Gene Therapy Briefs

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) should diminish its role in gene therapy by eliminating—in most cases—its review of the individual research protocols in human gene transfer studies, a report issued Dec. 5 by the Institute of Medicine (IOM) concluded. For commentaries on this issue, please see the section entitled Institute of Medicine (IOM) Committee on the Independent Review and Assessment of the Activities of the NIH Recombinant DNA Advisory Committee (RAC) on page 17.

RAC should only review individual research protocols in exceptional cases, IOM said, contending that the research is most cases is no longer novel or controversial enough to require the additional scrutiny. Over the past year, the report found, RAC selected only 20% of all submitted protocols for additional review.

While acknowledging the paramount importance of patient safety, the report also concludes that most individual RAC reviews no longer provide benefits beyond the existing regulatory and oversight framework and may be impeding scientific advancement with unnecessary red tape.

“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,” IOM stated (Koehler *et al.*, 2013, page 8).

The report 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, according to the IOM, 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 RAC should serve as a model by which NIH develops a process to rigorously review research on humans in any scientific realm that uses applications from emerging technologies or techniques that pose unknown or significant risks, IOM added. Citing fields such as nanotechnology, synthetic biology, and neurobiology, the report concluded: “Gene transfer research no longer stands alone as the only human application of an emerging technology that might benefit from additional avenues of oversight.”

Editas Medicine (<http://editasmedicine.com>, Cambridge, MA) has been launched by five pioneers in genome editing technology seeking to translate their research into a new class of therapeutics designed to enable precise and corrective molecular modification to treat underlying causes of diseases at the genetic level.

Editas—which has been awarded \$43 million in Series A venture financing—will draw on the work of its five founders in developing the gene editing methods of CRISPR (clustered, regularly interspaced short palindromic repeats)/Cas9 (CRISPR-associated protein 9) and TALENs (transcription activator-like effector nucleases):

- Feng Zhang, PhD, core member of the Broad Institute, investigator at the McGovern Institute for Brain Research, and joint assistant professor in the Departments of Brain and Cognitive Sciences and Biological Engineering at MIT
- George Church, PhD, founding core faculty member at the Wyss Institute for Biologically Inspired Engineering at Harvard University and Robert Winthrop professor of genetics at Harvard Medical School
- Jennifer Doudna, PhD, Howard Hughes Medical Institute investigator and professor of biochemistry, biophysics, and structural biology at the University of California, Berkeley
- Keith Joung, MD, PhD, associate chief of pathology for research and associate pathologist at Massachusetts General Hospital and associate professor of pathology at Harvard Medical School, a pioneer in the development and translation of genome-editing technologies
- David Liu, PhD, Howard Hughes Medical Institute investigator and professor of chemistry and chemical biology at Harvard University, a renowned protein evolution and engineering biologist

CRISPR/Cas9 acts through a mechanism in which the Cas9 protein binds to specific RNA molecules. The RNA molecules then guide the Cas9 complex to the exact location in the genome that requires repair. CRISPR/Cas9 uniquely enables highly efficient knock-out, knock-down, or selective

editing of defective genes in the context of their natural promoters, unlocking the ability to treat the root cause of a broad range of diseases.

Editas' founders reason that early published research on CRISPR/Cas9, plus a growing body of work on TALENs, suggests that both comprise novel gene-editing methods capable of overcoming challenges associated with previous technologies.

"Editas is optimizing and refining existing genome editing technology to create a versatile platform for the development of potential human therapeutics," Dr. Zhang said in a statement (Editas Medicine, 2013).

The \$43 million series A financing round was led by Flagship Ventures, