Molecular Therapy
Oncolytics
Meeting Report

Updates on Oncolytic Virus Immunotherapy for Cancers

Cole Peters,[1] Paola Grandi,[2] and Fares Nigim[1]

The 2018 annual Cambridge Healthtech Institute's International Immuno-Oncology Summit in Boston, MA convened late August, and academic and industry researchers were allowed to debate and discuss oncolytic virology during the virus immunotherapy portion of the conference. The breakthrough agent, TVEC/IMLYGIC, as well as most other oncolytic viruses (OVs) in clinical trials, are demonstrating an immense synergy with T cell checkpoint inhibitors. To this extent, the marriage of T cell checkpoint inhibitors and OV is now vastly accepted, indicating the next phase in OVs is the recruitment of the immune system, and tailoring the immune response toward tumor clearance is a far better strategy than directly lysing the tumor outright with virus. The next field-shaping question for OVs is how to convert a patient's immune response against their tumor. The talks this year focused on whether OVs can cause the emergence of a strong anti-tumor immunity intrinsically or whether vectors, which educate the immune system to detect tumor antigens, were more efficacious. Speakers presented novel transgenes to arm OVs and systems biology approaches to discover the best viral backbones to engineer into vectors. Here we summarize the meeting's keynote talks, thematic principles running through the summit, and current developments in the OV field.

The use of oncolytic viruses (OVs) has rapidly expanded in the past 5 years. From the start of ClinicalTrials.gov in 1996 to 2010, there were only 14 clinical studies recorded on ClinicalTrials.gov, and many of them started in 2006 to 2007, 5 years after the trial of oncolytic herpes simplex virus (oHSV) G207 in glioblastoma (GBM).[1,2] Today there have been more than 57 reports since 2010,[3] demonstrating the intense interest of clinicians, academics, and industry in developing this exciting therapeutic. Each year Cambridge Healthtech Institute holds an international summit focusing on cancer, gene, immune, and viral therapies, which draws a wide swath of academics and industry representatives interested in pursuing novel approaches to old afflictions. This year, the oncolytic virology portion of the summit began with a presentation from Samuel Rabkin of Harvard University/Massachusetts General Hospital on the long road from the first OV trial in the US to the current bonanza of translational studies. In short, the largest thematic shift in the OV field was the result of the amazing successes of T cell checkpoint inhibitors (TCIs), antagonizing antibodies against CTLA-4, PD1, and PDL1. TCIs help maintain active T effector cell killing within a tumor environment, effectively allowing a sustained adaptive immunity against a tumor to develop. In tandem with OVs, a synergy is created that significantly increases survival rates *in vivo* and has profoundly shifted the OV field toward engineering vectors to actively court an immune response to clear the tumor. This way of thinking was previously discriminated against in favor of engineering vectors with enhanced lytic potential, favoring researchers looking to remove tumors through viral replication and cell killing alone. Currently, few in the field now believe an OV-mediated cure will ever occur via virus-mediated cell killing alone, prompting a race to adapt and include the PD1 and CTLA4 antibodies into clinical trials and research with OVs. Here we summarize some of the important findings revealed at the conference as well as how the data presented here help shape and mold the new immunotherapy-focused path that OV research is taking.

Luring the Immune System to the Tumor

Recruiting an active immune response to incessantly attack the tumor has become the new focus of oncolytic virology. Robert Coffin began the talks by summarizing the recent successes of three trials combining OVs with anti-CTLA4 or anti-PD-1 antibodies. While demonstrated in academic models, the jump to patient trials is a remarkable step in the path to developing a realistic cure using viral vectors. Trials combining CAVATAK (ClinicalTrials.gov: NCT02307149 and NCT02565992), Pexavec (ClinicalTrials.gov: NCT02977156), ONCOS-102 (ClinicalTrials.gov: NCT03003676), or HF10 (ClinicalTrials.gov: NCT03162224) with anti-CTLA-4 or PD-1 antibodies are ongoing. However, combining anti-PD-1 antibody (Iplilmumab) with TVEC/IMLYGIC resulted in an increase in an objective response rate as compared to a single agent alone (ClinicalTrials.gov: NCT01740297). These results have yielded prudent evidence in support of the theory that OV agents are capable of recruiting an immune response to a tumor. The next step in the evolution of OVs is to maintain an active response at the tumor site. To best accomplish this, several speakers presented viral vectors armed with immune stimulatory transgenes or modifications to selectively enter tumors, causing a reliance on the virus' innate immunostimulatory nature. Replimune's RP1, RP2, and RP3 are a newer version of past HSV-1 viruses with the γ34.5 and ICP47 genes deleted. They express the gibbon ape leukemia virus fusogenic protein on their surface to induce fusion of infected tumor cells. Each of these viruses also expresses granulocyte-macrophage colony-stimulating factor (GM-CSF), a secreteable anti-CTLA4 antibody and a still proprietary co-stimulator. In this fashion, the RP viruses will infect and recruit immune cell infiltration as TVEC did, but they will more efficiently spread from cell to cell while releasing a localized T cell checkpoint inhibitor. Minimizing the locale of anti-CTLA4 antibodies in the context of an eventual combination of RP viruses with systemic PD1 antibody seems

