Molecular Therapy
Editorial

The Improbability of the Rapid Development of a Vaccine for SARS-CoV-2

The coronavirus SARS-CoV-2 (Cov-2) has emerged on the world stage as a pandemic. It is a highly infectious agent that can spread rapidly and has a mortality rate of ~2%–5%. Similar to its cousin, SARS-CoV-1 (Cov-1), CoV-2 employs the angiotensin converting enzyme 2 (ACE2) receptor and the serine protease TMPRSS2 to infect lung epithelial cells. CoV-2 also infects lung endothelial cells and macrophages and monocytes.[1] Intriguingly, macrophages do not express appreciable levels of ACE2 or TMPRSS2,[1] suggesting that this virus might use an entirely different receptor and a serine protease other than TMPRSS2 to infect these immune cells. An alternative, and possibly more likely explanation, based on a plethora of past studies with other coronaviruses, is that Cov-2 employs antibody-dependent enhancement (ADE) to infect immune cells.[2]

ADE is a phenomenon whereby antibodies bind to the targeted virus and then the resulting antibody/virus complex enhances uptake of the virus by host macrophages and other immune cells. ADE was originally observed with Dengue virus infection and also in the coronavirus feline infectious peritonitis virus (FIPV).[2] A relatively overlooked body of ~40 years of research exists with cats and coronaviruses. Cats infected with FIPV experience dry and wet forms of disease that ultimately result in serious pathologies, including respiratory and neurological issues that are usually fatal.[2] Moreover, in cats, it is well known that immunization with feline coronavirus spike protein leads to ADE and, in general, the worsening of infection upon exposure to infectious virus.[3–5] Interestingly, in cats infected with FIPV, the expression of ORF7 has been found to be required for macrophage infectivity and ADE, suggesting that coronaviruses have evolved molecular mechanisms to modulate macrophages.[6] Indeed, ADE has been observed to date in several coronaviruses, including CoV-1[7,8] and Middle East respiratory syndrome (MERS),[9] and, notably, Orf7 is present in the genomes of both Cov-1 and Cov-2,[10] ultimately suggesting that macrophages are involved in the basic biology of coronaviruses and ADE. Collectively, what is apparent is that the evolutionary adaptation of ADE by coronaviruses to infect macrophages as a means to not only replicate in these immune cells, but to also disseminate the virus infection distal from the lungs,[1] represents a bona fide and largely underappreciated challenge to antibody-based therapeutics and, in particular, the development of a humoral-based vaccine.

There is little doubt that humankind would love nothing more than to have a viable vaccine to CoV-2. However, there are objective realities for why we do not yet have a vaccine for coronaviruses in cats, Dengue, Ebola, and HIV in humans, and this is because all of these viruses induce some level of ADE. Moreover, it is exceedingly challenging to dissect and control an immune system that has co-evolved with viruses for millions of years. It is for these reasons, based on an abundance of previously published studies on ADE and coronaviruses, that I am concerned by the lack of focus and/or concerted efforts toward the rapid development of therapeutics specifically tailored for CoV-2. Coronaviruses are susceptible to RNA interference,[11,12] antisense RNA, and oligonucleotide therapeutics,[13–15] suggesting that both cellular and molecular gene and cell therapies could prove quite useful in treating coronavirus infections. What is important to note is that therapies exist that can generally work in a relatively short period of time and can be tailored to specifically target the virus at a fraction of the cost of a vaccine. It is not surprising that there is much hope for a vaccine to end this pandemic in a single shot so that we can all return to the "old normal," but there are, however, regrettably objective realities in biology, and ADE is one of them.[15] This is not to say ADE cannot be overcome, but rather that it should heavily factor into the equation in the development of a viable vaccine for Cov-2 and coronaviruses in general. The exceedingly difficult past ~35 years of challenges in trying to develop a vaccine for HIV have made clear to me that we should strive for the penultimate goal of a vaccine but always have a therapy in our back pocket.

CONFLICTS OF INTEREST

K.V.M. has an interest in developing therapeutics to treat various virus infections. Several intellectual patent disclosures for treating various viral infections, including CoV-2, have been filed at the City of Hope and The Scripps Research Institute, where he has carried out his research.

ACKNOWLEDGMENTS

This project was supported by the National Institute of Mental Health (NIMH) R01 113407-01 to K.V.M.

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https://doi.org/10.1016/j.ymthe.2020.06.005

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