MOLECULAR THERAPY
The Journal of the American Society of Gene Therapy

The End of the Beginning: Oncolytic Virotherapy Achieves Clinical Proof-of-Concept

"Now this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning."

Winston Churchill, after Britain's first victorious battle of World War II

Revolutionary technologies typically go through a series of ups and downs before successful assimilation into the mainstream, and novel cancer treatment platforms are no exception. Initial excitement based mainly on concepts frequently leads to unrealistic optimism. When confronted with technical hurdles to optimization this can quickly turn into unrealistic pessimism. For example, monoclonal antibody therapy, touted early on as a potential "magic bullet", was subsequently considered a doomed approach after early clinical setbacks. Stalwart pioneers ignored this unfounded pessimism and worked tirelessly despite these problems to bring monoclonal antibody treatments to patients. Everyone now agrees that agents such as rituximab (Rituxan; Biogen-Idec and Genentech), trastuzumab (Herceptin; Genentech), bevacizumab (Avastin; Genentech) and cetuximab (Erbitux; Bristol Meyers Squibb and Imclone Systems) have revolutionized the treatment of many cancers. Oncolytic virotherapy is another innovative therapeutic strategy that has awaited Phase III clinical trial validation. This critical milestone on the road to success may now have been achieved.

In November 2005, Shanghai Sunway Biotech (Shanghai, China) announced the approval of H101 by Chinese government regulators, specifically for the treatment of nasopharyngeal carcinoma in combination with cisplatin-based chemotherapy. H101 is an oncolytic adenovirus with an E1B-55kD gene deletion, similar to that present in the Onyx-015 (dl1520) oncolytic adenovirus. The E1B-55kD deletion may result in tumor-selectivity by varied mechanisms, although results clearly vary depending on experimental methods. Approval was reportedly based on results from a randomized, controlled trial of chemotherapy plus H101 versus chemotherapy alone. Virus was injected directly into head and neck cancers during standard cisplatin and 5-fluorouracil chemotherapy. This Phase III study design was originally proposed to the US FDA by our group at Onyx Pharmaceuticals in 1999 for Onyx-015. The basis for this study design was promising internally-controlled data from a trial of Onyx-015 plus chemotherapy in head and neck cancer patients. Virus-injected tumors had a significantly higher response rate ($p<0.01$) and longer time-to-progression ($p=0.04$) than control tumors. Unfortunately, that Phase III trial was halted prematurely (with less than 10 percent of patients enrolled) following a corporate takeover of the agent's licensee. Results from the Chinese trial have now apparently confirmed the ability of an oncolytic adenovirus to increase the response rate of head and neck cancers in combination with cisplatin-based chemotherapy. As presented by a company representative at the International Conference on Oncolytic Virotherapy (Banff, Canada, March 2005), intratumoral H101 plus chemotherapy produced a 79% (41/52) response rate compared with 39.6% (21/53) in patients treated with chemotherapy alone ($p<0.001$). Subsequent press releases reported a 27% increase in objective response rate with virus injection.

Although these results are clearly welcome news for the field, and confirm antitumoral efficacy, much work remains. Were tumor response assessments made by investigators who were blinded to patients' treatment groups? Were responses confirmed by central radiographic review? More importantly, full regulatory approval of such viruses in the US, for example, would require significant improvements in overall survival and/ or clinical benefit (*e.g.* quality-of-life). We still await data on these endpoints from this trial. Unfortunately, this trial is relatively small for a Phase III oncology trial, and as such is not adequately powered statistically to detect important differences in survival between treatment groups. The Onyx-015 trial had a planned sample size of over 450 patients, for example, compared to

MOLECULAR THERAPY
The Journal of the American Society of Gene Therapy

just over 100 patients reported from this trial. In addition, the control group on a Phase III approval trial must receive the standard of care for that patient population, including best supportive care if no beneficial therapy is available. The standard of care for locally-advanced nasopharyngeal carcinoma has now been established as radiotherapy combined with chemotherapy, which results in response rates of greater than 80% in many large trials. It is unclear why chemotherapy alone was used as the control treatment in this trial. These clinical, statistical and regulatory issues must also be answered for the replication-deficient rAd-p53 Gendicine (Shenzhen SiBiono GeneTech; Shenzhen, China), another agent that recently received marketing approval in China. Clinical data obtained from trials in China have the potential to complement, and potentially accelerate, the clinical development of new therapies in other countries. With this goal in mind, these studies should be performed according to rigorous scientific, regulatory and ethical standards. These include those of the International Committee on Harmonization (ICH) guidelines for Good Clinical Practice (GCP) and the Declaration of Helsinki.

This recent success follows other recent clinical advances in the field. While local non-surgical therapy can be beneficial for some tumor types and stages (*e.g.* locally-advanced head and neck cancer), the vast majority of patients will require systemically-active therapy. Systemic efficacy has now been clearly demonstrated with oncolytic viruses in the clinic. Systemic tumor regression has been observed following injection of a GM-CSF-armed oncolytic vaccinia virus (JX-594; Jennerex Biotherapeutics Inc., San Francisco) directly into melanomas (*Canc. Gene Ther.* (1998) **6:** 409-422)and this virus is now being developed for intravenous administration. Intravenous therapy with Newcastle Disease Viruses has induced objective tumor responses in colorectal, carcinoid and glioblastoma patients. Therefore, clinically-significant systemic antitumoral activity has now been demonstrated with oncolytic virotherapy.

It is doubtful that H101, or its cousin Onyx-015, will ever be developed for metastatic cancers due to limitations in delivery and potency. Oncolytic potency is reduced by deletions in the E1B-55kD gene (both viruses) and the Adenovirus Death Protein (H101 only), and the intraveous delivery of adenoviruses to tumors appears to be highly inefficient. Over 300 patients have been treated with Onyx-015 to date, and no systemic efficacy has been described. With other virotherapy agents, systemic efficacy is being addressed through improved viral delivery to tumors (*e.g.* by selecting viruses that traffic more efficiently to tumors via the blood), improved potency, and through induction of tumor-specific cytotoxic T lymphocytes (*e.g.* by arming oncolytic viruses to express cytokines such as GM-CSF). Of course, these approaches can be complementary and are being combined in third-generation agents.

The future for this field is bright. The possibilities seem endless when one considers combinations of different virus species, each armed with different combinations of transgenes expressing proteins with diverse mechanisms-of-action. To get there, however, the field needed clinical validation. That validation step now appears to have been achieved. In the words of Lord Churchill, "It is, perhaps, the end of the beginning."

DAVID H. KIRN
ASSOCIATE EDITOR, MOLECULAR THERAPY