[1]Brain Tumor Research Center, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, USA; [2]University of Pittsburgh, Pittsburgh, PA 15213, USA

Correspondence: Fares Nigim, MD, Brain Tumor Research Center, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, USA.
E-mail: f.nigim@gmail.com

crucial due to the toxicity observed from systemic combination of CTLA-4 and PD-1 antibodies.[4,5] These viruses are lined up for phase I/II trials in 2019 and 2020, as advertised by the company. oHSV1's therapeutic efficacy with anti-PD1 inhibitors is well researched in academic fields via *in vivo* modeling,[6–8] but this year's conference saw presentations that convincingly argue the jump from laboratory bench to clinic was well warranted. Interestingly, for oHSV1 agents, William Jia demonstrated that HSV1 infection of a tumor induces PDL1 expression, which, to date, has only been briefly looked at in terms of natural host defense during wild-type HSV1 infection.[9] To combat this, Virogen developed VG161, which expresses a PDL1 peptide that blocks interaction with PD1. To increase T cell activation at the tumor site, the virus platform also expresses interleukin-12 (IL-12), IL-15, or retinoic acid. While not slated for US clinical trials, the virus will be tested in China in 2019, after its validation in GBM, pancreatic, and gastric cancer cell lines and models. Sticking with the PD-1 antibody bandwagon, oHSV 1716 (Seprehvir), now owned by Sorrento-Therapeutics, is able to clear rhabdomyosarcomas in mice when treated simultaneously with anti-PD1 antibody. This clearance also protected mice from tumor re-challenge.[10] Now the path forward for Seprehvir is to remove the necessity of systemic PD-1 antibody by supplying a single-chain variable fragment (scFV)-PD-1 to be expressed locally at the tumor site.

Other oHSVs presented focused more on fundamental engineering questions than a combination with checkpoint inhibitors. Oncorus, which possesses the microRNA (miRNA)-targeted oHSV1, unveiled their miRNA screen to find organ-specific miRNAs that could be inserted into HSV1 ICP4, ICP8, and U_L8 UTRs. This follows the previous work done in Paola Grandi's lab, which engineered a retargeted gB HSV1 with ICP4 inhibited by miRNA124 sites to effectively kill GBM tumors while ablating viral growth in neurons.[11,12] Looking to increase the adaptability of the platform, Oncorus' goal is to determine key organ-specific miRNAs and insert said miRNA target sites into the virus, thereby creating a platform capable of tumor-precise entry, and transcriptionally inert in any off target infection. Breaking from the norms of oHSV1, Gabriella Campadelli Fiume presented work on an oHSV with *intact* y34.5 genes. Unlike rQNestin34.5, the transcriptionally regulated y34.5 of the Chiocca lab, Fiume's R-LMIIB virus relies entirely on retargeting via a scFV-HER2:gD fusion and gB mutation.[13,14] In essence, this is a fully virulent wild-type HSV1, but it is confined to infecting tumor cells overexpressing the scFV target. To this end, her lab has developed virus targeting prostate-specific membrane antigen (PSMA), epidermal growth factor receptor (EGFR)viii, as well as EGFR. In A20 adenocarcinoma and PDGR GBM models, the virus is capable of increasing survival, and, when expressing IL-12 (R115), causes infiltration of CD8 effector cells and resistance to re-challenge of survivors. Truly a remarkable finding, as one key aspect limiting the oncolytic potential of oHSVs is the deletion of the y34.5 genes, as reviewed in Bommareddy et al.[6] and Peters and Rabkin.[12]

