ONCOLYTIC VIRUSES: A MULTI-PRONGED APPROACH TO TUMOR KILLING

The development of oncolytic viruses to target solid tumors is an area of intense preclinical and clinical interest. Oncolytic viruses (OVs) are engineered using well studied viruses such as vaccinia, adenovirus and herpes simplex virus as well as lesser-known viruses such as Maraba virus (originally isolated from Brazilian sandflies) and foamy viruses. Viruses are engineered to have specific characteristics including tissue tropism (the ability to naturally infect specific organs), tumor selectivity, immunogenicity and a payload that can stimulate the immune system. GM-CSF is one of the most widely used payloads in OVs as it boosts the immune system and increases the production of T-cells.

OVs kill tumor cells through multiple mechanisms – tumor cells are directly lysed post infection releasing tumor antigens, immune mediators, cytokines etc. which induce an immune response. The payload in the viruses express therapeutic proteins that further activate the immune response and recruit cytotoxic T cells to the tumor to mediate killing. OVs have also been shown to mediate an abscopal effect where distant uninfected tumors regress in response to OV infection of one tumor site. Given the multi-pronged approach to tumor killing, OVs are actively being developed as stand-alone therapies and as combination therapies with immuno-modulators and checkpoint therapies.

One challenge with OVs is the balance between the induction of an antiviral response and an antitumor response. An antiviral response typically starts with the synthesis of proinflammatory cytokines including type I interferons, followed by the priming of T-cells by viral antigen presentation leading to viral clearance. In order for OVs to be maximally efficacious, it is important to manage the antiviral response and subsequent viral clearance. Many OV therapies in development are administered directly into the tumor with the intention of triggering direct tumor lysis and stimulating immune cells in the local tumor microenvironment. Systemic administration of OVs is more challenging due to the presence of anti-viral antibodies that reduce viral titer and contribute to viral clearance. Some of the approaches include masking viruses in polymeric materials or in extracellular vesicles as well as using novel viruses that humans have not been exposed to and therefore do not have pre-existing immunity. A good example of a novel OV is the Maraba virus that is being developed by Turnstone Biologics.

To date, Imlygic® (talimogene laherparepvec) is the only OV therapy for recurrent melanomas[1] but there are about 100 active or completed clinical trials using OVs either as single agents or in combination with existing chemotherapies, monoclonal antibodies or radiation[2]. Melanomas, gastrointestinal cancers including pancreatic tumors and brain tumors (glioblastomas, astrocytomas etc.) are the most popular indications in clinical trials but there is increasing interest in other tumor indications that have an unmet clinical need such as triple negative breast cancer. A recent report[3] showed that the combination of an oncolytic reovirus (pelareorep) combined with either atezolizumab, letrozole or trastuzumab in women with different types of breast cancers showed an increase in tumor infiltrating lymphocytes or TILs across all breast cancer subtypes. This is a favorable result as an increase in TILs correlates to a better response to immune checkpoint inhibitors and is clinical evidence that OVs can prime the immune system to attack tumors.

While there is limited clinical information on OV efficacy as most of the ongoing trials are in phase I or I/II, there is a growing body of preclinical knowledge on OV engineering and its application as a mono or combination therapy in solid tumors.

Interested in learning more about OV engineering? Check out our recent webinars on cell and gene therapies.

1 https://www.amgen.com/newsroom/press-releases/2015/10/fda-approves-imlygic-talimogene-laherparepvec-as-first-oncolytic-viral-therapy-in-the-us
2 www.clinicaltrials.gov
3 https://www.cancertherapyadvisor.com/home/news/conference-coverage/san-antonio-breast-cancer-symposium-sabcs/sabcs-2020-immunotherapy-in-depth/breast-cancer-oncolytic-virus-immune-response-treatment/