Gene Therapy Briefs

Spark Therapeutics (www.sparktx.com, Philadelphia, PA), a spinout of Children's Hospital of Philadelphia (CHOP), said May 27 it successfully completed a \$72.8 million series B financing. The financing round was led by Sofinnova Ventures. Joining Sofinnova as new investors in the company are Brookside Capital; Deerfield Management Company; Rock Springs Capital; funds and accounts managed by T. Rowe Price Associates, Inc.; Wellington Management Company, LLP; and two undisclosed dedicated healthcare funds.

CHOP, which cofounded Spark, also “participated significantly in the round,” the company said (Spark Therapeutics, 2014a). CHOP previously committed \$50 million in funding as part of the launch of Spark in October 2013, starting with an investment of \$10 million in a series A financing. CHOP's participation in this round brings its total equity investment in Spark to more than \$30 million.

“The funding will support the expansion of our team and ongoing development of our pipeline as we build the infrastructure needed for a first-in-class, FDA-approved gene therapy,” Jeffrey D. Marrazzo, cofounder and CEO of Spark Therapeutics, said in a statement (Spark Therapeutics, 2014a).

Funds will be used to advance the company's pipeline of gene therapy programs. These include development of its lead phase III program, which addresses a specific form of inherited retinal dystrophy caused by mutations in the *RPE65* gene.

The lead program is now in phase III and builds on an earlier clinical study in which 12 patients with *RPE65*-related blindness demonstrated significant improvement, moving in some cases from being profoundly blind to being able to function in sighted classrooms, recognize faces, and walk independently.

Spark said its latest financing would also support the company's growth over the next 3 years. On May 13, Spark announced plans to open a 28,000-square-foot facility in Philadelphia, at 3737 Market St., to house business operations, clinical research and development, and manufacturing (Spark Therapeutics, 2014b).

The Recombinant DNA Advisory Committee (RAC; http://oba.od.nih.gov/rdna_rac/rac_about.html) of the **U.S. National Institutes of Health** (NIH; www.nih.gov) will no longer review all proposed gene therapy clinical trials, NIH director Francis S. Collins, MD, PhD, said. “Given the progress in the field, I am confident that the existing regulatory authorities can effectively review most gene transfer protocols and that a streamlined process will reduce duplication and delays in getting gene transfer trials initiated,” Dr. Collins said in a statement (NIH, 2014).

Dr. Collins has directed NIH to implement recommendations issued in December 2013 by the **Institute of Medicine** (IOM; <http://iom.edu>) on the role of the RAC. The IOM recommended that RAC should only review individual research protocols in exceptional cases, contending that the research in most cases is no longer novel or controversial enough to require the additional scrutiny. “Oversight and review should focus only on the cases where the existing regulatory structure lacks that capacity to do so, or when there is significant expression of public concern,” the IOM stated in *Oversight and Review of Clinical Gene Transfer Protocols: Assessing the Role of the Recombinant DNA Advisory Committee* (Institute of Medicine, 2013).

The IOM identified and recommended specific criteria for future RAC review—namely, protocols that cannot be adequately reviewed by other oversight and regulatory bodies, as well as protocols meeting one or more of the following criteria:

- Protocols that use a new vector, genetic material, or delivery method that is being used on human subjects for the first time, thus presenting an unknown risk.
- Protocols that rely on preclinical safety data obtained using a new preclinical model system of unknown and unconfirmed value.
- Protocols that involve a vector, gene construct, or method of delivery associated with possible toxicities that are not widely known, and that may render it difficult for local and federal regulatory bodies to evaluate the protocol rigorously.

In those cases, the IOM recommended, the NIH director should consult with other regulatory and oversight authorities to determine whether RAC review is warranted. But even if proposed research doesn't meet these criteria, the director should have the flexibility to select research protocols for RAC review that may present what he or she may deem to be significant societal or ethical concerns.

The IOM was asked to study whether human gene transfer research raised issues of special concern that warranted continuing extra oversight of individual clinical protocols by the RAC. As part of its report, the IOM also recommended that NIH consider replacing the RAC with a similar body that would review risky clinical research. NIH is still “considering” that recommendation, spokeswoman Renate Myles told *ScienceInsider* (Kaiser, 2014).

Kite Pharma (www.kitepharma.com; Santa Monica, CA) has licensed from the U.S. National Institutes of Health (NIH; www.nih.gov) intellectual property related to T-cell receptor (TCR)-based product candidates that target the NY-ESO-1

antigen for the treatment of cancers expressing NY-ESO-1. The NY-ESO-1 antigen may be expressed in numerous tumor types, including sarcoma, bladder cancer, esophageal carcinoma, non-small cell lung cancer, breast carcinoma, ovarian carcinoma, prostate carcinoma, multiple myeloma, and hepatocellular carcinoma and melanoma, among other tumor types. In return for the license, Kite agreed to make undisclosed “clinical, regulatory and sales milestone payments” to the NIH, as well as pay the NIH royalties on net sales of products covered by the license (Kite Pharma, 2014a).

