Gene Therapy Briefs

Sangamo BioSciences (www.sangamo.com) said it will acquire Ceregene, a developer of adeno-associated viral (AAV) gene therapies, in a deal that expands Sangamo's capabilities in AAV manufacturing. The price was not disclosed.

Sangamo will acquire all of Ceregene's preclinical and clinical therapeutic programs—including its ongoing phase 2 trial to evaluate its CERE-110 product, an AAV vector carrying the gene for nerve growth factor (NGF), in patients with Alzheimer's disease. In March, Ceregene obtained from Roche's Genentech subsidiary a license for exclusive worldwide rights to NGF and another gene, neurotrophic factor 4/5 (NT-4/5); financial terms were not disclosed.

CERE-110 is designed to address the loss of cholinergic neurons associated with memory loss and cognitive decline in Alzheimer's by using AAV to produce a steady supply of NGF in the brain. The double-blind, placebo-controlled phase 2 trial is in its follow-up stage, which will evaluate the effect of treatment on established clinical end points in cognitive function and quality of life. Results are expected to be released in 2015.

Ceregene and collaborators at the Alzheimer's Disease Cooperative Study (ADCS), based at the University of California, San Diego (UCSD), won a \$5.4 million grant in 2008 from the NIH's National Institute on Aging to support the trial of CERE-110 in 50 patients with mild to moderate Alzheimer's.

With its acquisition, Sangamo will receive more than 120 issued, pending, or in-licensed patents that include patent families covering the AAV vector platform and manufacturing methods, as well as therapeutic transgenes, and a Ceregene-developed needle device for direct administration of AAV to the brain. Sangamo said the deal will also give it access to, among other things, GMP master cell banks as well as a database of preclinical efficacy and toxicology studies and other documentation supporting Ceregene's Investigational New Drug (IND) applications.

Sangamo said the documentation will help it prepare and file IND applications for its engineered class of DNA-binding proteins that the company calls zinc finger DNA-binding proteins or ZFP Therapeutics®—especially those that target the brain. By engineering ZFPs to recognize a specific DNA sequence, Sangamo has enabled creation of sequence-specific ZFP nucleases (ZFNs) for gene modification and ZFP transcription factors capable of controlling gene expression, and thus cell function.

Sangamo's lead pipeline product, SB-728, uses a ZFN-based approach to modify the gene encoding CCR5, the major coreceptor used by HIV to infect immune cells. The company's first application of the technology is an autolo-

gous ZFN-CCR5-modified T cell product (SB-728-T) that is the subject of an ongoing phase 2 trial, and two phase 1/2 and two phase 1 studies in patients with HIV and AIDS. The company also has a preclinical program to develop an SB-728 hematopoietic stem cell product, and a research-stage program to develop SB-728 as an *in vivo* product.

Sangamo said a subsidiary would merge into Ceregene, which would continue as a wholly owned subsidiary of the Company. The acquisition, expected to close in September, is subject to customary conditions that include approval by Sangamo shareholders.

In a regulatory filing with the U.S. Securities and Exchange Commission, Sangamo said it is required to pay Ceregene stockholders a double-digit percentage of any upfront and milestone payments it receives if it grants a third-party license to develop and commercialize CERE-110 for Alzheimer's or another Ceregene drug candidate, CERE-120 for Parkinson's disease or Huntington's disease.

If Sangamo commercializes either product itself, it is required to pay Ceregene stockholders royalty-like "earn-out" payments as a percentage of net sales ranging "in the low double digits" depending on the amount of net sales, subject to reductions by Sangamo, according to the filing.

The acquisition can be terminated by either company if it is not closed by November 15, or sooner by mutual consent, the filing added.

GenVec (www.genvec.com) said it has withdrawn a plan to liquidate and dissolve the company approved by its board in May, in favor of a new strategy that seeks to maximize the value of its technology and assets—including a hearing loss collaboration with Novartis.

GenVec's new strategy has led to a change at the top. President and CEO Cynthia Collins has left the company and resigned from its board of directors. Succeeding Collins in her executive and board roles is Douglas J. Swirsky, GenVec's SVP and CFO since 2006.

"GenVec's decision to withdraw its plan of dissolution is a result of our increased confidence that milestones in our collaborations can be realized, and [in] our ability to bring our expenditures in line with our resources," Swirsky said in a statement. "Not including potential milestone payments from Novartis, we have cash, cash equivalents, and investments to fund our operations through at least the end of 2014."