Unlike HSV1, oncolytic vesicular stomatitis virus (oVSV) and adenovirus also benefit from PD-1 blockade without causing an increase in PDL1 expression. Stephen Russel, a champion of injecting only a single dose of virus to avoid robust antibody response, displayed an oVSV expressing interferon-β (IFNβ). While a counter-intuitive concept, the expression of IFNβ by the virus in cells that normally express no IFNβ causes an immune cell infiltration and promotes an anti-tumor immune response. oVSV-IFNβ spread better than oVSV alone and was synergistic with anti-PD1 antibody. Arming OVs with innate immune modulators, inherently anti-viral, seems to be catching on, as others have added IFN to their vectors as well as other innate modulatory proteins, like TRIF.[15–17] Paradoxically, the next step for VSV-IFNβ is to concomitantly treat with a JAK/STAT1 inhibitor ruxolitinib. To skirt the problems with antibody neutralization, ViraTherapeutics developed an oVSV with the lymphocytic choriomeningitis virus glycoprotein. This curtails antibody neutralization and was demonstrated to be safe for direct injection into the brain. Lastly, regarding the immune-infiltration focused OVs at this year's talks, Sean Lawler presented data from the phase II GBM trial using GMCI, a HSV-1 thymidine kinase expressing oncolytic adenovirus. In animal models, GMCI causes a CD8+ T cell-dependent tumor clearance and protection from re-challenge.[8] In clinical trials, GMCI increased patient CD8+ T cell growth. In addition, another trial has begun, combining Valacyclovir + adenovirus (Ad)V-tK, followed by radiation and temozolomide (TMZ), under Nino Chiocca. Ad-TK and TMZ increases survival over TMZ alone and was the stimulus for another trial for combination of Ad-TK with PD1 (ClinicalTrials.gov: NCT03576612). *In vitro*, GMCI also causes an increase in exosome exit from cancer cells, which may result in the bystander effect observed, or even Ad-TK delivery via exocytosis.

Direct Manipulation of the Adaptive Immune System by Viral Vectors

Cancers are an intrinsically mutational entity and, as such, create neoantigens thst should activate an adaptive immune response.[18] However, the tumor microenvironment is capable of causing a local immunosuppression that reduces the efficacy of an "au natural" immune response. The immune suppression within the tumor microenvironment relies on a variety of factors and cell types, specifically regulatory T cells (T_{REG}), myeloid-derived suppressor cells, and cancer-associated macrophages and fibroblasts.[19–22] Despite this immune suppression, the prospect of using a cancer's neaoantigen to direct an immune response would enable a new level of personalized medicine whereby a patient's individual tumor antigen is used to create their own immune response and cure. This idea was put to clinical trial in 2014 in melanoma, and, after its success, is being repeated world-wide.[23]

OVs are intrinsically immune-stimulatory and seem like an obvious choice for delivering a tumor peptide to induce an immune response. Delivering a neoantigen in the context of a virus should promote an *in situ* vaccine response to the tumor, overpowering the tumor-mediated immunosuppression.[24] A good vaccine response requires an antigen for immune cells to recognize but

also an adjuvant to stimulate the antigen-expressing cells that facilitate memory cell development. Viruses elicit this activation and are thus well suited for cancer vaccine strategies. Emilee Knowlton of ProImmune presented a platform to find the neoantigens a viral vector should express. The concept relies on using mass spectrometry to determine the T cell epitopes of effector cells within a patient's tumor. Theoretically, these neoantigens cause an immune-stimulatory response. Thus, the presence of the epitope on infiltrating cells predicts neoantigens that could be used for therapy. In this way, future OVs could be armed with immune-dominant peptides to induce a T cell response against the tumor. Additionally, if done during a patient's treatment, it provides a method to test whether a vector causes a response against the tumor antigen more than a viral peptide. In practice, Turnstone has developed an antigen-expressing prime-boost method for inducing an anti-tumor immune response. The MG1 virus has been engineered to express MAGEA3, PSA, and HPV peptides for use in several cancers. An adenovirus expressing the antigen is given to patient before a vaccine booster of MG1 expressing the peptide is delivered. This causes a T cell-mediated clearing of the tumor and protection from re-challenge *in vivo*. The initial adenovirus inoculation is absolutely necessary, as, without it, an anti-MG1 immune response ablates the anti-tumor effect.[25,26] Interestingly, the prime boost causes an incredibly rapid T effector response (~2 weeks post boost). MG1 enters B cell follicles where B cells primed by the Ad-MAGEA3 are maturing, somehow decreasing the time to T effector cell development.[27] In addition to MAGEA3, Turnstone is testing Ad-HDCT + MG1-HDCT and observed HDCT-recognizing T cells and a subsequent large TIL influx into tumors. A clinical trial for non-small cell lung cancer (NSCLC), breast cancer, and esophageal cancer is underway for MG1-MAGEA3 boost + Ad-MAGEA3 vaccine. MG1 is delivered in three doses after adenovirus and in increasing doses to counteract an increase in anti-MG1 antibody. Initial enzyme-linked immune absorbent spot (ELIspot) of patient samples shows reactivity to MAGEA3, peaking at day 10 and remaining until day 50 (ClinicalTrials.gov: NCT02285816). In addition, Turnstone has begun trials with MG1/Ad3-MAGEA3 and PD1 in NSCLC (ClinicalTrials.gov: NCT02879760) as well as HPV E6+ cancer (ClinicalTrials.gov: NCT03618953).

