# Ark floats gene therapy's boat, for now

In August, gene therapy's turbulent ride through the clinical rapids took a new twist as Ark Therapeutics released positive top-line results from a phase 3 trial of its adenoviral gene therapy Cerepro (sitimagene ceradenovec) for malignant brain tumors. Although the news boosted the London-based firm's shares, the course to market authorization and registration remains strewn with uncertainty—as Introgen, of Austin, Texas, found, to its cost, when the US Food and Drug Administration (FDA) recently refused its Biologics License Application (BLA) for Advexin (contusugene ladenovec), an orphan-designated adenoviral gene therapy for treating head and neck cancer and Li-Fraumeni syndrome.

Ark's 'study 904', which was approved by the UK Gene Therapy Advisory Committee in 2004, randomized 236 people with brain cancer to receive Cerepro plus standard care or standard care alone, which consists either of surgery and radiotherapy or of surgery and radiotherapy plus the alkylating drug Temodar/Temodal (temozolomide) from Schering-Plough in Kenilworth, New Jersey. Subjects given Cerepro and temozolomide showed a 42-day improvement over standard care in median survival, reaching significance ($P < 0.032$). Side effects hemiparesis, aphasia and pyrexia could be blamed on ganciclovir, which is part of the Cerepro protocol and is "pretty toxic," says analyst Stephen Dunn of Boca Raton, Florida–based securities firm Dawson James.

The data, due for a full airing at the European Association of Neuro-Oncology in Barcelona as *Nature Biotechnology* went to press, seem strong. Cerepro—which consists of the herpes simplex virus gene for thymidine kinase (TK) encased in an adenoviral vector in which the E1 and part of the E3 regions have been deleted to prevent replication—was tested in people with operable, high-grade malignant glioma. Doctors injected Cerepro into the cavity left by the removed tumor during the surgery. In the following days, physicians administered ganciclovir—Basel, Switzerland-based Roche's approved drug for cytomegalovirus (sold under the brand names Cytovene and Cymevene). The transformed cells expressing TK convert the prodrug ganciclovir into highly toxic deoxyguanosine triphosphate, which kills any remaining cancer cells. "All the TK does is provide a target for a second drug," says Dunn. "It's an interesting way of doing it, and safe."

A more detailed verdict on Cerepro is expected in January of next year, when data on mortality, one of study 904's secondary endpoints, will be reported; 45% of study participants remained alive at the start of August. It seems likely that Ark will use the trial results showing significant improvements in median survival compared with various control groups to apply for a new marketing authorization

AP Photo/ Peter Dejong

Bubble boy at the Amsterdam aquarium. Three-year-old Wilco Conradi was among the first to receive retroviral gene therapy to correct the fatal gene defect that causes severe combined immunodeficiency disorder, at the Hôpital Necker-Enfants Malades in Paris.

# IN brief

## Heplisav's topline

The investigational hepatitis B vaccine Heplisav could provide difficult-to-immunize patients with more robust protection than that offered by currently marketed vaccines. Heplisav—jointly developed by Berkeley, California–based Dynavax and partner Merck of Whitehouse Station, New Jersey—was evaluated against London-based GlaxoSmithKline's Engerix-B in a phase 3 trial in patients with end-stage renal disease. The study shows that Heplisav offers 95.1% seroprotection, compared with 81.1% with Engerix-B. The new vaccine combines Dynavax's immunostimulatory sequence (ISS 1018), a short DNA sequence that targets Toll-like receptor 9, with hepatitis B surface antigen. Because Heplisav stimulates the innate immune system, it triggers a robust and rapid antibody response even in patients that respond poorly to existing vaccines using two—rather than three—doses. But the US Food and Drug Administration (FDA) put Heplisav on hold after a single case of Wegener's granulomatosis occurred in this phase 3 trial (*Nat. Biotechnol.* **26**, 484, 2008). The recently released data will form part of the companies' response to the FDA's request for more data. Robin Davison of Edison Investment Research is skeptical of the vaccine's future: "The hepatitis B vaccine market is already well served. Although nonresponders are always a problem, a niche market is a smaller one,' he says. *–Susan Aldridge*

