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Taming Measles Virus to Create an Effective Cancer Therapeutic

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Measles virus (MV) has been a longtime bane of the human race. Once described by Rhazes (10th century Persian physician) as "more dreaded than smallpox,"[1] it remains globally one of the leading causes of death among young children.[2] In the 5 years before the introduction of the 1963 measles vaccination program, there were over 4 million cases of measles reported in the United States, and nearly twice as many deaths were attributed to measles as to polio infections during that same period.[3] Yet for all the misery MV has caused and continues to inflict on mankind, it now appears that a genetically engineered version of the virus may be on its way to becoming an effective treatment for another deadly human malady, late-stage incurable myeloma. In this issue of *Mayo Clinic Proceedings*, Russell et al[4] from Mayo Clinic report, for the first time, the use of a cytolytic replicating MV to completely eliminate widespread tumors in a patient with advanced incurable myeloma.

The choice of MV as a therapeutic agent for myeloma was not happenstance, but rather the result of several years of thoughtful biological experimentation and rational virus engineering. Russell et al recognized several features of myeloma that would complement the life cycle of MV. Myeloma is the second most common hematologic malignancy in North America, and although treatable, it is essentially an incurable disease with a 5-year survival rate of less than 40%. A hallmark of the disease is the seeding of malignant plasma cells throughout the bone marrow, ultimately impairing the production of normal blood cells and creating lesions in the bone (see Figure 2, A in Russell et al[4]). During natural infections, MV gains access to the bone marrow through infection of the reticuloendothelial system, thus making it an ideal agent to attack myeloma cells exactly where they hide. CD46, a cell surface antigen, is the receptor for MV and is highly overexpressed on the surface of myeloma cells, making them prime targets of infection.[5] Measles virus is rapidly neutralized and inactivated in the bloodstream by antibodies that arise following vaccination or natural infections.[6] Neutralizing antibodies provide a safety shield against MV infections for most North Americans. In many myeloma patients, however, neutralizing antibodies directed against MV are at very low levels or absent because both the disease and the current therapies used to treat it are immunosuppressive.

The "oncolytic" or "cancer lysing" MV vector used by Russell et al[4] was originally derived from the Edmonston measles vaccine strain by another Mayo Clinic scientist, Roberto Cattaneo, and his colleagues in 1990, using DNA recombinant technology. For the study reported in this issue of the *Proceedings*, the virus was further modified to contain the mammalian *NIS* gene that encodes the sodium iodide symporter, a pump protein responsible in part for the concentration of iodine in the thyroid. On productive infection of a patient by the MV encoding the *NIS* gene (MV-NIS), tumor cells express large amounts of the symporter protein on their surface and become endowed with the ability to concentrate radioactive iodine.[7] Thus, MV-NIS—infected tumor cells can be imaged using radioactive iodine tracers like the gamma-emitting iodine 123, which is readily detected using clinically available scanning techniques. This property was exploited in the report by Russell et al to illustrate the exquisite specificity of MV-NIS for tumor tissue and to assess the extent and duration of infection. Future studies will likely use the tumor-specific expression of NIS to concentrate the high-energy beta-emitting isotope iodine

131, creating a "kill zone" around the infected cell and enhancing therapy.

