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## A Toxidromic Approach for Chemical Medical Countermeasure Development

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### **Characterization and Treatment of Chronic Sulfur Mustard-Induced Pulmonary Injury and Associated Mortality**

Dana Anderson, U.S. Army Medical Research Institute of Chemical Defense

Danielle Zimmerman, USAMRICD

Austin Lewis, USAMRICD

Wesley Holmes, USAMRICD

Sulfur mustard (SM) is a vesicant agent that was first used in WWI. SM attacks epithelial tissue of the skin, eyes and respiratory tract. Most casualties are associated with dermal or ocular exposures, but most of the mortality caused by SM is linked to inhalation exposures. The result of such exposures is an acute obstructive injury followed by chronic morbidities such as bronchitis, bronchiectasis, fibrosis and bronchiolitis obliterans. This is a progressive pulmonary injury that can compromise potential return to duty of the warfighter. The objective of this study is to investigate the chronic pulmonary morbidities associated with inhaled SM vapor. This project will use an established and validated SM exposure model and dose that reliably produces pulmonary fibrosis in untreated rats. We will use this model to test the efficacy of selected treatments for SM-induced chronic pulmonary effects. Subsequently, we are establishing an exposure model using rabbits to more systematically investigate the time-course of development of SM-induced pulmonary injury in a second species. Once the rabbit exposure model and time-course of SM-induced pathology have been described, the most effective therapeutics from the rat model will be evaluated further in rabbits. Studies are 28 days long to allow the development of the chronic morbidities. End points for the rat studies include weights, pulse oximetry, clinical scores (5-7 days per week); whole body plethysmography (Buxco, weekly); and, at euthanasia, pulmonary mechanics (Flexivent), blood gases, CBC, histopathology and lung lavage/lung tissue collection for biochemical assays. For the rabbit model development, we plan to use an exposure system similar to that used for rats which involves an anesthetized, intubated animal. The rabbits will be intubated with standard medical endotracheal tubes. The vapor generation chamber and concentration of SM will be modified to accommodate the larger tidal volume of a rabbit. The initial study endpoints will be survival, clinical measures, and pathology to determine if the injury is similar to what is seen in rats and reported in humans. The use of the chemical warfare agent SM on the battlefield remains a clear threat to the United States military and allied forces. The lungs are a primary target of SM exposure, which is associated with high rates of both acute and chronic morbidities. While there is currently no therapeutic measure to alleviate the pulmonary injury, this project represents a realistic approach toward that end.