and its downstream adaptor STING, are required to induce the expression of type I IFNs and pro-inflammatory cytokines that are responsible for the auto-inflammatory manifestations of Trex1-/- mice. Pre-clinical validation of cGAS as a small molecule drug target for type I interferonopathies has been elusive due to the lack of a selective cGAS inhibitor with appropriate properties for long-term dosing in genetic models. Ventus has developed a novel cGAS inhibitor with favourable pharmacokinetic properties and confirmed that it completely suppresses the type I IFN response to HSV infection. Using this novel cGAS inhibitor, we have generated the first evidence that selective pharmacological modulation of cGAS activity in a TREX1 deficient mouse model can reduce systemic inflammation. A robust reduction in systemic cGAMP, the cGAS product, was observed following two weeks of dosing. As the central clinical presentation in Trex1-/- mice is autoimmune myocarditis, the inflammatory response in the heart was profiled in compound-treated mice. Strikingly, reduced cGAMP levels correlated with a down-modulation of interferon-stimulated gene (ISG) expression, as well as pro-inflammatory cytokine and chemokine expression in the heart. Ongoing studies, are exploring the impact of cGAS inhibition on dermal inflammation in mouse models, as well as human cell systems and skin explant cultures. The selected student will profile the inflammatory markers and characterize the signaling pathways suppressed by pharmacological inhibition of cGAS using in vitro models.

Contact information

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