PsiOxus, which developed the enadenotucirev oncolytic adenovirus, presented several new viral platforms for expressing immunostimulatory molecules called TSIGN. Vectors such as NG348 express CD80 and scFV:CD3 to turn infected cancer cells into pseudo-professional antigen-presenting cells, complete with the CD80 co-stimulatory molecule for T cell development. Other vectors in their TSIGN platform express CD80 in the context of immune-stimulatory transgenes like MIP1α of IFNα. PsiOxus is also developing vectors to express bispecific T cell engagers (BiTEs) to link infiltrating T cells to an antigen overexpressed on the cancer cells near the oncolytic adenovirus infection. Currently, PsiOxus' enadenotucirev has been generated to express BiTEs to EPCAM and CD3 or CD4,[28] which endows longer interactions between T cells and targeted cancer cells, increasing the development of anti-tumor responses. The final *in situ* vaccine talk was given by Liang Deng and focused on the heat-inactivated modified vaccinia vector Ankara (iMVA). Injection of this heat-inactivated virus into B16-F10 melanoma tumors caused an anti-tumor T cell response that protected survivors from re-challenge.[29] Interestingly, the heat-inactivated iMVA performed better than live virus in these models. The development of the immune response was dependent on Batf3 and STING expression and was enhanced by PD1/L1 and CTLA4 antibodies.

The conference also saw presentations focusing on aspects of OV development that are interesting for investigators looking to engineer novel vectors. Industry speakers presented methods of ramping up vector production in a way that maximizes yield while maintaining vector stability and uniformity. This included a presentation from BIA separations on processing vectors in a way that reduces shear forces. Interestingly, BIA found that reducing the shear forces during vector isolation resulted in a greater IFN response when tested *in vitro*. They accomplished this using a specialized diethylaminoethyl (DEAE) column and were able to isolate virus and exosomes with their Patfix system. Larissa Pikor, also from Turnstone, presented their company's collaboration with John Bell to determine novel regions of vaccinia virus that are capable of being removed while remaining oncolytic. They accomplished this using a transposon screen and by selecting novel variants on several cancer cell lines. Pooling the novel variants created a "viral fight club," whereby the fittest OV emerged as a dominant species during the screen, later sequenced to determine the non-essential regions of the virus. This approach is quick and translatable to any oncolytic DNA vector. Their results suggested vaccinia virus requires most of the genes present within the middle or core of the viral genome, while its periphery was permissive to mutations and insertions. The oncolytic vaccinia OSKV vector has 25 kb of identified non-essential regions removed, allowing for an unprecedented amount of space for future transgene arming. Even more beneficial, the OSKV replicates in cancer cell lines as efficiently as its parental OV but does not cause pox marks in animals like most current vaccinia vectors do.

Conclusions

The evidence that combining OV with immunotherapeutic agents significantly amplifies the therapeutic effect of both agents is now well accepted.[6] OV's antitumor effect involves multiple mechanisms, including direct cytotoxic killing and immune response activation. However, the ability of OVs to trigger an immunological response toward a tumor seems to outweigh the direct oncolytic potential. In this fashion, OVs are situated to become useful cancer vaccine-producing agents, capable of replenishing themselves while also promoting an immune response. The main question now is whether to allow this response to occur without engineering or to find a way to best promote a directed immune response to the tumor via antigen-presenting viruses. The OV field still shows promise to cure cancer; it is only a matter of time before we optimize the delivery of vectors and create an agent(s) that

reproducibly coordinates with the host immune system to effectively eradicate the tumor. Hopefully by next summer, when the next meeting occurs, many of the ongoing trials will demonstrate proof of concept and clarify many of the above-mentioned themes.

AUTHOR CONTRIBUTIONS

C.P. and F.N. conceptualized and wrote the draft with the final help of P.G.

CONFLICTS OF INTEREST

The authors declare no competing interests.

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