Gene Therapy Briefs

Oxford BioMedica (www.oxfordbiomedica.co.uk) said May 1 it will manufacture clinical-grade material using its LentiVector gene delivery platform technology for Novartis (www.novartis.com).

Oxford BioMedica said it will also provide certain process development services and expects to receive between £2.5 million (about \$3.9 million) and £4 million (about \$6.2 million) from Novartis over the next 12 months.

Under the agreement, Oxford BioMedica will be responsible for manufacturing several batches of a lentiviral vector encoding CTL019 technology. This vector will be used to transduce patients' T cells in an *ex vivo* process before they are reinfused. CTL019 targets a protein called CD19 that is associated with a number of B cell malignancies including chronic lymphocytic leukemia, B cell acute lymphocytic leukemia, and diffuse large B cell lymphoma.

"The strategic investment in our specialist manufacturing capabilities is a pivotal step towards building a financially self-sustaining business and this collaboration is an example of how we can commercialize our expertise," Oxford BioMedica CEO John Dawson said in a statement.

LentiVector uses a stripped-down version of the equine infectious anemia virus (EIAV). The technology is designed for long-lasting delivery of genetic material into target cells without toxicity or adverse immune reaction; integration of genes into nondividing cells; and a capacity for multiple therapeutic genes.

According to Edison Investment Research, Oxford BioMedica's deal with Novartis is expected to raise the gene-based therapy firm's valuation from £58.5 million (\$91 million) to £60.1 million (\$93.6 million) in that same timeframe. Edison calls the transaction "an attractive deal for Oxford BioMedica," adding that it could eventually lead to a longer term supply agreement.

Imperial College London (www.imperial.ac.uk) is working with the British Heart Foundation (BHF; www.bhf.org.uk), the Royal Brompton Hospital (www.rbht.nhs.uk), and other hospitals in and outside the United Kingdom on a pair of recently launched gene therapy trials for heart failure—the first two such trials to be conducted in the United Kingdom.

The therapy involves raising the levels of SERCA2a protein in heart muscle cells by inserting extra genes into the cells, using a harmless virus. Research by the BHF and Royal Brompton has identified SERCA2a as an important factor affecting the contraction of heart muscle cells in people with heart failure.

Doctors plan to study the gene therapy in two separate clinical trials. CUPID2 will assess whether cardiac gene therapy to increase SERCA2a is safe and can improve both quality and length of life, and reduce emergency hospital

admissions, for heart failure patients. The trial, to involve 200 patients with heart failure from Royal Brompton and other sites worldwide, will begin treating people with heart failure over the next few weeks at Royal Brompton's Cardiovascular Biomedical Research Unit, and will be funded by Celladon (www.celladon.net/).

The second trial, called SERCA-LVAD, is due to start recruitment this summer. Cofunded by the BHF, this trial will test SERCA2a gene therapy in 24 U.K. heart failure patients already fitted with mechanical heart pumps, known as left ventricular assist devices (LVADs). It will give vital information about the effectiveness of the therapy by measuring the amount of the SERCA2a gene and protein that has been introduced into heart muscle.

"Our goal is to fight back against heart failure by targeting and reversing some of the critical molecular changes arising in the heart when it fails," Alexander Lyon, ***DEG, BHF Senior Lecturer at Imperial, and consultant cardiologist at Brompton, the U.K. lead investigator for both studies.

Trials will be led by cardiologists and scientists at Brompton and Imperial, in collaboration with doctors at several U.K. hospitals including Royal Brompton's Harefield Hospital in London, Papworth Hospital in Cambridge, and Scotland's Golden Jubilee National Hospital.

Avian influenza A H7N9 and its spread in China was the focus of a pair of recently published studies. Weeks before Shanghai officials on May 11 declared the end of their emergency response program for H7N9, because no new human cases had been reported over the previous 20 days, a team of Chinese researchers summarized preliminary findings of their investigations of the first reported cases, and of follow-up monitoring of close contacts of people with confirmed cases of the virus.

The team analyzed data from H7N9 cases reported to the Chinese Center for Disease Control and Prevention as of April 17, and then published its findings April 24 on the website of *The New England Journal of Medicine* (Li *et al.*, 2013). The study found that among 82 persons with confirmed H7N9 virus infection, a total of 17 people (21%) died after a median illness duration of 11 days, while an additional 60 remained critically ill; 4 were discharged from the hospital after treatment for clinically mild cases of avian flu; and 1 pediatric patient was not admitted to the hospital.