By withdrawing the dissolution plan approved in May, 2 months after it reported a 47% year-over-year drop in annual revenue last year, GenVec can also take the time necessary to find licensees or collaborators "who assign a reasonable value to our technologies, rather than valuing the technology in the shadow of dissolution," Swirsky added.

The board now has five members. Departing the board with Collins were Edward M. Connor, Jr., MD, Adel A.F. Mahmoud, MD, PhD, and Kevin M. Rooney, following unanimous approval by directors to withdraw the dissolution plan approved in May, and approve the new operating strategy.

GenVec has struggled to develop successful gene therapy treatments, despite winning a conditional approval in June 2012 for a vaccine intended to treat foot-and-mouth disease in cattle. Two months later, in September 2012, GenVec cut 30% of its workforce, or 23 positions, to save cash, saying the reduction would allow it to fund operations through the third quarter of 2014, even without any milestone payments it may receive through an ongoing collaboration with Novartis. At the time, GenVec reported about \$20.9 million in cash, cash equivalents, and short-term investments at the end of the second quarter of 2012.

GenVec ended 2012 with a 47% revenue loss, down to \$9.4 million, a slide the company blamed on year-over-year declines of \$5.6 million in its hearing loss and balance disorders program, \$1.5 million in its HIV program, and \$1.2 million in its foot-and-mouth disease program.

Audentes Therapeutics (www.audentes.com) has closed on \$30 million in Series A financing led by OrbiMed Advisors, with participation by 5AM Ventures and Versant Ventures. The startup biotech develops and commercializes new treatments for rare muscle diseases, using AAV gene therapy technology.

Audentes said it will use the funding to further advance its two AAV-based lead programs—AT001 for X-linked myotubular myopathy (XLMTM), and AT002 for Pompe disease—as well as evaluate additional candidate programs. The company is headquartered in San Francisco, California.

“This financing is a tremendous step forward for the development of new potential treatments for patients affected by very serious orphan muscle diseases,” Matthew R. Patterson, Audentes’ president and CEO, said in a statement.

Patterson joined Thomas J. Schuetz, MD, PhD, and OrbiMed Advisors in founding Audentes in November 2012. Dr. Schuetz will act as an independent director of Audentes’ board, which will be chaired by Jonathan T. Silverstein, J.D., a general partner and a co-head of global private equity with OrbiMed Advisors; and include Kush M. Parmar, MD, PhD, a principal with 5AM Ventures; Thomas Woiwode, PhD, a venture partner with Versant Ventures; and Patterson.

Twelve days after announcing the Series A financing, Audentes was granted an exclusive worldwide license by ReGenX Biosciences to develop and commercialize products to treat XLMTM and Pompe disease, using ReGenX’s NAV rAAV8 and rAAV9 vectors. In return, Audentes agreed to pay ReGenX an upfront payment and milestone fees, both undisclosed, and royalties on net sales of products incorporating NAV rAAV8 and rAAV9.

ReGenX holds exclusive rights to a portfolio of over 100 patents and patent applications pertaining to its NAV technology and related applications. The company plans to initially develop treatments for rare, genetic diseases that include hypercholesterolemias, the mucopolysaccharidoses, and retinitis pigmentosa, while ensuring continuing access to its NAV technology through partnerships, licenses, and global collaborations.

At least 320,000 mammalian viruses within nine viral families await discovery by investigators, according to a team of researchers from the United States, Bangladesh, and Mexico that applied a new framework for the discovery of novel viruses in wildlife to produce the first-ever estimate of the number of viruses that exist in a mammalian host.

Collecting evidence of all or most of the viruses could provide information critical to early detection and mitigation of disease outbreaks in humans, the team concluded in its study “A Strategy to Estimate Unknown Viral Diversity in Mammals,” published September 3 in the journal *mBio*, published in association with the American Academy of Microbiology (Anthony *et al.*, 2013).

“We estimate the cost of discovering these viruses to be ~\$6.3 billion (or ~\$1.4 billion for 85% of the total diversity), which if annualized over a 10-year study time frame would represent a small fraction of the cost of many pandemic zoonoses,” the team observed in the study.

The economic impact of the severe acute respiratory syndrome (SARS) pandemic alone has been calculated to be \$16 billion. “We’re not saying that this undertaking would prevent another outbreak like SARS. Nonetheless, what we learn from exploring global viral diversity could mitigate outbreaks by facilitating better surveillance and rapid diagnostic testing,” said Simon Anthony, DPhil, a scientist at the Center for Infection and Immunity (CII) at Columbia University’s Mailman School of Public Health.