Aside from MV-NIS, there are numerous other oncolytic viruses (OVs) currently under clinical development, including variants of herpes virus, poxvirus, picornavirus, rhabdovirus, reovirus, Newcastle Disease virus, parvovirus, and adenovirus.[8] In rodent tumor models, each of these viruses has shown excellent systemic activity when infused intravenously, often resulting in long-lasting durable cures.[9] So far, however, this intravenous antitumor activity has not translated into clinical use for any of these other OV agents. The general disconnect between mouse and human studies is multifaceted and likely reflects, in part, the limited number and scope of intravenous studies carried out with OVs to date. From rodent tumor models, we know that natural barriers in the blood prevent intravenous OV delivery to tumor beds.[10] These barriers include neutralizing antibodies, blood complement factors, scavenger cells, and a variety of additional poorly described virus sinks or undefined structures which irreversible bind and inactivate viruses. Together, these physical barriers create a "threshold effect," such that effective virus delivery to sites of metastatic tumor growth occurs only at high virus concentrations. The study by Russell et al[4] reported in this issue of the *Proceedings* is part of a larger clinical trial initiated several years ago and involved slow escalation studies beginning at doses 100,000 times lower than the effective dose used in the 2 patients they singled out for individual reporting. The striking oncolytic activity of MV reported in their article is likely only evident now because a critical threshold of virus concentration in the blood was achieved, allowing the virus to overcome natural blood barriers. Interestingly, in patient 2, who had an equally impressive but less durable response than patient 1, there was a consistently lower level of detectable virus in the blood as early as 1 minute after infusion, suggesting that differences in virus sinks between patients may affect outcomes. A similar threshold effect was observed in an intravenous phase 1 study performed with JX-594, a poxvirus-based OV product evaluated for the treatment of solid tumors, wherein virus delivery to tumors occurred only at the highest dose tested.[11]

Both patients in the report by Russell et al lacked detectable neutralizing antimeasles antibody at the beginning of their treatments, likely a critical factor for the virally mediated tumor responses they experienced. For future studies using MV-NIS, it will be essential to select patients with myeloma who lack antimeasles antibodies or use other strategies to protect the infused agent. For instance, the MV-NIS could be hidden from the patient's immune system by using carrier infected cells,[12] or genetic modification could be made to MV-NIS to prevent it from being recognized by preexisting MV neutralizing antibodies. Other OVs in development (eg, rhabdoviruses) are not human pathogens, and it is likely that most North Americans will not have preexisting immunity, providing these platforms an advantage as systemic agents.[13]

One common worry about the use of replication-competent virus vectors as therapeutics for cancer is a fear of "off-target infections" leading to virus-mediated toxicities. This is a reasonable concern because immunosuppressed cancer patients can succumb to infection with a variety of wild-type pathogenic viruses including MV.[14] However, as with all OV platforms, the MV-NIS vector is highly attenuated for growth in normal tissues yet retains the capacity to infect and destroy tumor cells. Russell et al[4] illustrate the exquisite specificity of MV-NIS infection, which in these patients is clearly targeted and restricted to the tumor bed. Through the use of single-photon emission computed tomography/computed tomography for NIS expression coupled with positron emission tomography for glucose-avid sites, the investigators were able to confirm the tight linkage between virus replication and areas of myeloma growth. Within the first few hours after infusion, both patients experienced fever and other flulike symptoms, but these adverse effects were short lived and easily treated. These findings are in line with those of many other clinical studies using a spectrum of assorted OV platforms and confirm the general safety of this approach.[8] The study by Russell et al does not provide the first evidence that OVs can have systemic activity against cancers. The clinically advanced Talimogene laherparepvec or T-Vec virus being developed by Amgen Inc has shown systemic activity but requires multiple local injections, and therapy appears to be a consequence of initiation of a profound antitumor immune response that

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attacks even uninjected tumor sites[15] rather than virus-mediated killing. In the OV field, there continues to be debate over whether the best therapeutic viruses are those like T-Vec, which are used exclusively as locoregional therapeutics, or systemically administered viruses like MV-NIS that have the potential to infect widespread metastatic tumors. To date, this debate has been somewhat one-sided because no OV product has previously documented clinical efficacy against systemic cancers when administered intravenously. Russell et al[4] now provide compelling evidence that a single infusion of an OV can lead to complete systemic antitumor responses, even in patients with advanced cancer. For the rest of the OV field, these are exciting results that finally validate the clinical potential of this class of therapeutics. However, there is much research to be done. We still know remarkably little about the best way to deliver OVs intravenously to patients. The speed and duration of infusion, the quantity of virus, and the number of doses to be administered are all poorly understood at this time, but the study by Russell et al now provides a benchmark to strive for and improve upon.

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