

Pete Mitchell: Chemistry & Biochemistry

Mentor: Mark Quinn, Igor Schepetkin, Liliya Kirpotina -- Microbiology & Immunology

Regulating T-cell Responses: Screening and Characterization of Possible Kinase Inhibitors in Ex vivo/In vitro Models

Protein phosphorylation is a key component of T-Cell Receptor (TCR) signaling pathways. Upon activation of a TCR, protein kinases, such as Lck, phosphorylate proteins downstream of the cascade, which results in recruitment of scaffold and adaptor proteins. Transcription factors are modulated following this cascade, which may lead to proliferation and production of cytokines as part of an immune response to the activation of TCR mediated signal transduction. However, when the transcriptional regulation goes awry in lymphocytes, immune dysfunction can occur. Over- or auto-reactive lymphocytes resulting from intracellular pathway disruptions can lead to disorders, such as chronic inflammation, diabetes, and cancer. One approach to manage immune dysfunction is by targeting the deregulated activation of protein kinases and their cascades. The objective of this project is to screen selected sesquiterpene lactones (SLs) for anti-proliferative activity and low cytotoxic effects, followed by characterizing of any affected protein kinases in murine and human models. Cells were pre-treated with a compound for 20 minutes, activated with anti-CD3/CD28, and then T-cell proliferative assays or ELISA were employed. From our experimentation, Erk1/2 was shown to have dose-dependent phosphorylation and was used to gauge other SLs for Erk1/2 selectivity. Additionally, the mechanism of the Erk1/2-SL interaction (estafiatine) was investigated. The data are still preliminary and more experiments are needed to draw conclusions, in particular to the mechanism.