Investigators from the CII and EcoHealth Alliance—an international organization of scientists dedicated to the conservation of biodiversity—collected 1897 biological samples from the Indian flying fox or *Pteropus giganteus*, the largest flying mammal and a mammalian wildlife host identified as the source of several outbreaks of Nipah virus.

Returning to the laboratory, the team used the polymerase chain reaction to identify 55 viruses in nine viral families. Only five of these were previously known, including two human bocaviruses, an avian adenovirus, a human/bovine betacoronavirus, and an avian gammacoronavirus. The other 50 were newly discovered, including 10 in the same family as Nipah virus.

The researchers estimated that another three rare viruses were unaccounted for in the samples, upping the estimate of viruses in the flying fox to 58. That number was extrapolated to all 5,486 known mammals, producing the estimated total of at least 320,000 viruses.

That estimate could be much higher, the team said, based on use of high-throughput sequencing methods developed at the CII and the expectation of finding additional viral families. Among questions likely to affect viral count depending on their answers: How representative of all flying foxes are the samples from flying foxes in Bangladesh? Do all mammal species harbor a similar number of viruses? And to what extent are viruses shared from species to species?

Also, the cost of the flying fox expedition in Bangladesh is relatively low compared with a similar undertaking for animals living in more remote areas—a factor the team said could further raise the cost of collecting samples.

Dr. Anthony is one of two corresponding authors for the study; the other is Peter Daszak, PhD, president of EcoHealth Alliance.

Two papers published the same day in the journal *Science* illustrate the potential of treating debilitating inherited

conditions through lentiviral vector gene transfer into hematopoietic stem/progenitor cells (HSPCs) and hematopoietic stem cells (HSCs).

The first paper, "Lentiviral Hematopoietic Stem Cell Gene Therapy in Patients with Wiskott-Aldrich Syndrome" (Aiuti *et al.*, 2013), chronicled the use by researchers from France, Germany, Italy, Turkey, the United Kingdom, and the United States of a lentiviral vector encoding a functional version of the gene encoding WASP, a cytoskeleton-regulating protein implicated in the inherited immunodeficiency Wiskott-Aldrich syndrome (WAS). Luigi Naldini, MD, PhD, scientific director of the San Raffaele Scientific Institute (Milan, Italy), and his team applied the vector to genetically correct HSPCs from three patients with WAS, which they then reinfused.

"All three patients showed stable engraftment of WASP-expressing cells and improvements in platelet counts, immune functions, and clinical score," Dr. Naldini and colleagues reported, adding that according to vector integration analyses, gene-corrected HSPCs resulted in highly polyclonal and multilineage hematopoiesis.

The researchers noted that "lentiviral gene therapy did not induce selection of integrations near oncogenes," and that they did not observe aberrant clonal expansion 20 months to 32 months posttherapy. "Although extended clinical observation is required to establish long-term safety, lentiviral gene therapy represents a promising treatment for WAS," the researchers concluded.

In "Lentiviral Hematopoietic Stem Cell Gene Therapy Benefits Metachromatic Leukodystrophy" (Biffi *et al.*, 2013), Dr. Naldini and a team of researchers from Germany, Italy, Lebanon, the Netherlands, the United Kingdom, and the United States took a similar approach in transferring a functional arylsulfatase A (ARSA) gene into HSCs from three presymptomatic patients who showed genetic, biochemical, and neurophysiological evidence of late infantile metachromatic leukodystrophy (MLD), an inherited lysosomal storage disease.

The researchers found that the patients showed extensive and stable ARSA gene replacement after reinfusion of the gene-corrected HSCs. As with the first study, vector integration analyses showed no evidence of aberrant clonal behavior.

"Notably, the disease did not manifest or progress in the three patients 7 to 21 months beyond the predicted age of symptom onset," the researchers wrote. "These findings indicate that extensive genetic engineering of human hematopoiesis can be achieved with lentiviral vectors and that this approach may offer therapeutic benefit for MLD patients."

The researchers cautioned, however, that although their data are promising, long-term follow-up of patients is needed in order to establish the full therapeutic potential of this gene therapy strategy for MLD: "In addition, our data position lentiviral gene transfer as a feasible means to engineer human hematopoiesis to its near entirety—an approach that could be exploited for treatment of other diseases."

Both studies were published online July 11, and in print on August 23.

Dr. Naldini was corresponding author for the WAS study and one of two corresponding authors on the MLD study, joined there by Alessandra Biffi, group leader of the HSC gene therapy for lysosomal storage disorders research unit at the San Raffaele Scientific Institute.

References

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—Alex Philippidis