BY ANNA PEISL/GETTY IMAGES

Will Gene Therapy Go Mainstream?

The products are safe. The science is rock-solid. Patients are champing at the bit. But as much as the industry may be lining up behind gene therapies, marketing and operational questions abound. **Larry Dobrow** reports on the current state of the gene therapy union

Within the healthcare marketing community, gene therapy is an object of intense fascination. In understanding the potential curative promise of such drugs, marketers have fallen over themselves to tout their virtues and rip off list after list of "best practices" for promoting them—even though it's hard to codify best practices when so few of the products have actually reached the market. Nonetheless, you'd be hard-pressed to find even a C-list pharma marketer who hasn't long since awakened to the eventual virtues of gene therapy. Enthusiasm within the scientific and investment communities couldn't be higher.

And yet within patient populations and many provider circles, gene therapy remains an object of interest for different reasons. The moniker *gene therapy* is one of them, given how in certain uneducated circles it conjures images of mad scientists attempting to, say, create a superhuman being or performance-enhance their livestock. So with gene therapy targeting any number of conditions on its way, the question needs to be asked: Is the US market ready for gene therapy and everything that comes with it?

The short answer is yes, of course it is. The products are marvels. So far there hasn't been a major safety hiccup. Are you joking? Seriously, dude.

The longer answer is more complicated, marketing and pharma execs say. To a person they marvel at the transformative science … and fret about manufacturing and operational challenges and the ever-thorny question of asking payers to pick up six-figure tabs. They're also a little wary about making predictions when the landscape seemingly reinvents itself monthly—and that's before a huge dump of clinical-trial data arrives sometime in the second half of 2015.

"I wish I could say we have an extensive roster of clients and we're starting to take messages to various audiences," says Amy Graham, general manager of Ogilvy CommonHealth Specialty Marketing. "But to be honest, there is an extremely limited number of clients that have gotten anywhere near needing an ad agency yet." Adds FreshBlood CEO Bob Finkel, "We all know that [gene therapy] is the future. The science behind it is solid. But there's always going to be a bit of a wait-and-see attitude with anything that's novel. That means you need education, awareness and so much else to lower the barriers to resistance."

Thus any potential look at the challenges of marketing gene therapies must necessarily begin with a cursory look at the current

environment—which, frankly, will likely evolve between the moment *MM&M* hits "publish" on this piece and the one in which you read it. 23andMe, known for most of its life as a provider of $99 DNA tests, launched a drug discovery unit it dubbed 23andMe Therapeutics. While it claimed it wasn't becoming a quote-unquote drug company, 23andMe hired well-regarded former Genentech EVP of research and early development Richard Scheller to serve as the new unit's chief scientific officer. It's also partnered with a host of pharma giants, among them Pfizer and Genentech, during the last 18 months or so.

Along those lines, formal collaborations between big pharma and smaller gene-therapy specialists are thriving: between Bristol-Myers Squibb and uniQure (for cardio therapies), between Bayer and Dimension Therapeutics (Hemophilia A), between Celgene and bluebird bio (cancer). Such partnerships are born largely out of pragmatism. Big Pharma has the financial resources and the will, while gene therapy specialists have the production know-how.

"It's a rapidly evolving field," notes Hans Duerr, head of Bayer's global hematology business. "Many companies need a partner that's looking at this holistically and learning from other indications. Dimension understands how to package the gene the right way. They have the focus to produce [gene therapies] on a commercial scale."

SMALL COMPANY/BIG COMPANY

Consider the example of Dutch gene therapy firm uniQure, which markets lipoprotein lipase gene therapy Glybera in Europe. The company's secret sauce, such as it is, is its ability to handle the technical demands associated with the production of gene therapies. "We're driven by our abilities to design and manufacture," says CEO Jörn Aldag. "We have a fully integrated value chain; we can manufacture to industrial scale. We go well beyond proof of concept." Left unsaid? Many pharma giants and would-be gene therapy companies don't.

That tech platform was among the primary factors that made uniQure an ideal partner for Bristol-Myers Squibb. Announced in early April, the collaboration gives BMS access to uniQure technology and a pre-clinical gene therapy program in the cardiovascular space designed to restore the heart's ability to synthesize S100A1, a regulator of heart function. UniQure will handle manufacturing of clinical and commercial supplies while BMS will head up regulatory activities and commercialization and pay for all R&D–related expenses. Ultimately, the two companies may end up collaborating on as many as 10 programs. "It's very validating," Aldag says.

