Amgen spikes interest in live virus vaccines for hard-to-treat cancers

Oncolytic viruses have a long, checkered history in cancer therapy—perceived as safe but ineffective. So Amgen's announcement in January that it would pay BioVex of Woburn, Massachusetts, $425 million in upfront cash and $575 million in milestones, provided an endorsement of tumor-targeting viruses, placing them under a new spotlight. Thousand Oaks, California–based Amgen based its purchase on promising phase 2 results in 50 patients with metastatic melanoma. After treatment with the genetically modified virus OncoVEX, the company's lead candidate, detectible disease was completely eliminated in eight individuals. In four others who received treatment, disease burden decreased by at least 30%. "What we've seen so far is impressive—durable responses and shrinking tumor masses in a cancer that's notoriously difficult to control," says Roger Perlmutter, Amgen's executive vice president for R&D.

Today's oncolytic virus immunotherapies aim for heightened therapeutic potency and tumor selectivity, says Mark Monane, a senior analyst with Needham & Company in New York. Their benign toxicity profile suggests they are ideal for combination therapy, he says. "You don't [have to] give anything up by using them, which is attractive to pharma because the whole trend in cancer treatment is to combine therapies with different mechanisms of action." But Monane cautions that until phase 3 results, expected at the end of this year, confirm what has been seen in earlier studies, the future of oncolytic treatment remains an open question. "We need to find out if we're watching a big science experiment or the start of a new therapeutic platform with real-world potential," he says.

Amgen

Amgen's R&D muscle will spur BioVex's oncolytic virus immunotherapies.

Among the 17 oncolytic virus therapies now in development, OncoVEX leads the pack, with phase 3 trials ongoing in both metastatic melanoma and head and neck cancer (**Table 1**). OncoVEX is an oncolytic herpes simplex type 1 virus (HSV-1) that has been enhanced to show greater selectivity for growth in transformed cells through deletions in *ICP34.5*, which encodes a protein involved in preventing apoptosis, and by expressing US11 as an immediate-early, rather than late, gene. Once the OncoVEX vector infects tumor cells, it elicits an enhanced antitumor immune response owing to both the deletion of *ICP47*, which normally blocks antigen presentation in wild-type viral infections, and the expression of granulocyte macrophage colony stimulating factor (GM-CSF), which activates phagocytic cells and promotes the differentiation of antigen-presenting dendritic cells.

Table 1 Selected oncolytic virus therapies in development for cancer

Company	Product	Description	Indication	Status
Shanghai Sunway Biotech (Shanghai)	Oncorine	Modified adenovirus with deletion of an E1B-55kd portion	Head and neck cancer	Approved (China)
BioVex	OncoVEX^{GM-CSF}	HSV-1 with deletions in *ICP34.5* and *ICP47* modified for immediate-early expression of *US11* and production of GM-CSF	Head and neck cancer, metastatic melanoma	Phase 3
Oncolytics Biotech	Reolysin	Formulation of human reovirus type 3	Head and neck cancer	Phase 3
Jennerex Biotherapeutics	JX-594	Recombinant vaccinia virus with thymidine kinase deletion and expression of GM-CSF	Liver cancer	Phase 2
Neotropix (Malvern, Pennsylvania)	NTX-010	Naturally occurring oncolytic Seneca Valley picornavirus	Small cell lung cancer	Phase 2
Catherex (Philadelphia; under license from MediGene)	NV-1020	HSV-1 with reduced *ICP34.5* dosage, with thymidine kinase under control of an *ICP4* promoter	Colorectal liver metastases	Phase 1/2
	G-207	HSV-1 mutant with deletions in the neurovirulence gene *RL1*	Newly diagnosed glioblastoma	Phase 1

Source: Biocentury; Thomson

The OncoVEX treatment involves injection directly into the tumor, a delivery route that conveniently sidesteps the bloodstream, which avoids preexisting antibodies that would destroy the virus. Also, a localized injection allows the delivery of viral loads high enough to overwhelm the tumor's immunosuppressive microenvironment, according to Yvonne Saenger, an assistant professor at Mount Sinai School of Medicine, in New York.

All oncolytic viruses, including OncoVEX, replicate preferentially in cancer cells. Once inside the cells, the virus replicates and eventually bursts—the lytic effect originally intended as the primary goal of the therapy. According to Robert Coffin, chief technology officer at BioVex, cancer cells that burst after treatment dump tumor antigens into circulation attracting dendritic cells from the immune system's frontlines. Dendritic cells present the viral antigens to T cells, which, once primed to recognize the tumor's antigens, search out metastases with a matching profile. Coffin says that untreated skin lesions near sites of injection, and also more distant lesions in the liver, lung and other organs often respond to OncoVEX treatment. "And these effects are of long duration, which suggests we're producing a systemic vaccine that prevents recurrence," he says.

The latest generation of oncolytic viruses have an edge over their predecessors by combining traditional lytic effects with vaccination. The new strains, says David Kirn, CEO with Jennerex Biotherapeutics, in San Francisco, are double-edged—they must avoid being cleared by the immune system while also harnessing it against tumors. "The trick is to use viruses that persist long enough to stimulate anticancer effects," he says. Unfortunately, the adenoviruses used previously, such as Onyx-015, developed by Emeryville, California–based ONYX Pharmaceuticals, were neutralized by the immune system before reaching tumors, thus abrogating their clinical utility.

Yet recent successes with other drugs that stimulate immune cell responses suggest that immune reactions can be directed against tumors, says Alan Melcher, a professor of clinical oncology at the University of Leeds, in the UK. Such therapies include Bristol-Myers Squibb's ipilimumab, a human monoclonal antibody that binds cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) on T-helper cells to harness natural anticancer immunity, and Dendreon's Provenge (sipuleucel-T), an autologous vaccine for prostate cancer

IN brief

Large drugs outdo small

Biologics are twice as successful as novel small-molecule drugs in gaining market approval, according to a new study. At the 13th Annual Biotechnology Industry Organization (BIO) CEO and Investor Conference, BIO and BioMedTracker, of San Diego, presented their analyses of the approval rates of 4,275 drugs in development from 2003 to 2010. They found that drug success rates from phase 1 to approval was 9% for all indications. Overall rates for secondary indications rates were lower: 14.5% for lead indications and 3.2% for secondary. A further analysis of the types of drugs achieving approval showed that biologics were almost twice as likely as new molecular entities (NMEs) to get approved for a lead indication (26% and 14% respectively). Notably, over 85% of the NMEs are small-molecule drugs. In addition, "The biologics do not include vaccines," says Michael Hay, senior biotechnology analyst at BioMedTracker, who listed the biologics included in the data set as bacterial products, cellular therapies, monoclonal antibodies, natural and synthetic proteins, nonviral gene therapies, viral gene therapies, peptides and polyclonal antibodies. Hay also observed that, "Monoclonal antibodies make up over half of the biologic drugs in the data set." Worth noting, non-NMEs were most likely to get approved for any indication (lead or secondary, 41% and 10%, respectively), suggesting that developers of follow-on products benefit from the experience of drug developers who forge the first regulatory pathway for a new drug class. *Bethan Hughes*

Irish bioprocessing school

The National Institute for Bioprocessing Research and Training (NIBRT) opened its doors in Dublin on February 21 to provide research, training and education for all aspects of bioprocessing. According to its new director, Professor Ian Marison, the 6,500 m^2, purpose-built building will provide infrastructure ranging from small-scale pilot suites to a factory-scale production environment, and will focus on biologics and small molecules. The government-funded NIBRT will be run as a collaborative effort by four Irish universities. The aim is to support local companies and to attract new industrial partners both at home and abroad. Marison says that what makes NIBRT special is that its activities will be solely driven by industry need. Once a biomanufacturing need is identified, the NIBRT will put together diverse expertise to solve it in collaboration with industry. If a problem is deemed especially important, the NIBRT may recruit a basic research laboratory to work on it long term. The ethos is flexibility. The institute might engage in contract research for companies or can collaborate as equal partners. The NIBRT can also host visiting industrial scientists, and vice versa. This flexibility will also be reflected in new intellectual property, which can be generated and owned by the universities, by the industrial stakeholders or as a partnership. *Jennifer Rohn*

prepared by incubating (activating) a patient's own antigen-presenting cells *ex vivo* with a fusion of prostatic acid phosphatase (an antigen specific to prostate tissue) and GM-CSF. Indeed, for BioVex and its competitors, the main goal is to create viable off-the-shelf cancer vaccines. What remains unknown, Melcher says, is how much of the benefit seen in clinical trials so far can be attributed to immune responses as opposed to lytic effects. That's crucial for BioVex, which relies on drumming up a systemic immune response to hit micrometastases and other tumor fragments that are invisible with standard imaging techniques. The fact that liver and other visceral tumors in melanoma patients shrink after OncoVEX injections in skin offers clear evidence of systemic immunity, Coffin says. Yet Ronald Rodriguez, an associate professor of urology and oncologist at Johns Hopkins Medicine, in Baltimore, cautions that melanoma, which is regulated by the immune system, is also one of a handful of cancers that can regress spontaneously.