## Cloning shop

Two Austin, Texas–based companies have joined forces to create a 'one stop' cloning and licensing service for livestock breeders. The merger of Start Licensing and Viagen will enable customers to secure licenses for reproducing breeding stock to preserve traits of prized animals—such as disease resistance and superior-quality meat—and contract in-house cloning services from one provider. Start Licensing, set up in 2005 by Geron of California and Phoenix, Arizona–based Exeter Life Sciences, manages and licenses a portfolio of 80 patents for nuclear transfer cloning technologies, including those developed at the Roslin Institute in Edinburgh, while ViaGen, a subsidiary of Exeter, offers cloning services for breeders who lack in-house expertise. The move comes just months after the US Food and Drug Administration (FDA) concluded that food from cloned animal sources is safe to eat (*Nat. Biotechnol.* **26**, 249–250, 2008). Steve Stice of Aruna Biomedical, Georgia, previously of ViaGen, thinks the technology will struggle to find more than a niche market. "There is a demand, but how big is debatable. Until the major food producers are willing to say they will use these animals in their production systems, the market will be fairly limited," he says. Smithfield Foods, a major pork producer, owns a stake in the new enterprise but is not planning to produce meat products from cloned animals. *–Hayley Birch*



**Table 1** Additional selected gene therapies in advanced clinical development

| Company (location) | Gene therapy | Stage of development |
|---|---|---|
| Amsterdam Molecular Therapeutics (Amsterdam) | Glybera (alipogene tiparvovec); AAV-1 vector encoding lipoprotein lipase | Orphan status; pre-registration trial of 13 subjects with lipoprotein lipase deficiency |
| Introgen (Austin, Texas) | INGN-241; an E1-deleted, replication-incompetent adenoviral vector encoding melanoma-differentiation-associated gene-7 (mda-7; interleukin-24) | Phase 3 in metastatic melanoma |
| GenVec Gaithersburg, Maryland) | TNFerade; an E1-, E3- and E4-deleted adenoviral vector encoding human TNF-α under the control of the radiation-inducible early growth response promoter | Phase 3 in pancreatic cancer |
| MolMed (Milan) | Retrovirus encoding herpes simplex virus thymidine kinase transduced *ex vivo* into hematopoietic stem cells | Phase 3 in graft-versus-host disease |
| Vical (San Diego) | Allovectin-7 (velimogene aliplasmid); DNA plasmid encoding the human leukocyte antigen-B7 (HLA-B7) and β2-microglobulin complex in context of cationic lipid mixture (DMRIE/DOPE) | Orphan status; phase 3 in chemotherapy-naive patients with metastatic melanoma |
| Oxford Biomedica (Oxford, UK) | Prosavin; combined lentivirus and equine infectious anemia virus vectors encoding aromatic amino acid decarboxylase, tyrosine hydroxylase and GTP-cyclohydrolase-1 | Phase 2 in Parkinson's disease[a] |
| Targeted Genetics (Seattle) | tgAAC-94; AAV-2 encoding IgG1 Fc and the TNF-α receptor | Phase 2 in rheumatoid arthritis |

Source: the Investigational Drugs Database.

[a]Phase 2 detailed interim results of the study are expected to be reported at the 16th Annual Congress of the European Society of Gene and Cell Therapy in Bruges, Belgium, November 13–16, 2008.

for Cerepro in glioma in Europe. In 2006, the European Medicines Agency's (EMEA) European Committee for Medicinal Products for Human Use returned the company's previous marketing application, which had been based on a small phase 2 trial. But, as EMEA's deputy head of sector for safety and efficacy Marisa Papaluca Amati is quick to point out, "It was a withdrawal, not a rejection."

