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Oncolytic Viruses: Time to Compare, Contrast, and Combine?

5th International Meeting on Replicating Oncolytic Virus Therapeutics

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Creeping cautiously at 15 mph into the teeth of a driving snowstorm along a dark, deserted Canadian highway at 4 AM, returning from the 5th International Meeting on Replicating Oncolytic Virus Therapeutics, provided an ideal opportunity for some thoughtful reflection. To avoid contemplating the possibility of our imminent demise—perhaps by plunging off the mountain or being mowed down by a truck—we used the time to reflect on the content of the meeting and to formulate our ideas about the current state of the field.

The concept of oncolytic virotherapy has been around for a sufficiently long period of time that there is now increasing pressure for developers of this technology to deliver clinical trials that give rise to at least some suggestion of therapeutic potential. Encouragingly, a variety of such trials are now under way, and some data from these trials were presented at the meeting. Results were presented from trials using vectors derived from several of the usual suspects, including measles, reovirus, vaccinia, herpesvirus, and adenovirus, along with several newcomers, such as Seneca Valley virus and coxsackievirus A21. A real sense of achievability and safety emerged from these presentations, with no significant adverse events described that might otherwise blight the ongoing studies. In addition, there were sufficient anecdotal and incidental reports of individual patients who have done surprisingly well in these early phase I/II trials to sharpen the perception that the advent of phase III randomized trials is now a priority. Encouraging data on the ability to combine virus therapy with established standard-of-care therapies (such as radiation and chemotherapy) suggested that this is the most likely context in which we will see the first virotherapy adopted as an addition to routine clinical treatment. Although a positive result from a phase III study would provide a massive boost to the field, we must also be aware that such studies are fraught with potential dangers. A single negative result might have a disproportionately large adverse effect on market confidence, and it is therefore imperative that randomized studies involve rational designs with realistic end points. The engagement of experienced clinical trialists with basic scientists will be an important part of this process.

Other, more basic topics were addressed, including how to deliver viruses through the circulation without their disappearing into a blur of immune-mediated neutralization and/or misappropriation by host cells. One solution discussed was coating the virus in synthetic polymers to confer stealthy passage through the circulation; another was associating the virus with immune cells that would then chaperone the virus to the sites of tumor growth. A recurring theme was the idea that many oncolytic viruses might subsequently access the tumor from the circulation via direct infection of tumor-associated vasculature. This mechanism of delivery might provide the advantage of both feeding the underlying tumor cells with locally amplified sources of virus and ensuring a tumor-localized vascular collapse.

Even though it should be possible to deliver a virus or viral vector to a tumor, it is almost impossible to prevent it from turning up in off-target tissues as well. Therefore, an emerging theme at this year's meeting was addressed in several talks that described the incorporation of target elements for tissue-specific microRNAs (miRNAs) into viral genomes to ensure further tumor selectivity of virus replication. The rationale is to speed degradation of the virus in nontumor tissues expressing a specific miRNA that would recognize and attack a virus displaying an miRNA target sequence. In contrast, the lack of expression of these miRNAs in the tumor would allow the virus to replicate without further hindrance.

Finally, much attention was devoted to just how the immune system interacts with both cell-free and tumor-associated oncolytic viruses. The importance of both the adaptive and innate immune response to viral infection, replication, and therapy was frequently addressed. Moreover, there were suggestions that a potent antiviral immune response may even be contributing to the therapy that is observed in some models of tumor regression. Other investigators showed encouraging data suggesting that the potent inflammatory reactivity associated with tumor-cell killing by oncolytics can lead to the focusing of adaptive T-cell responses against tumor-associated antigens back onto the tumor, with significant therapeutic benefits over and above those induced by direct viral tumor-cell killing.

For us, clawing our way through the March snow in the Canadian Rockies, one

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predominant theme throughout this excellent meeting was the increasing number of oncolytic viruses that are being tested. It seems remarkable how many species harbor viruses that might eventually turn out to be the cancer-specific, tumor-cell-killing, immune-activating answer to oncologists' prayers! As with all fields of drug discovery, this expansion of the product base is to be encouraged. New viruses, from multiple sources, will undoubtedly yield new opportunities for selectively attacking cancer cells and will form the candidates for the trials of years to come. At some point, however, simple expansion of the repertoire of oncolytic vectors surely must be accompanied by some detailed comparison. A noticeable omission among the presentations was speculation about how these emerging candidates might compare with the well-established viruses that are discussed year in and year out. Such comparative studies are, of course, fraught with difficulty. Scientifically, it is very difficult to compare two different viruses. What titers should be used—the same number of plaque-forming units, the maximum achievable titer, or the maximum tolerated dose? What tumor models should be used? Not all viruses replicate in the same rodent or human tumor cell lines. Indeed, what are the end points that should be compared—intratumor viral titers, tumor regression, immune reactivity, or virus dissemination and/or toxicity? Moving beyond the purely scientific issues, there are many reasons for investigators to be hesitant to launch comparative studies between viruses. Often a laboratory has years of experience with a single virus type and may not have the facilities, knowledge, or abilities to take on new viral systems.

Apart from even these considerations, few of us really want to engage in the childish pursuit of asking who has the biggest or best, afraid as we are of being on the losing end of such comparisons. Finally, perhaps a dominant disincentive to embark on comparisons between both preexisting and emerging oncolytic viruses is the patent. Many viruses are now associated with companies that have invested huge amounts of money in their development and clinical future. Even academic groups are often tied to their viruses through institutional and/or external commercial interests. The chances of persuading a company to allow direct comparison of its product with that of another seem remote in the extreme.

Nonetheless, if we are to attend future meetings at which several new viruses are described each year, and a wide variety of existing viruses are also being developed, at some point somebody, somewhere, will stand up and ask that terrible question: "How does this exciting new virus compare with the exciting old viruses already presented by our esteemed colleagues?" Maybe the time has come to put aside the cliché involving apples and oranges that is often used in this context, and for us at least to investigate whether, and how, meaningful comparisons might be coordinated. Pooling of viruses, models, readouts, and even resources would be needed, along with open collaboration and the courage to stand by the results!

A final theme, which was addressed in at least one talk, is the question regarding how these oncolytic viruses would fare when combined. There seems to be enormous potential in combining the diverse effector mechanisms of different virus types to produce multiple synergistic antitumor effects. In addition to many of the same problems inherent in the apples-and-oranges argument for comparison, the cliché of creating a new viral monster applies to the suggestion for combination (or recombination!). Nonetheless, the clear indication from continuing clinical studies that combination therapy of virotherapy and chemotherapy/radiation therapy is the way forward suggests that combination virotherapies should be explored equally well.

What was clear from this year's meeting in Banff was that even the same virus can behave in very different ways and can operate through very different mechanisms, in different tumor models. With new agents being tested in a burgeoning field, along with the very real promise of randomized phase III trials, surely there is real benefit to be gained in understanding how different oncolytics perform under standardized conditions—if only to understand how they can be best developed for the patient. It is clear that the mantra of "compare, contrast, and combine" will be a very difficult one to carry forward for many reasons—but, having survived a snowstorm in 4 AM darkness on TransCanada Highway 1, we now see everything as possible.