

COMBATting FUTURE BIOLOGICAL THREATS – HOST-DIRECTED INTERVENTIONS TO EMERGING THREATS FOR RAPID RESPONSE

High Throughput Screen For Novel Small Molecule Inducers Of Trained Immunity

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Trained immunity is characterized by epigenetic and metabolic reprogramming in response to specific stimuli. This rewiring can result in increased cytokine and effector responses to pathogenic challenge, providing non-specific protection against disease, including against pathogens for which the host has no prior immunity. It may also improve immune responses to established immunotherapeutics and vaccines, enhancing their durability. Despite the promise of training for next-generation therapeutic design, most current understanding and experimentation is conducted with complex and heterogeneous biologically derived molecules, such as β -glucan or the BCG vaccine. This limited collection of training compounds also limits study of the genes most involved in training responses as each molecule has both training and non-training effects. Small molecules with tunable pharmacokinetics and delivery modalities would both assist in the study of trained immunity and its future application for therapeutics. To identify novel small molecule inducers of trained immunity, we screened a library of 2000 drugs and drug-like compounds. Identification of well-defined compounds can improve our understanding of innate immune memory and broaden the scope of its clinical applications. We identified over 2 dozen small molecules in several chemical classes, including the traditionally immunosuppressive glucocorticoids, that induce a training phenotype in the absence of initial immune activation – a current limitation of reported inducers of training. This study represents the first link between glucocorticoids and trained innate immunity. We chose 7 of these top candidates to characterize and establish training activity in vivo. In this work, we expand the number of compounds known to induce trained immunity, creating new avenues for the study and application of innate immune training.