Meanwhile, another company in the field—Oncolytics Biotech of Calgary, Alberta—aims to generate a systemic response using a route other than intratumoral injections. Oncolytics delivers its lead candidate, Reolysin, now in phase 3 for platinum-refractory head and neck cancer, intravenously. Reolysin is a formulation of wild-type reovirus of the serotype 3 strain Dearing. As it is one of the most ubiquitous viruses on the planet, most people are sensitized to it at an early age. This is problematic for oncolytic treatment because antibodies neutralize it almost immediately on exposure. Oncolytics Biotech gets around that problem by giving massive doses: five trillion viral particles a day. "Your immune system isn't designed to fight that level of infection," says Matt Coffey, the company's COO, who points out that most natural infections result from exposure to viral particles numbering a million or less. Reoviruses infect only rapidly dividing cells with an activated Ras signaling pathway—cancer cells among them—and so generally cause few side effects. People treated typically experience little more than minor flu symptoms. But Reolysin's mode of action is primarily cancer cell lysis. Coffin describes immune stimulation from Reolysin as a "lucky side effect," and indeed, the virus's genome is too small—just 23,500 base pairs—to be outfitted with GM-CSF. The mechanism of action (targeting cells with RAS mutations) suggests potential utility in treating pancreas, colon and lung cancers, all of which are particularly problematic cancers to treat at present.

Not to be outdone, Jennerex Therapeutics delivers its leading candidate, JX-594, by intratumoral and intravenous injection. JX-594 is a replication-competent Wyeth strain vaccinia virus engineered to express GM-CSF under the control of a synthetic early/late promoter and to express *lacZ* under the control of the *p7.5* promoter. The vector's thymidine kinase gene is also inactivated, rendering the virus dependent on host cell thymidine kinase and enabling selective growth in cancer cells; normal cells express only low levels of thymidine kinase, whereas tumors express it at levels sufficient to support viral replication, Kirn says.

The Jennerex oncolytic virus is currently headed for phase 3 clinical trials in liver cancer, putting it third in line behind OncoVEX and Reolysin. Moreover, in Kirn's view, the capacity of JX-594 to harness two cell-killing properties—lysis and immune stimulation—expands the universe of potential indications. Vaccination might work well with highly immunogenic cancers, he says, such as melanoma, kidney and prostate cancer. But high doses delivered intravenously (Jennerex gives more than a billion vaccinia particles per infusion) might be appropriate in cancers for which the role of immunity isn't so clear, he says. Intratumoral injections will deliver a cargo with great accuracy. "Interventional radiologists can put needles anywhere in the body with a high degree of accuracy," Kirn says. "We see this as a game-changing paradigm. Radiologists are going to become cancer surgeons by injecting viruses and they're anxious to do it."

The important question, Monane says, is whether oncolytic viruses can evolve into a new therapeutic platform with clinical payoffs. Asked to compare among the various approaches, Monane responded that he can't pick any favorites. "In the end, it doesn't matter how any of them do it," he said. "What matters is how patients respond, and at the moment all we have is phase 2 data. The proof of the pudding is phase 3; and a positive trial for BioVex or any other company will be pivotal for the entire oncolytic virus space."

Still, Saenger, a principal investigator in the BioVex phase 3 melanoma trial, says OncoVEX delivers a precious chance for durable remission, particularly in patients with unresectable stage IIIB–IVA melanoma and injectable skin lesions. "It appears to work best in patients with early-stage metastatic disease," she says. "There's a window of opportunity there, when the cancer is spreading on the skin but hasn't moved yet to the liver. After dosing with OncoVEX, injected and peripheral lesions flatten and recede, the lymph node disease stabilizes and stops growing, and patients don't develop any new lesions. It's a real change in the course of progression."

Charlie Schmidt *Portland, Maine*