The Time Has Come: The Paradigm Shifting Potential of Oncolytic Immunotherapy

October 2020

Authored by Philip Astley-Sparke and Robert Coffin. Ph.D.

All cancer involves a failure of the immune system in one of two ways: 1) either in recognizing a tumor as foreign or 2) in sustaining an immune response once initiated. The latter problem of immune system shutdown has been relatively well-addressed over the last decade, at least with respect to the inhibition of effective immunity mediated through the PD1/PD-L1 axis. However, if a patient's cancer is never sufficiently recognized as foreign in the first place, and the body fails to induce a robust anti-tumor immune response, then the mechanism of overcoming inhibition of the response (e.g. the anti-CTLA-4 mechanism) or preventing it from being blocked once generated (e.g. the anti-PD1/L1 mechanism) is moot. For this reason, despite all the advances in immuno-oncology, it remains the case that the majority of patients see little or no benefit. So how do we shift the treatment paradigm and deliver more effective therapies for patients?

We believe oncolytic immunotherapy ("OI") provides the most practical and effective means to ensure a tumor is recognized as foreign and that a robust anti-tumor immune response is induced. Oncolytic immunotherapy is a dual mechanism of action where upon injection of a lytic virus into a tumor, the virus selectively replicates within the tumor, bursting cancer cells open and exposing the cancer antigens within to the immune system to trigger necrotic cell death, a major immune danger signal. Immune policing, or antigen presenting, cells are attracted to the injection site, where they internalize the released antigens, drain to lymph nodes, and prime T cells to destroy tumors with a similar antigen complement throughout the body. In other words, the local oncolytic action of the virus injected into the tumor leads to the generation of a truly systemic anti-tumor immune response ('immunotherapy').

We were not the first to think of using a virus to treat cancer, but we are the first to get the approach to work. T-VEC (Imlygic), the first and only FDA-approved oncolytic immunotherapy, took us over 10 years to develop, providing unrivalled experience in the field and valuable insights about what an optimal oncolytic therapy should be. With this historical knowledge and the advances in understanding the interaction between the immune system and cancer over the last decade, we are able to design powerful, next-generation oncolytic immunotherapies that we believe are poised to change the paradigm in cancer treatment.

Effective and Practical

As we think about efficacy, OI has clear theoretical advantages over other therapeutic modalities:

- **Universal Neoantigen Vaccine**: Oncolytic immunotherapy effectively generates a universal neoantigen vaccine directly in the patient. The entire array of neoantigens are exposed to the immune system in a patient-specific fashion, together with the activation of both the innate and adaptive sides of the immune system. No other technology is simultaneously off the shelf with the attendant CMC and logistics benefits and patient-specific. Further, there is no guess work needed to choose which neoantigens might be first identified through sequencing of the tumor and then used to manufacture a vaccine.
- **Multi-Modal Approach**: If the right viral species and delivered transgenes are deployed then the approach delivers an optimal combination of mechanisms of action to the patient in a single

therapy. We do not believe any other technology has the potential to provide this multi-modal approach.

On the practical side, oncolytic immunotherapy offers an off-the-shelf formulation in a vial that is relatively inexpensive to manufacture. It is injected into a subset of a patients' tumors, no more technically complicated than taking a biopsy, with imaging guidance for deeper tumors such as those in the liver and lungs. It is administered as a straightforward outpatient procedure and is generally well-tolerated, allowing patients to quickly return to their daily lives, and also allowing for the modality to be pushed early into the disease course where the impact on increasing cure rates is likely to be the most pronounced. When compared to other tumor vaccination approaches that require complex processes and high costs, oncolytic immunotherapy emerges as a much more viable approach. The potential barriers for commercial adoption mainly relate to patient referral patterns, where radiologists need to be involved to make deep seated injections in those patients where needed, but these barriers are often perceived rather than real. At a macro level, with community hospitals in the US being rolled up into integrated networks, treating physicians and radiologists are increasingly under one institutional umbrella, which should help alleviate this concern.

However, theory is one thing. Hard data and patient experience are what matter. The potential of oncolytic immunotherapy was first revealed in April 2015, with powerful patient testimonies at the Oncology Drug Advisory Committee, where the first oncolytic drug approved by the FDA, T-VEC, was recommended for approval (22 votes to 1). Roll forward to the final publication of the pivotal study on which T-VEC was approved and it is apparent that one in four patients in the pre-visceral setting were effectively cured, and in the real world, the results have been even more impressive. While single agent TVEC is less effective in patients who have developed visceral metastases, the data makes a compelling case that T-VEC should be the standard first line therapy in patients with unresectable Stage III and early Stage IV melanoma, which, for reasons that are unclear, has yet to become the case. The evidence for the clinical utility of T-VEC has continued to mount in combination with checkpoint blockade drugs, including in a controlled setting.

The T-VEC data is early demonstration of the potential of oncolytic immunotherapy, but T-VEC is a first-generation therapy. While the data alone, and in combination, demonstrates the safety and potential for efficacy, it also highlights the opportunity to take the technology to the next level, which we've sought to achieve by re-designing OI for optimal effect. In particular, we are designing therapies to benefit patients with other types of cancer (i.e. beyond melanoma) and for patients with visceral disease, as we are convinced that OI can become a cornerstone approach to cancer treatment.

One Plus Two Equals Four

Our insights and historical experience have allowed us to design the next generation of oncolytic immunotherapies, "oncolytic immuno-gene therapies" that deliver a 1-2 punch to both directly kill the tumor and activate a systemic immune response against the patient's cancer. Signal 1, or the first punch, is the effective presentation of tumor antigens to the immune system, in a highly immune activating 'inflamed' tumor microenvironment. We have achieved this through careful selection of the underlying virus, sampling the natural diversity of herpes simplex virus in the human population to select an optimal clinical strain, and then arming that strain with select genes to augment the natural ability of the virus to kill tumors in an immunogenic fashion. Our lead therapeutic candidate RP1 encodes a fusogenic protein ("GALV-GP R") that not only adds to the tumor-killing ability of the virus, but also increases immunogenic cell death. RP2 and RP3 are further genetically armed with other therapeutic payloads. With this approach, we block feedback loops that reduce the potency of the immune response

as it's generated and simultaneously provide very potent 'Signal 2' co-stimulatory signals into T cells to maximally activate them as they are generated. This 'one-two punch' can also be combined with systemic anti-PD1 therapy to maximize the overall therapeutic effect.

Our oncolytic immuno-gene therapy product candidates have the unique ability to maximize the activation of Signal 1 and Signal 2 simultaneously, which we don't believe can be achieved with antibody-based approaches, other biological approaches, or with small molecules. When the patient's immune system has been maximally activated, we believe that we have the potential to prevent many cancer patients from ever succumbing to their disease. With our current suite of investigational therapies, with sequentially increasing immunological potency through RP1 to RP3, we are taking oncolytic immunotherapy to the next level and are already not only demonstrating meaningful additional clinical efficacy in tumor types that already respond to immune-based therapy, but also situations where no or minimal efficacy has been seen.

RP1 encodes two proteins to increase tumor killing and the immunogenicity of tumor cell death, and has already generated a compelling rate of complete responses in ongoing human clinical trials in combination with anti-PD1 therapy (nivolumab) in cutaneous squamous cell carcinoma in the initial patients treated. It also has shown that melanoma patients with extensive visceral disease and those refractory to immune checkpoint blockade can respond. Further, biomarker data strongly supports the clinical responses showing that patients with little evidence of pre-existing immune response (low levels of PD-L1) can achieve responses. Anecdotal early activity has also been observed in patients with other tumor types, and a cohort of patients with anti-PD1 relapsed and refractory non-small cell lung cancer is expected to begin enrollment this year. This data to date with RP1 has been generated following injection not only into superficial disease, but also through imaging-guided injection into deeper tumors, including in the liver and lungs, opening the way for broad utility across patients and cancer types.

The next more immunologically potent product candidate, RP2, which additionally encodes an anti-CTLA-4 antibody-like molecule, has demonstrated clinical responses in heavily pre-treated patients with immune-insensitve tumor types (esophageal cancer, uveal melanoma and mucoepidermoid carcininoma) as single agent. RP3, additionally expressing a pair of immune costimulatory pathway activating ligands (CD40L and 4-1BBL), is due to enter the clinic by the end of the year. No other oncolytic immunotherapies have been optimized with an equivalent complement of immune-activating capabilities, combining: 1) a carefully selected underlying viral strain: 2) increased and fusion-enhanced immunogenic cell death; 3) blockade of the anti-CTLA-4/B7 axis; and 4) pleiotropic activities of the CD40 and 4-1BB pathways that provide additional immune co-stimulation, further leading to the release of inflammatory cytokines such as IL-2 and IL-12.

As a result, the paradigm-shifting potential of oncolytic immunotherapy is now clear. We believe the pieces have come together on how to maximize the activation of the body's immune system to treat cancer, inducing an immune response where none was present before. This is a key part of the immuno-oncology equation that oncolytic immunotherapy is uniquely positioned to accomplish. In the words of Victor Hugo, "There is nothing powerful enough to resist the force of an idea whose time has come."

Philip Astley-Sparke (CEO) and Robert Coffin (President & Chief of R&D) are co-founders of Replimune Inc. (NASDAQ REPL), a company at the forefront of oncolytic immunotherapy and were previously CEO and CSO respectively of BioVex Group Inc which developed the only currently FDA approved oncolytic product.