On the other side of the coin are large organizations like Bayer. Long among the leaders in hemophilia, the company recognized the potential of gene therapies to revolutionize the space some time ago. "One of the key challenges that's always existed in hemophilia is, 'How do I make it easier for patients to stay adherent and get regular prophylaxis?'" Duerr explains. Indeed, while Bayer's Kogenate has ranked among the leading Hemophilia A treatments for two decades, it requires two- or three-time-weekly injections. Bayer's gene-therapy push aims to reduce this burden on patients—to a single injection per week, perhaps, or even oral treatments at some point in the future. "The development that has been accomplished over the last couple of years has been spectacular," he says.

But even as Duerr describes himself as an "inherent optimist," he still sees a need to temper expectations. "With [Hemophilia A] it's not as simple as, 'Here's a cure—one injection and you're done for life,'" he explains. "That's difficult to prove. You'd have to test for extremely long periods of time. It's hard to make predictions."

The DNA of ACGT

It's not inaccurate to say that, in 2001, few healthcare entities devoted a lot of thought to gene therapy. On the product front, pharma companies were focusing energy and resources on prospecting for the next blockbuster. On the marketing front, they were still giddy in the wake of the opening of the DTC door a few years earlier. If you were deep into gene therapy in 2001, you likely spent many hours inside a lab or within the walls of academia.

In retrospect, then, the foresight and ambition of the Alliance for Cancer Gene Therapy's founding fathers and mothers seem all the more impressive. Back in 2001 the organization's co-founder and first president, successful business exec Edward Netter, was helping tend to a daughter-in-law stricken with breast cancer. To hear current ACGT executive director Margaret Cianci tell it, his entire outlook was changed after he attended a lecture at the Mt. Sinai School of Medicine by Dr. Savio Woo, the founding director of the Baylor College of Medicine's Center for Gene Therapy and a former president of the American Society for Gene Therapy.

"When Edward heard Dr. Woo speak about treating cancer at the molecular level, and the promise in the research, he said, 'We have to fund this kind of work,'" Cianci recalls. Netter and his team (including his wife, Barbara, ACGT's current president) set about finding a catchy name that would line up with the initials *A*, *C*, *G* and *T*, representing the four proteins in the DNA strand: adenine, cytosine, guanine and thymine. After assembling an A-list board of directors and scientific advisory council, the group went to work.

It speaks volumes about the organization's serious-mindedness and sense of purpose that it immediately found itself working alongside huge talents, among them groundbreaking cancer researcher Dr. Judah Folkman. Early grant recipients included Juno Therapeutics scientific founder Dr. Michel Sadelain and leukemia research giant Dr. Carl June; the group's first two classes of "young investigators" included Dr. Bob Vonderheide and current Ziopharm Oncology CEO Laurence Cooper.

What distinguished ACGT then—and continues to distinguish it now—was its specific focus. "We knew we wanted to fund a scientific platform—gene therapy—as opposed to cancer in a particular location—a tissue, an organ, whatever," Cianci says. Nearly 15 years later the group remains stalwart in its mission. "Dr. June put it nicely: What we're trying to solve is no longer a scientific problem. It's an engineering one," she continues. "How can we ramp up the pace? How can we keep the cost of drugs down? How can we give access to as many patients as possible? We need to overcome those obstacles as an organization, but we also need to overcome them as a society."

All the ACGT's work and investment hasn't yet resulted in a gene therapy for cancer making it to market—yet. Cianci says that should change within the next two years, likely with leukemia drugs from Novartis or Juno. Such potential successes would focus additional attention on the alliance and its researchers, which Cianci says will be more than welcome.

"The more people are aware of gene therapy's track record of success, the more they might choose to contribute to us," she notes. "We're averaging three to five grants a year. We want to increase that."

That said, ACGT has enjoyed more than its share of validation, whether from external voices acknowledging the role it's played in furthering awareness of gene therapy or from early supporters like Dr. Woo. "When he retired, we had a gala for him," Cianci says. "For him to stand up and say that working on this organization with the Netters was the greatest thing he's done, that was beyond anything we could have imagined. It was wonderful and exciting. But there's still so much left to do."

Which is why Bayer—and, presumably, any number of pharma companies that could soon find themselves in a similar situation—isn't making any assumptions about patient uptake of gene therapies. Kogenate may require regular shots, but it has stood the test of time; patients have come to rely on it. That's part of the reason why Duerr doesn't expect any gene therapy that treats Hemophilia A to render Kogenate obsolete anytime soon.

"Hemophilia is characterized by very strong brand loyalty and the strong experience customers have with existing products," he says. "What we anticipate, assuming successful development and licensure of gene therapy products, is that there will be a wave of patients who will jump on [new products] quickly, but that will be a relatively small segment. Others will take a more measured approach."

Why? Because of any number of factors. Let's say Bayer develops a therapy that, with a single shot, greatly moderates the effect of Hemophilia A, making thrice-weekly shots a thing of the past. What happens if the new therapy has a fuller expression in some patients than in others? What if those patients with the less-full expression need surgery or a tooth extraction?

