BROAD-SPECTRUM THERAPEUTICS FOR VIRAL DISEASES: A MEDICAL COUNTERMEASURE PLATFORM FOR EMERGING THREATS

A Safe And Effective Neutralizing Dna Aptamer Therapy For Combating Sars-cov-2

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Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been straining the health-care system for over two years and continues with more than one million new infections and thousands of deaths around the world each day. Although available vaccines and approved therapies have shown tremendous benefits, the continuous emergence of new variants of SARS-CoV -2 and the side effects of existing treatments persistently challenge the healthcare system, making the development of effective therapy urgent and critical. To address this, using systematic evolution of ligands by exponential enrichment (SELEX), we developed a series of single-stranded DNA aptamers that can universally recognize the Spike (S) protein of the original SARS-CoV-2 virus, as well as S protein of Delta, Delta plus, Alpha, Lambda, Mu and Omicron variants of SARS-CoV-2. In an in vitro study, our aptamers showed high binding affinity and high specificity to variants of the S protein as well as excellent inhibition of the binding of S protein to ACE2 receptors in Vero E6 cells. Among the aptamers, AYA2012004_L and its modified AYA2012004_L_M1 showed up to 70% inhibition of the binding of pseudo-virus-like particles (VLPs) expressing S protein to ACE2 receptor expressed in HEK293K cells. In vivo studies were conducted in rodent model, transgenic mice expressing human ACE2 by the human cytokeratin 18 promoter (K18 hACE2), to demonstrate the uptake of VLPs by lung cells when treated with SARS-CoV-2 VLPs. Both aptamers AYA2012004_L and AYA2012004_L-M1 were able to neutralize the uptake of VLPs by the lungs. Safety studies showed that our aptamers did not induce any inflammatory response in the lungs of Th1 and Th2 mouse models or with human PBMCs. The aptamers appeared to be detectable in mice lungs and traces of the aptamer were detected in other vital organs (e.g., kidney, heart, liver, spleen) with no signs of degenerative histopathology. Body weight of mice showed no significant change in 30 days of aptamer administration. AMES test also confirmed that our aptamers were not mutagenic and proved safe in in vivo studies. Overall, the findings imply that our selected aptamers can prevent SARS-CoV-2 from entering host cells and suppress the viral infection. Also, the findings suggest that our aptamers are promising as a safe and effective therapeutic agent for COVID-19 treatment.