CAMO (COMPARING ANIMAL MODELS TO ORGANOIDS) - TESTING MEDICAL COUNTERMEASURES WITH MICROPHYSIOLOGICAL SYSTEMS AND COMPARING TO TRADITIONAL ANIMAL MODELS AND CLINICAL TRAILS

Evaluation of Host Response to Neurological Infection with Burkholderia Pseudomallei ATS2021 Strain in C57BL/6 Mice

Charles Shoemaker USAMRIID **Christopher Cote** USAMRIID **Kevin Mlynek** USAMRIID **Christopher Klimko** USAMRIID **Sergei Biryukov** USAMRIID **Sherry Mou** USAMRIID **Melissa Hunter** USAMRIID **Nathaniel Rill** USAMRIID **Jennifer Dankmeyer** USAMRIID **Jeremy Miller** USAMRIID **Yuli Talyansky** USAMRIID **Michael Davies** USAMRIID **Ronald Toothman** USAMRIID **Joel Douglas** USAMRIID **Cheryl Taylor-Howell** USAMRIID **Tamara Clements** USAMRIID **Suma Ravulapalli** USAMRIID **Taalin Hoj** USAMRIID **Joel Bozue** USAMRIID **Dave Deshazer** USAMRIID **Keersten Ricks** USAMRIID **Christopher Stefan** USAMRIID **Christopher Stefan** USAMRIID

Melioidosis is an emerging infectious disease in the U.S. caused by the bacterium, Burkholderia pseudomallei. Melioidosis has a variable and inconsistent clinical presentation, ranging from asymptomatic to an acute sometimes fatal pulmonary severe illness, or chronic infection. A subset of patients will develop rare, but serious neurological melioidosis. Typical clinical signs and symptoms include fever, headache, seizures, unilateral weakness, and paralysis. Despite the lengthy treatment regime, up to 20% of patients succumb to the infection. Most cases of neurological melioidosis are reported in the endemic areas of Australia and India. In 2021, four cases of melioidosis associated with an aromatherapy spray imported from India were reported in the U.S; this B. pseudomallei strain was subsequently called ATS2021. Two of the cases involved children who developed neurological melioidosis where one died and the other exhibited long-term sequelae.

In an attempt to understand the host response to B. pseudomallei in the brain, C57BL/6 mice were exposed to aerosolized B. pseudomallei ATS2021 and serially sampled for bacterial burden and host-RNA analyses. We applied a targeted transcriptomic approach against a range of neuroinflammatory genes to brain homogenates from mice collected in this study. In general, we observed a pronounced inflammatory response across the high bacterial dose groups, particularly up to 5 days post-challenge. Some of these significant genes included LCN2 (lipocalin-2), GBP2, and CXCL10. Of particular interest was the consistent elevation of LCN2, which was upregulated in both brain and blood at the transcriptional and protein level, and which is an acute-phase host response element that is secreted by astrocytes during inflammation and is commonly associated with neuronal death and various neuroinflammatory diseases. Subsequently, we utilized a cell profiling module to identify changes in neuronal cell types based on relative abundance of marker genes associated with oligodendrocytes. In the two highest dose groups, we observed significant drops in oligodendrocyte signatures, particularly on days 3 and 5. In total, 27 genes constitute the oligodendrocyte cell profile, of which, 23 had significant expression differences for at least one time-point. Total numbers of significant genes were dependent upon infectious dose. We observed early and pronounced downregulation of many of these genes, as early as day 1 in the highest dose group. These data suggest a dysregulation in oligodendrocytes in infected hosts. In this report, we begin to characterize the host-response to neurological melioidosis in mice and these data could lead to novel medical countermeasure or diagnostic strategies.

Opinions, interpretations, conclusions, and recommendations are those of the authors and are not necessarily endorsed by the U.S. Army or the Department of Defense Health Agency. Research was conducted in compliance with the Animal Welfare Act and other federal statutes and regulations relating to animals and experiments involving animals and adheres to principles stated in the Guide for the Care and Use of Laboratory Animals, National Research Council, 2011. The facility where this research was conducted is fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International.