Stony Brook University OVPR COVID-19 Seed Grant Program 2020

Investigating the role of the Sts enzymes in coronavirus-induced hyper-inflammation: establishing a foundation for immunomodulatory-based therapeutic intervention.

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Effective host immunity balances the need to eliminate invading pathogens with the need to avoid host damage. During a normal immune response, numerous biological feed back loops provide the requisite tuning. However, under the right circumstances a well-balanced immune reaction can spiral out of control. Such appears to be the case in a small percentage of Covid-19 patients who progress to the severe respiratory distress stage of the disease. The underlying factors that promote disease progression are currently not clear. This Seed Project focuses on the role of two related host immuno-regulatory proteins in the development of severe inflammatory Covid-19 disease. Sts-1 and -2 are a pair of atypical enzymes that negatively regulate *in vivo* immune responses. Genetic inactivation of Sts in mice leads to aberrant immune responses, including hypersensitive cellular immune responses and increased susceptibility to autoimmunity in diverse models. The role of the Sts enzymes as critical regulators of host immunity is also demonstrated by human genome-wide association studies that link Sts variants to a number of autoimmune disorders. In order to determine a role for Sts in Covid-19 disease and whether therapeutic targeting of Sts could prevent Covid-19 disease progression, we will use mouse models of coronavirus (CoV) infection to investigate a role for Sts in CoV-induced inflammatory responses.