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

Human Derived Monoclonal Antibodies Are Protective Against Lethal Machupo Virus Challenge In Guinea Pigs

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Arenaviruses are Priority A pathogens that cause severe hemorrhagic fever in humans and represent a serious concern for public health. Those that can infect humans are antigenically divided into Old World (OW) and New World (NW) arenaviruses. NW arenaviruses include Junin virus (JUNV), Machupo virus (MACV), Chapare virus (CHAPV), Guanarito virus, and Sabia virus and can cause debilitating disease with fatality rates upwards of 30% throughout South America. Specifically, MACV causes sporadic outbreaks in Bolivia where it is endemic. In humans, MACV infection generally results in febrile illness that can result in hemorrhage and in severe cases multi-organ failure and lethal shock. In a subset of cases, infection also causes neurological disease with encephalitis. Currently there are no FDA-approved licensed therapeutics or vaccines available to prevent or treat patients infected with any arenavirus. Building upon the successful strategy employed for the development of the broadly protective monoclonal antibody (mAb) cocktail MBP134 for Ebola virus, and a strategy we have used to subsequently develop mAbs against Marburg virus and Crimean-Congo hemorrhagic fever, we isolated novel MACV mAb therapeutic candidates from B-cells of survivors of MACV outbreaks in Bolivia. This discovery effort yielded a panel of 32 MACV glycoprotein (GP)-specific mAbs. These MACV mAb candidates were down-selected through a series of in vitro assays, including kinetic, expression, effector function, epitope binning, and neutralization assays. These studies revealed that only one mAb, MACV019, was capable of neutralizing MACV, therefore kinetic, effector function, and expression analysis was the primary determinant for initial down-selection. Using in vivo rodent models of MACV disease, mAbs with potent protective efficacy were first identified by treating MACV infected immunocompromised (STAT1 KO) mice with mAb at 1 mg 1-day post-challenge. From these studies, nine mAbs emerged as promising candidates, providing partial protection (20-70%) against lethal disease. These antibodies were subsequently tested at a single dose of 5 mg 1-day post-challenge in Hartley guinea pigs. MACV019 and MACV061 emerged as the most effective mAbs, resulting in 66% and 50% protection, respectively. Further optimization of the dosing scheme via treatment of guinea pigs with MACV019 on days 1-, 4-, and 7-days post-challenge (4 mg total) resulted in 100% protection against lethal challenge, with treated guinea pigs experiencing little clinical disease or weight loss. Future studies will test this mAb, and MACV061, under increasingly stringent conditions to determine the point of breakthrough. With the goal of developing mAbs with pan-arenavirus potential, we tested the ability of our MACV-specific mAbs to bind recombinant GP from additional arenaviruses by ELISA. These studies revealed that MACV061 could also bind JUNV GP. In upcoming studies, we will test the therapeutic potential of MACV061 against lethal JUNV disease in Hartley guinea pigs. If successful, we will seek to test the therapeutic efficacy of cocktails of MACV019 and MACV061 against lethal MACV and JUNV disease in guinea pigs, and this cocktail could function as a pan-arenavirus therapeutic. This work is critical for the development of potent mAb therapeutics against arenaviruses for which none are currently available.