The median age of people with confirmed H7N9 infection was 63 years, within a range of ages from 2 to 89 years. Of the 82 people with the infection, 73% were male, and 84% were urban residents.

Animal exposure appeared to be a more significant factor in the disease than age. Of 77 persons for whom data were available, 4 were poultry workers, and 59 (77%) had a

history of exposure to live animals. Of the 59, 45 patients (76%) reported a history of recent exposure to chickens, 12 (20%) to ducks, and 4 (7%) to swine. Exposures occurred while patients were either working at or visiting a live animal market. Traditionally, Chinese people prefer to buy live poultry and have it butchered because they believe the meat will taste better than the frozen meat usually purchased by Western consumers.

However, human-to-human transmission of H7N9 virus could not be ruled out in two family clusters reviewed by the research team.

Shanghai suspended all live poultry businesses as a precaution against the further spread of H7N9 virus to humans on April 6. However, city officials will solicit public opinion before deciding whether to close live poultry markets permanently or allow them to reopen, the Shanghai online news outlet Eastday.com reported on May 12.

The number of human cases appears to have decreased after closure of live animal markets, the WHO reported in the May 10 risk assessment "Human Infections with Avian Influenza A(H7N9) Virus." As of that date, a total of 131 confirmed cases of human infection with the virus in eight provinces and two cities (Beijing and Shanghai) were reported to the WHO by China's National Health and Family Planning Commission. Another case, involving a patient who had recently traveled from Jiangsu, China, was reported by the Taipei Centers for Disease Control.

A separate study published in *The Lancet* (Chen *et al.*, 2013) offered a disease profile of H7N9 based on four cases—the first infected patient from Zhejiang Province, and three cases that emerged after retrospective testing of 486 patients admitted to hospitals with pneumonia between March 7 and April 9. That study showed a disease profile characterized by bilateral pneumonia progressing to acute respiratory distress syndrome, and multiorgan dysfunction resembling human infections with avian influenza virus H5N1 or severe seasonal or pandemic flu.

"The presence in most of the viruses isolated in people of amino acid substitutions associated with viral adaptation to human beings is worrying. The absence of these changes in epidemiologically linked viruses isolated from poultry suggests that these changes arose during human infection," Marion Koopmans and Menno D. de Jong wrote in a commentary on the *Lancet* study published April 25.

The NIH's National Institute of Allergy and Infectious Diseases (NIAID; www.niaid.nih.gov/Pages/default.aspx) halted its 4-year-old clinical trial of the investigational HVTN 505 prime-boost vaccine regimen developed by the NIAID Vaccine Research Center. The halt came after a scheduled interim review by an independent data and safety monitoring board (DSMB) found that the regimen neither prevented HIV infection nor reduced the amount of HIV in the blood of vaccine recipients who became infected with the AIDS virus.

The DSMB review also found that patients were more likely to contract HIV infection via HVTN 505 than by taking a placebo. Of the trial's 2,504 patients, 41 of 1,250 who were given the experimental vaccine regimen became infected with HIV, compared with 30 of 1,244 placebo patients. Those numbers shrank to 27 regimen patients and 21 placebo patients when findings were limited to the number of infections 28 weeks after dosing.

The NIAID said in a statement that the increased number of HIV infections was "non-statistically significant," but added: "It is not clear why this occurred and further analysis is needed to draw any firm conclusions. Based on the finding, the DSMB recommended closer follow-up of participants beyond their month 24 study visit. NIAID concurred, and will, in concert with the study investigators, be amending the study protocol to allow for closer, extended follow-up of the vaccine recipients."

The NIAID-supported HIV Vaccine Trials Network conducted HVTN 505, which was led by Scott M. Hammer, M.D., chief of the Division of Infectious Diseases at Columbia University. The phase 2 study consisted of three immunizations with a primer recombinant DNA-based vaccine over 8 weeks, followed by a single immunization with a booster, a recombinant vaccine based on a disabled adenovirus type 5 (Ad5) that carried the vaccine contents and was designed to help stimulate the immune system. The Ad5 vaccine encoded HIV proteins found both inside the virus and on its outer envelope.

