MEETING REPORT:

2016 ONCOLYTIC VIRUS IMMUNOTHERAPY

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Cambridge Healthtech Institute's 4th annual Immuno-Oncology Summit in Boston (USA) brings together the competitive geniuses racing to create the next cure for cancer. A conference highlighting the explosive growth of Oncolytic Viruses was aptly located in Boston's Marriott Long Wharf Hotel also erupting with skyscrapers to house venture capital firms, biotech's, and industry giants like GE. A varied poster presentations and eighteen speakers made up of CEOs, entrepreneurs, physicians and researchers presented data, opinions, and advice on thirteen clinical trials, Oncolytic Virus platforms, and the ins and outs of the task at hand: How do we cure cancer?

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Multiple Doses vs. Single Shot?

The largest issue at the meeting was the debate on whether Oncolytic Viruses (OVs) are best utilized as a vaccine, given in multiple doses, or as a single shot cure. Both methods present a number of pros and cons, and no consensus was reached during the conference. A common problem with OVs is their usual inability to replicate to detectable levels within the tumor long after the original treatment. Multiple dosing supplies the tumor with fresh virus at multiple times bolstering the amount of virus and theoretically increasing the efficacy. **Jenifer Gansert from Amgen Inc**. presented an analysis of T-VEC

(Talimogene Laherparepvec's) OPTIM phase III clinical trial that led to FDA approval in October 2015. T-VEC is delivered in several doses over five weeks. This keeps the levels of the virus high, and doubles as an immune stimulator. Immune stimulation after multiple doses was also observed by **Joe Connor (Virttu Biologics)** in a phase I trial using Seprehevir for mesothelioma. One consensus between all presentations is the necessity of an immune activation to truly clear the entire tumor; however, differences in the rapidness of the response and benefit for the OVs were hotly disputed at the summit, covered later in this article.

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The premise of a 'single shot cure' was championed at the summit by **Stephen J. Russell, of the mayo clinic and CEO of Vyriad**. The 'single shot cure' approach relies on one high dose to saturate the tumor area, infecting tumor cells before any inhibitory immune response can take place to block the virus from spreading. This was backed up in preclinical models whereby multiple injections of VSV-NIS-IFNβ were only more effective when low amounts of virus were used per dose. When high numbers of virus particles were used per dose, there was no difference in survival efficacy. Induction of an antibody response mitigates the benefit of multiple injections as the antibodies quickly neutralize the virus. **Manel Cascallo's (VCN Biosciences)** data from two clinical trials with VCN01-Ad PH20 showed neutralizing antibodies appear regardless of dose, low or high. For this reason, they are dosing patients with a single dose of 10^13 viral particles in a single dose IV injection. Critics of this approach suggest that the magnitude of virus supplied at once is dangerous to the patient. While toxicity could become an issue, several speakers maintained that high doses of virus were required for achieving the best therapeutic effect.

Mechanisms of Action

A dedicated session about mechanisms of actions of OVs opened with keynotes and chaired by **Dr. Fares Nigim from Mass General Hospital – Harvard Medical School**. Among the renowned speakers of this session was **Dr. Caroline Breitbach from Turnstone Biologics**, her data showed clearly how PexaVec induced robust infiltration of neutrophils, but only when the high dose of virus was injected. Similarly Turnstone's newer Maraba MG1 virus incited Th1 like responses in models, but only when high levels of virus were used.

Virus Cytotoxicology vs. Immune Control

"The comparison of T-VEC with T-Stealth garnered heated contention"

The role of the immune system in OV therapy is still up for debate. The argument on relying on virus cytotoxicity vs immune control of the tumor was debated throughout the talks. **Matthew Mulvey's presentation, CEO of Benevir**, hinged on the bleaker aspects of the immune system, mainly that the immune system's ability to seek and destroy viruses far surpasses its ability to destroy tumors. To complement this grim reality Benevir's T-Stealth™ virus contains the immune activating abilities of T-VEC with the MHC peptide processing inhibition thanks to a BHV TAP channel blocking protein, akin to HSV1's ICP47, which is deleted in most HSV1 vectors to promote early Us11 expression. A comparison of T-Stealth against a T-VEC clone (Δ34.5, ΔICP47ORF, GM-CSF, IE Us11) showed better survival efficacy and metastases clearance in MBT2 bladder tumor models. However, the immune system was essential for OV benefit as CD8 T-cells were necessary, and PD1 and CTLA-4 blockades increased the efficacy. The comparison of T-VEC with T-Stealth garnered heated contention from T-VEC supporters after the talk.