In the meantime, another frontrunner in adenoviral gene therapy, Introgen's Advexin, has hit a snag at the FDA.

Paradoxically, while the EMEA accepted Introgen's marketing application for Advexin (a recombinant, E1-deleted serotype 5 adenoviral vector encoding the p53 tumor suppressor), about a month later the FDA said that the company's biologics license application (BLA) was incomplete.

Safety probably is not the issue in the FDA's refusal to accept Advexin's BLA, Dunn says. It could be the prospective biomarker analysis they used in the trial. "I'm wondering if the FDA didn't just go back on their word," after claiming that such data would be acceptable, Dunn ponders. This is significant because Introgen specifically designed their phase 3 trial to prospectively segment patients according to p53 abnormalities and p53 protein levels in pretreatment tumor samples (the company declined to reveal the identity of the mutations).

Preliminary results from this open-label, multicenter, randomized study, which

# SELECTED research collaborations

| Partner 1 | Partner 2 | $ (millions) |
|---|---|---|
| Ablynx (Ghent, Belgium) | Merck Serono (Darmstadt, Germany) | 453 |
| SBI Biotech (Tokyo) | MedImmune (Gaithersburg, Maryland) | * |
| PDL (Redwood City, California) | Bristol-Myers Squibb (New York) | 710 |
| Archemix (Cambridge, Massachusetts) | Ribomic (Tokyo) | 200 |
| Cytos (Zurich) | Pfizer (New York) | 131.8 |

* Financial details not disclosed.

compared Advexin with the standard-of-care methotrexate in 123 people with end-stage head and neck cancer, were released in May at the American Society of Gene Therapy meeting in Boston. In the intent-to-treat population, median survival was 6.1 and 4.4 months in the Advexin and methotrexate arms, respectively, which was not significant. Even so, biomarker analysis revealed that survival was increased in Advexin-treated subjects with favorable p53 profiles compared with those with unfavorable p53 profiles (7.2 versus 2.7 months). Introgen declined to comment on the FDA's decision to turn down the BLA and indicated that talks to remedy the situation are ongoing.

According to Antonio Giordano, a pioneer in gene therapy and professor of molecular biology at Temple University in Philadelphia, who also uses adenoviral vectors in his research, the FDA's thumbs-down was "not a surprise." The viral gene therapy approach in general "presents lots of well known limitations," he says, especially with regard to immune responses.

Indeed, previous instances of wayward inflammatory responses in people receiving viral gene therapies have been at the root of some of the field's darkest moments. In 1999, Jesse Gelsinger died of massive organ failure after receiving a high dose in his hepatic artery of an adenoviral gene therapy for ornithine transcarbamylase in a trial at the University of Pennsylvania (*Nat. Biotechnol.* **23,** 519–521; 2005). Thus far, such adverse events have not been a concern for either Ark's or Introgen's adenoviral therapies.

But immune responses have compromised some adeno-associated virus (AAV) gene therapies. In one case, media coverage implicated Targeted Genetics of Seattle, Washington's AAV-2 gene therapy for rheumatoid arthritis in compromising the immune response of a participant in a phase 2 trial; however, the US National Institute of Health's Recombinant DNA Advisory Committee has since clarified that Jolee Mohr's death by histoplasmosis was much more likely due to the tumor necrosis factor (TNF)-α inhibitor she was taking systemically rather than the locally delivered AAV vector carrying the gene for the TNF-α receptor. T cell–mediated destruction of AAV-transduced cells has, however, been thought to account for self-limited and asymptomatic liver toxicity reported in two subjects on a human factor IX gene therapy for hemophilia (*Nat. Med.* **12**, 342–347, 2006) and elevated levels of creatine phosphokinase seen in certain people receiving Glybera (alipogene tiparvovec) from Netherlands-based Amsterdam Molecular Therapeutics, an AAV-1 gene therapy to treat lipoprotein lipase deficiency. Amsterdam has since gone on to complete enrollment and treat its last patient in the phase 3 study of its orphan-designated gene therapy—and an application for marketing authorization is expected later this year.