Neither vaccine contained HIV or was capable of infecting study participants with the virus, according to the NIAID. The agency noted that both vaccines had been found safe in earlier clinical trials when tested in animals and when used in hundreds of people.

BioMarin Pharmaceutical (www.bmrn.com) has licensed a factor VIII gene therapy program for hemophilia A from University College London (UCL; www.ucl.ac.uk) and St. Jude Children's Research Hospital (www.stjude.org).

BioMarin said it expects to select a development candidate this year, initiate and complete IND-enabling toxicology studies next year, and launch proof-of-concept human studies by the end of 2014.

"Gene therapy is emerging as a powerful and viable way to treat genetic disorders and is complementary to our current suite of commercial products and research programs," BioMarin CEO Jean-Jacques Bienaimé said in a statement. "Hemophilia is an attractive target for gene therapy as factor levels in the blood serve as good biomarkers, relatively low factor levels are required for a clinically important benefit in severe patients, and the current standard of care of intravenous infusions three times a week is quite onerous."

"We remain committed to maintaining a rich pipeline with the goal of filing an IND every twelve to eighteen months," Bienaimé added.

BioMarin said the license and commitment to support the research program was made possible by UCL Business, UCL's wholly owned technology transfer company, working with Professor Amit Nathwani of the UCL Cancer Institute.

The factor VIII licensing deal, together with expenses stemming from BioMarin's acquisition of Zacharon Pharmaceuticals, led BioMarin to estimate its range of spending on R&D in 2013 at between \$340 million and \$380 million. BioMarin finished 2012 with \$302.2 million in R&D expense, up nearly 41% from \$214.4 million in 2011.

Eyeveusys, the developer of a new nonviral gene therapy process for use in treating eye diseases, announced an undisclosed equity investment from the Boehringer Ingelheim Venture Fund (BIVF; www.boehringer-ingelheim-venture.com). The investment—BIVF's sixth since its launch in 2010, and its first to a French company—marks the start of Eyeveusys's next round of funding, planned to take place before

the end of the second quarter, and designed to fund the business to completion of its phase 2a clinical trials.

Neither the amount of next-round funding to be raised, nor the size of BIVF's equity investment, was disclosed. Eyeevensys did say, however, that its first-round investors—Innobio, managed by CDC Entreprises; Inserm Transfert Initiative; and CapDecisif Management—intend to participate in the new round, which aims to build on the €1.6 million (about \$2.1 million) raised during the first funding round.

Eyeevensys says it intends to use next-round funding to finalize its preclinical trials within 18 months, and complete phase 2a. Founded in 2009, Eyeevensys is currently focusing on the rare disease uveitis, as well as age-related macular degeneration, which according to the company is becoming more prevalent as populations age.

Long term, the company will focus on more common eye disorders such as diabetic retinopathy, for which repeated intraocular protein injections remain restrictive.

"We plan to complete a new round of funding between now and June. Discussions are already underway with potential new investors," Ivan Cohen-Tanugi, Ph.D., chairman of Eyeevensys, said in a statement. He said BIVF's investment "brings us credibility, further raises our profile, and gives us access to their wealth of experience in pharmaceutical and biotechnology R&D. This sends a strong signal to our target market."

Eyeevensys's technology involves the electrotransfer of plasmids into the ciliary muscle, resulting in stable, sustained expression of therapeutic proteins. The new therapeutic approach is designed to be less invasive than current therapies, because the frequency of injections can be stretched out from every 2 or 4 weeks to every 6 months. The first preclinical results in animal models have shown the expression of therapeutic proteins for up to 9 months.

Eyeevensys also announced the appointment to its board of directors of Michel Pairet, D.V.M., Ph.D., Boehringer Ingelheim's head of nonclinical research and development. He previously oversaw the company's worldwide research and corporate investment fund.

References

- Chen, Y., Liang, W., Yang, S., *et al.* (2013). Human infections with the emerging avian influenza A H7N9 virus from wet market poultry: Clinical analysis and characterisation of viral genome. *Lancet* 381, 1916–1925.
- Li, Q., Zhou, L., Zhou, M., *et al.* (2013). Preliminary report: Epidemiology of the avian influenza A (H7N9) outbreak in China. *N. Engl. J. Med.* (in press).

—Alex Philippidis