doi:10.1038/mt.2009.314

Molecular Therapy

Oncolytic Viruses: An Approved Product on the Horizon?

Looking back over the past 15 years of oncolytic virus (OV) research, I cannot help being impressed by the creativity, ingenuity, and passion of those committed to seeing this platform succeed. Clever ideas that have led to novel targeting strategies, deciphering and exploitation of host–virus interactions, and innovative ways to deliver viruses to tumor beds are only a few of the basic science discoveries that have fueled excitement in the field.[1–3] However, just as in professional sports where "winning is everything," all that really matters in the end is what happens in the clinic. OVs captured the imagination of the scientific community, the public, and, perhaps unfortunately, even Hollywood—lest we forget "I Am Legend." The excitement of being able to create miniature biological machines that can specifically target and kill tumor cells while leaving normal tissues unscathed perhaps raised unrealistic expectations about how rapidly these therapeutics could be implemented in the clinic. In reality, our ability to generate new and exciting replicating virus–based therapeutics has rapidly outstripped the resources available to test them in the clinic in a timely fashion. Indeed, what has continued to fuel the skepticism that OVs will ever be more than an interesting academic exercise has been the paucity of clinical activity in early-phase trials.

In a recent review, Ivy *et al.* pointed out that more than 44 small-molecule inhibitors of vascular endothelial growth factor receptor signaling are in development—many in phase III studies.[4] Will we ever see the day when 44 OVs are in clinical development? Unlikely. There are tremendous differences between these therapeutic platforms, perhaps the most important being the complexity of the biological interactions between the virus and the patient. Steve Russell, Eva Galanis, and colleagues at the Mayo Clinic have developed a model for OV development that takes into account the challenges of developing a complex biological agent. They have created infrastructure "in house" that allows them to develop and control their therapeutics at the earliest stages when the platform is most vulnerable and requires nurturing in terms of engineering, manufacturing, and clinical testing. Their approach is to develop, in the academic setting, multiple viral products through at least phase I and possibly early phase II testing. The products that show safety, signs of efficacy, and/or targeting will be passed off to an industrial partner(s) for the pivotal trials.

Phase III studies are not for the faint of heart—they are expensive, time-consuming, and, if negative, can spell the end of a promising therapeutic. The OV field needs a winner, and three companies have compelling phase II data that they believe justifies carrying their products into phase III. The Biovex product OncoVEX$^{GM\text{-}CSF}$ (herpesvirus-expressing granulocyte macrophage-colony-stimulating factor) had a 26% objective response rate in a phase II trial of malignant melanoma patients. Particularly encouraging were responses at both injected and distant tumor sites, including visceral lesions, implying that there was systemic activity.[5] Biovex has now entered an international phase III study under the US Food and Drug Administration (FDA) Special Protocol Assessment process for patients with stage III and IV malignant melanoma.

Oncolytics Biotech has been developing Reolysin (reovirus type III) for more than a decade, sponsoring 10 clinical trials designed to test safety and efficacy in a variety of indications and routes of administration. Recently, Hardev Pandha, Kevin Harrington, and Alan Melcher have championed this platform at both the preclinical and clinical levels.[6,7] Pandha reports that their work demonstrates that "multi-dosing with Reolysin in an outpatient setting is both safe and feasible, results in minimal shedding and despite high seropositivity to reovirus in the community we have observed significant antitumor effects." Oncolytics Biotech has obtained from the FDA a Special Protocol Assessment to conduct a phase III trial testing intravenous administration of reovirus in combination with paclitaxel and carboplatin in patients with head and neck cancer.

David Kirn, the chief executive officer of Jennerex Biotherapeutics, has "seen it all," having been responsible for the clinical testing of the adenovirus Onyx-015 and been a longtime champion of the

OV platform. His company is focusing on the development of vaccinia virus–based therapeutics, with the lead product, JX-594, showing exciting systemic responses in phase I trials in a spectrum of solid tumors and in phase II trials in hepatocellular carcinoma.[8] James Burke, a key investigator in the Jennerex trials, is particularly excited about the potential of activating antitumor immunity in patients during oncolysis. According to Burke, "JX 594—and armed OV therapies in general—represent an opportunity to further harness the immune system to fight cancer. Perhaps more important than direct anticancer oncolysis, these viruses may allow the creation of autologous cancer vaccines in vivo—eliminating the costly, time-consuming, and labor-intensive method of creating cancer vaccine *ex vivo*—not to mention the possibility of increased relevance immunologically and in terms of activity."

Jennerex plans to initiate phase III trials in liver cancer in 2010. Kirn feels confident that the OV field has reached a watershed moment in its development: "The history of oncolytic viruses in the clinic to date has demonstrated the safety, mechanism of action of our therapeutics and made those of us in the field true believers. However, for the greater oncology community to embrace this technology and initiate sustained investment in this platform, we require positive phase III results. Now, more than ever, a successful OV pivotal trial seems to be within our grasp."

John Bell
Associate Editor

REFERENCES

1. Nakamura, T, Peng, KW, Harvey, M, Greiner, S, Lorimer, IA, James, CD *et al.* (2005). Rescue and propagation of fully retargeted oncolytic measles viruses. *Nat Biotechnol* **23**: 209–214.
2. Bartee, E and McFadden, G (2009). Human cancer cells have specifically lost the ability to induce the synergistic state caused by tumor necrosis factor plus interferon-β. *Cytokine* **47**:199–205.
3. Power, AT and Bell, JC (2007). Cell-based delivery of oncolytic viruses: a new strategic alliance for a biological strike against cancer. *Mol Ther* **15**: 660–665.
4. Ivy, P, Wick, JY and Kaufman, BM (2009). An overview of small-molecule inhibitors of VEGFR signaling. *Nat Rev Clin Oncol* **6**:569–579.
5. Senzer, NN, Kaufman, HL, Amatruda, T, Nemunaitis, M, Reid, T, Daniels, G *et al.* (2009). Phase II clinical trial of a granulocyte-macrophage colony-stimulating factor-encoding, second-generation oncolytic herpesvirus in patients with unresectable metastatic melanoma. *J Clin Oncol* **27**:5763–5771.
6. Vidal, L, Pandha, HS, Yap, TA, White, CL, Twigger, K, Vile, RG *et al.* (2008). A phase I study of intravenous oncolytic reovirus type 3 Dearing in patients with advanced cancer. *Clin Cancer Res* **14**:7127–7137.
7. Pandha, HS, Heinemann, L, Simpson, GR, Melcher, A, Prestwich, R, Errington, F *et al.* (2009). Synergistic effects of oncolytic reovirus and cisplatin chemotherapy in murine malignant melanoma. *Clin Cancer Res* **15**:6158–6166.
8. Park, BH, Hwang, T, Liu, TC, Sze, DY, Kim, JS, Kwon, HC *et al.* (2008). Use of a targeted oncolytic poxvirus, JX-594, in patients with refractory primary or metastatic liver cancer: a phase I trial. *Lancet Oncol* **9**:533–542.