For other gene therapy vectors that recombine their genetic payload into chromosomes, such as retroviruses, insertional mutagenesis also remains a concern. "Whenever there is an alteration, [there will be] a number of checks and balances that modify the change," says Papaluca Amati, so efficacy without serious side effects is "very tricky" to achieve. What she emphasizes is the balance between risk and benefit. In 2003, a French gene-therapy trial using a retroviral therapy against X-linked severe combined immune deficiency disorder had the side effect of causing leukemia in four children. The important point, says Papaluca Amati, is that three of the four patients with leukemia were cured. "All of those children would have been long dead [without gene therapy], and now they're up and running."

Another big hurdle for the field as a whole is a lack of worldwide standards for dosing gene therapies. "Many of the failures we've seen are related to the fact that there's no understanding of how much active substance was made available by gene therapy," she notes.

Even so, several dosage/preliminary efficacy gene therapy studies have recently shown encouraging results. Last month, researchers at the University of Florida published positive data on their phase 1 trial of an AAV-2 vector encoding the *RPE65* (retinal pigment epithelium–specific 65-kDa protein) gene in subjects with Leber congenital amaurosis (*Hum. Gene Ther.* doi:10.1089/hgt.2008.107).

And, as the space heats up, smaller gene-therapy firms driven by leading-edge research are likely to be partnered and taken over by larger companies. Papaluca Amati does not keep financial charts, but she carefully tracks drug sponsors who consult the agency for guidance. "Since 2005, we've started seeing the big 20 pharma corporations making investments" in gene therapy, she says, a clear indicator that the field is gathering steam. "When you want to know what season is there and when the weather will change, you have to see which birds are flying." She says drug developers are becoming less concerned about their candidates being shot down, too, thanks to a closer relationship between the FDA and EMEA, which are establishing monthly meetings.

Amati also disagrees with the notion that European regulators are more liberal, noting that neither the FDA nor EMEA have yet approved a gene-therapy product for sale. "We are absolutely on an equal stance," she says.

**Randy Osborne** *Mill Valley, California*

| Details |
|---|
| Merck agreed to pay Ablynx $ 13.9 million up-front cash and up to $453 million in milestones to co-discover and co-develop Nanobody-based therapeutics against two targets in oncology and immunology. Ablynx's Nanobodies are based on variable heavy chain antibody fragments from llamas. |
| SBI Biotech has granted MedImmune an exclusive license to research, develop and commercialize SBI Biotech's anti-ILT7 protein for the potential treatment of systemic lupus erythematosus and other autoimmune diseases. ILT7 is a cell surface protein uniquely expressed on plasmacytoid dendritic cells. SBI Biotech receives an undisclosed up-front payment and is eligible for milestones and royalties. |
| PDL, based in Redwood City, California, will receive $30 million up-front for rights to elotuzumab, an anti-CS1 glycoprotein antibody currently in phase 1 for multiple myeloma. PDL could get $480 million more for reaching development and regulatory milestones and up to $200 million based on sales. |
| Archemix granted Ribomic a worldwide nonexclusive license to develop aptamers against multiple targets. Under the terms of the agreement, Archemix will receive an up-front payment of $6 million. Archemix is eligible to receive milestone payments and royalties that could exceed $200 million. |
| Pfizer and Cytos will collaborate to develop, manufacture and commercialize vaccines based on Cytos' Immunodrug technology based on the chemical crosslinking of antigens on virus-like Qb carrier particles packaged with a CpG oligonucleotide. Cytos will receive $8.8 million up-front and up to $123 million in milestones and manufacturing technology transfer fees, plus up to double-digit royalties for exclusive, worldwide rights to undisclosed vaccines. |