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

Development Of Mrna-based Biologics Targeting PD-1 For Enhanced Melioidosis Management

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Melioidosis, caused by the Tier 1 select agent Burkholderia pseudomallei, is well-known for its ability to evade the immune system, often leading to severe outcomes in immunocompromised individuals. The infection notably upregulates the PD-1/PD-L1 pathway, contributing to T-cell depletion and reduced immunological response. With an increasing prevalence of antibiotic resistance, there is an urgent requirement for novel therapeutic strategies. The primary objective of this study is to investigate the immunological components of melioidosis, specifically examining the involvement of the PD-1/PD-L1 pathway in immune exhaustion. We aim to develop innovative biologics using mRNA technology that can effectively block this pathway and enhance the immune system of the host. Our research focuses on targeting the interaction between PD-1 and PD-L1 to provide a new approach to treating melioidosis. This approach tackles the complexity of the disease and the increasing resistance to existing antibiotic therapies. This research advances by designing and evaluating mRNA-based biologics, building on previous findings that PD-1 expression plays a crucial role in immune suppression during melioidosis. These biologics have been designed to produce the soluble form of PD-1, which has been specifically modified for delivering intranasally. This strategy aims to directly disrupt the PD-1/PD-L1 pathway, enhancing the immune response at critical infection locations. Our initial findings suggest a notable increase in PD-1 expression in both granulomatous lung tissue and IFN-γ+ CD4 + T cells in infected mice. In addition, inhibiting the PD-1 pathway has been demonstrated to increase the proportion of effector T cells compared to regulatory T cells in PBMCs from convalescent patients, which were stimulated with heat-inactivated B. pseudomallei. The observations provide robust evidence for the therapeutic efficacy of PD-1 targeted biologics. Currently, we have achieved successful expression of the secreted soluble PD-1 protein in vitro utilizing our own modified mRNA. This accomplishment serves as a crucial initial stage in the advancement of biologic development. The results of this study are anticipated to have a substantial impact on biodefense measures, offering a pioneering therapeutic solution for diseases such as melioidosis. These infections present considerable risks in both military and civilian environments, particularly in endemic areas. The implementation of this approach may have broader implications for not just melioidosis but also other infectious and non-communicable diseases, thereby improving the readiness and overall health security of the Joint Force. This research aims to revolutionize the treatment of melioidosis by utilizing state-of-the-art mRNA technology to create biologics that specifically target crucial immunosuppressive pathways. It establishes a basis for additional investigation into mRNA-based immunotherapies for different diseases, potentially broadening the range of effective treatments against a wide variety of bioterrorism threats.