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New and Emerging Platforms

One of the most striking features of the summit was the number of different platforms currently being tested and developed. Already described are the vectors that specifically stimulate the induction of anti-tumor immune response whether innate (VSV- NIS-IFNβ), or adaptive (TVEC, T-Stealth, and PexaVec). Not yet mentioned is **Steven Thorne's (Western Oncolytics**) VV with mutations affecting the glycosylation of its envelope proteins which minimize neutralization by antibody. **Caroline Breitbach** also presented data on maraba MG1 hDCT which presents the melanoma enriched antigen DCT in infected cells raising a tumor specific T cells response. We also saw multiple methods of specifically targeting tumor cells. E**nnio Antonio Chiocca (BWH – Harvard Medical School)** displayed plans for a phase I trial using the HSV1 rQnestin34.5v2 vector which should only replicate in cells with nestin expression and rapid growth. Brian Champion of Psioxis showed Enadenotucirev's translationally regulated in tumor cells. The Ad late promoter driven transgene will only express in permissive cells keeping the products isolated to tumors. To add to this Psioxis has developed a plethora of transgenes which can be easily swapped into Enadenotucirev to

quickly produce OVs. **Eric Quemeneur (Transgene)** and **Noriyuki Kasahara (U. Miami, Tocagen)** presented their pro-drug expressing viruses which convert 5-FC, provided in trans, into 5-FU killing tumor cells infected and nearby infected cells. 4D technologies were heralded by two presenters David Kim and Anthony Davies. Their presentations described how to design and implement a streamlined directed evolution platform, which produced hundreds of AAV vectors selected for specific superiorities such as the ability to infect lung epithelia and be administered via aerosol. Adding to this barrage of OV methodologies was **John Bell's (Univ. Ottawa)** call for multi-valent OVs. His data indicate that the tumor microenvironment contains non-tumor cells that are susceptible to OV infection because of the wound response and rapid growth within the tumor. These non-tumor cells provide the cancer with nutrients and should be destroyed. Bell argues the need to destroy this heterogeneous population requires multiple modes of killing to eradicate the area, such as inciting an immune response, oncolysis, and metabolism of a prodrug. His group's VSVd51-aMIR6 was synthetically lethal in combination with an EZH2 inhibitor exhibiting the benefits of combining multiple single therapies in one virus. **Howard Kaufman (Rutgers, NJ)** agreed with Dr. Bell that although more complex than what's being done today it seems that multivalency will become the go to therapy in the future, especially since as of yet biomarkers for virotherapy are few.

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Combinations or Single-Shots?

One of the standout points of the summit was the panel discussion with **Robert Coffin, Stephen Russell, John Bell, Matthew Mulvey, and David Kim**. They discussed the end of single agent therapy and the need to validate OVs as single agents before quickly moving to more probable cures in combination with other agents. The successes in tumor medicine show a trend towards the combination of therapies, not single agents. Much like the accomplishments of HAART against HIV, OV therapy looks to improve patient outcomes by merging with other chemotherapies and perhaps even other Oncolytic Viruses. No one can predict the future but OVs seem to be securing themselves in accepted practice for tumor treatment in clinics. Next year's summit will likely showcase the implementation of several of the earlier stage viruses presented here in clinic, as well as a year's worth of patient data from the ongoing trials currently going on.

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Authors have no disclosures. Article can be cited as Nigim F et al. or Peters C et al.

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2017's Immuno-Oncology Summit August 28-Septembr 1, 2017

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For more information about 2017's Oncolytic Virus Immnotherapy Conference, taking place in Boston, MA on August 28-August 29 2017, please contact dbarry@healthtech.com