NIH’s National Cancer Institute (NCI; www.cancer.gov) is conducting a phase II clinical trial of a mouse-derived TCR product candidate targeting the NY-ESO-1 antigen at the NIH pursuant to a cooperative research and development agreement (CRADA) between Kite and the NCI. Kite is investigating murine TCR technology platforms developed by the NCI Surgery Branch for the treatment of solid tumors under the CRADA. Preclinical evaluation in the Surgery Branch of murine TCRs targeting the NY-ESO-1 antigen identified a murine TCR with comparable or enhanced activity relative to the equivalent human-based NY-ESO-1 TCR. TCR product candidates are designed to recognize antigens irrespective of their cellular localization and as presented by the major histocompatibility complex (MHC) on the tumor cell.

Kite Pharma’s agreement with the NIH came just 4 days after GlaxoSmithKline (www.gsk.com; Brentford, London) said it will develop and commercialize the lead clinical cancer program of Adaptimmune (www.adaptimmune.com; Oxford, United Kingdom). Like Kite and NIH, GSK’s new collaboration with Adaptimmune focuses on TCR engineering technology—namely, a T cell expressing a modified TCR to recognize a tumor antigen (epitope) associated with a human leukocyte antigen (HLA) molecule. Adaptimmune has created TCRs designed to target NY-ESO-1 and other targets. The collaboration could yield more than \$350 million for Adaptimmune over the next 7 years (Adaptimmune, 2014).

On June 23, Kite Pharma disclosed that it was set to close on an initial public offering of 8.625 million shares—7.5 million shares of common stock at \$17 per share, and another 1.125 million shares of common stock sold to underwriters after they exercised in full their 30-day option to purchase the shares at the IPO price, less customary underwriting discounts and commissions (Kite Pharma, 2014b).

The initial public offering was expected at deadline to have raised \$146.625 million, not counting expenses and discounts - above the proposed maximum aggregate offering price of \$115 million discussed in the company’s Form S-1 registration statement with the U.S. Securities and Exchange Commission (SEC; www.sec.gov) relating to a proposed initial public offering of common stock shares (U.S. Securities and Exchange Commission, 2014). Jefferies, Credit Suisse Securities (USA), and Cowen and Company acted as joint book-running managers for the offering. Stifel acted as comanager.

VBL Therapeutics (www.vblrx.com; Or Yehuda, Israel), a gene therapy developer targeting cancer and immune-inflammatory diseases, is seeking to raise up to \$75 million through an initial public offering. VBL plans to list on the NASDAQ under the symbol VBLX (Renaissance Capital, 2014).

Founded in 2000 as Vascular Biogenics Ltd., VBL bases its clinical pipeline on two platform technologies. The company’s Vascular Targeting System™ (VTS™) is designed to enable systemic administration of genetically targeted therapy to either destroy or promote newly formed, or angiogenic, blood vessels. The company’s VTS-based lead oncology product candidate is VB-111, a gene-based biologic that is being developed for recurrent glioblastoma (rGBM). The program has been awarded fast track designation by the U.S. Food and Drug Administration (FDA; www.fda.gov) for the prolongation of survival in patients with glioblastoma that has recurred following treatment with standard chemotherapy and radiation, as well as orphan designations in both the United States and Europe.

VB-201, the lead product candidate from VBL’s anti-inflammatory program, is a first-in-class, specific innate immunity disease-modifying medicine under development for the effective treatment of chronic immuno-inflammatory diseases. According to VBL, VB-201 is currently in phase II clinical trials for psoriasis and ulcerative colitis and offers the potential to deliver long-term control for a spectrum of other immuno-inflammatory diseases including inflammatory bowel disease, rheumatoid arthritis, and atherosclerosis. The compound is positioned to work as a standalone treatment or as part of a combination period.

VBL’s anti-inflammatory program is based on the Lecinoxoid platform technology. Lecinoxoids are a VBL-developed class of small molecules designed to be structurally and functionally similar to naturally occurring molecules known to modulate inflammation (VBL Therapeutics, 2014).

Lysogene (www.lysogene.com; Paris, France) said May 21 that it has closed on €16.5 million (about \$22 million) in series A financing. Paris-based Sofinnova Partners led this financing round, becoming the firm’s main institutional investor. New and co-lead investors include the French public investment bank Bpifrance, through its Innobio fund, and Novo Seeds, part of Novo A/S.

“Today, we are in a strong position to successfully face our challenges: the company is preparing the pivotal clinical study for its lead product and quickly plans on developing a second product addressing another genetic pathology involving the central nervous system, a field where patients’ and families’ needs still remain highly unfulfilled,” Lysogene CEO Karen Aiach, MBA, said in a statement (Lysogene, 2014a).

Lysogene specializes in intracerebral gene therapy aimed at treating neurodegenerative diseases, such as Sanfilippo syndrome type A. Last year, Lysogene successfully completed a phase 1–2 study (Eudract 2010-019962-10/NCT01474343) using its lead product (SAF-301) in patients with Sanfilippo syndrome.

SAF-301 uses an rh.10 serotyped adeno-associated virus (AAVrh.10) as a vector to deliver, via injection, functional versions of the *SGSH* and *SUMF1* genes directly into a young patient’s brain. Lysogene obtained orphan designations for SAF-301 in Europe in 2010, and in the United States last year (Lysogene, 2014b).

The company was founded in 2009 by Aiach and Prof. Olivier Danos, PhD, who is chief scientific advisor and from 2008–2011 was director of the Gene Therapy Consortium at University College London, where he developed a good manufacturing practice AAV facility.

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—Alex Philippidis