"It's going to be critical for companies to offer a full suite of products," Duerr says.

PATIENTS, PHYSICIANS AND PAYERS

While there's no set timetable for the arrival of gene therapies, marketers are already getting ready to sell them—or, rather, their efficacy and safety—to any number of potential publics, some more skeptical than others. Experts agree that the top concern, whether valid or not, is affirming that gene therapy products are safe. This shouldn't be much of a challenge at all: Aldag notes that over the course of more than 100 clinical trials of adenovirus-based gene therapy, there hasn't been a single material adverse event reported.

"Obviously we can't guarantee no long-term safety problems, but there have been no adverse events that are drug-related. None," he says. "From a general and from a regulatory perspective, AD-based gene therapy is considered safe by the authorities, the industry and increasingly by doctors."

Even less of a challenge, and one that makes believers shake their heads bemusedly, is the notion that gene therapy is the equivalent of "playing God" and thus crosses an ethical line drawn somewhere in the far-off sand. "Gene therapy is a radical departure from all forms of medicine that have been in existence until now," says Margaret Cianci, executive director of the Alliance for Cancer Gene Therapy (see sidebar, p. 26). "But let's be clear: Nothing is being done that influences future generations or anything like that. It's not the type of research we're funding, nor anyone else in the US."

Don't underplay the patient–customer service angle. Myriad Genetics, a maker of diagnostics like myRisk Hereditary Cancer, which evaluates 25 genes associated with eight cancer sites, believes that supporting individuals (physicians included) with questions about products or conditions is crucial. According to EVP, corporate communications Ron Rogers, Myriad has more than 80 genetic counselors on staff and more than 200 in its customer-service department. "There has to be an ease of use with this information," he says.

There's reason to believe such approaches will resonate among patient and caregiver audiences. "They get it," Finkel says. "They know it's not Botox or some other elective procedure. For some people, [gene therapies] could be the difference between life and death, not between looking beautiful or looking ugly." And that doesn't even get into the high level of interest among today's empowered patients. "Patients know their options," Duerr says. "They're informed about clinical trials. There is lots of awareness in disease communities."

Some experts joke that there's more awareness in these communities than there is among physicians themselves. At the same time, most of their questions are likely to be about the logistics of the process rather than about the validity of the science. "I was chatting with a physician who's published a lot of work in hemophilia. Some of the things that came up were like, 'Is it even ethical to have patients in gene therapy trials?'" Graham reports. "We're going to have to address their concerns and questions. It's a tremendous learning curve for many of them."

"AD-based gene therapy is considered safe by the authorities, the industry and increasingly by doctors." —Jörn Aldag, CEO, uniQure

Of all potential audiences for marketing in and around gene therapies, payers will likely prove hardest to crack. It's unlikely that the next wave of gene therapies, which mostly target small patient populations, will threaten the economic underpinnings of the healthcare system the way that Gilead hep.-C cures Sovaldi and Harvoni supposedly did (it's worth noting for the 275th time: A single $80,000 drug regimen is a lot cheaper than a lifetime's worth of chronic care). "The impact of gene therapies on the system, at least for now, isn't as meaningful. It's digestible for the system," Aldag says.

But if or when gene therapies are approved to treat conditions with large populations—like the cardiovascular ones BMS and uniQure are targeting or Parkinson's disease—all bets are off. Aldag is hopeful that pharma companies and insurers will have adopted new financial models by the time gene therapies of that kind hit the market, but he's far from certain that they will.

"The key message regarding reimbursement is that it's a one-time treatment and doesn't require delivery of product to a hospital, and that you can provide higher value to patients who are already being treated or help patients where there's no treatment at all," Aldag explains. "If you look at this modality versus the lifetime cost of a therapeutic, you can price a gene therapy very profitably at a cost way inferior to the current lifetime cost to the healthcare system."

Aldag then brings up the dreaded "A" word: annuity. "I think payers will increasingly accept annuity payments over the lifetime of a patient," he says. "There won't be enormous peaks of upfront price—it would be spread over time. There's no risk of dosing a patient for $1 million and then three days later he gets run over by a car."

Will payers buy it, literally and figuratively? Several declined requests to discuss the eventualities associated with the economics in or around gene therapy. Graham, for one, is skeptical. "Some commentators say it might require Congressional action to make this happen—and, well, we've been really successful getting consensus around health legislation," she cracks.

"You have to get the third-party payers convinced that gene therapy is not experimental but rather an appropriate treatment path for specific individuals," Finkel adds. "In the long run they'll save money—never been an easy argument to make with payers." ■