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

Live-attenuated, Rearranged V4020 Vaccine For Venezuelan Equine Encephalitis: Preclinical Studies

David Saunders Uniformed Services University School of Medicine **Peter Pushko** Medigen, Inc. **Joseph Mattapallil** Uniformed Services University School of Medicine **Igor Lukashevich** University of Louisville, Louisville, KY **Dylan M. Johnson** University of Louisville, Louisville, KY **Irina Tretyakova** Medigen, Inc. **Donghoon Chung** University of Louisville, Louisville, KY

Venezuelan equine encephalitis (VEE) is a naturally occurring viral infection, primarily in endemic areas in South America. It is highly infectious, easily aerosolized, and capable of causing significant, debilitating symptoms within 24-48 hours of infection. There are no FDA-approved countermeasures available. Live, attenuated virus vaccines offer the potential for long-term immunity with a single dose. A live, attenuated vaccine may be a particularly advantageous VEE countermeasure. We are currently developing a novel VEE vaccine, V4020, which is intended to improve on the safety and efficacy profile of the historic TC83 live, attenuated VEE vaccine developed by the US Army. The V4020 experimental vaccine includes attenuating mutations from VEEV TC83 vaccine, as well as structural gene rearrangement to provide additional attenuation and resistance to reversion. V4020 was designed using an infectious clone manufactured using a serum-free process. In preclinical studies, BALB/c mice were vaccinated subcutaneously with a single 104-105 PFU dose of V4020 virus, or with 0.5-5.0 ug of pMG4020 plasmid expressing V4020 virus intramuscularly (by electroporation). Mice had no adverse reactions to vaccinations and developed high titers of neutralizing antibodies (PRNT80 up to 1:2560). Following challenge with the wild type VEEV, all vaccinated mice survived with no morbidity, while unvaccinated controls succumbed to infection. Safety was demonstrated by intracerebral passages in mice with no evidence of reversion. The safety and immunogenicity of V4020 vaccine was further confirmed in New Zealand rabbits vaccinated transdermally using hollow microneedles with either 104 PFU of V4020, or with 20 ug of pMG4020. Finally, cynomolgus macaques were vaccinated subcutaneously with 104 PFU of the V4020 vaccine resulting in protection from aerosol challenge. No adverse reactions to vaccination were noted. Currently, neurovirulence and neuroinvasion of the V4020 vaccine virus is being compared with the TC83 vaccine in preclinical toxicology studies in anticipation of Phase 1 clinical trials.