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*

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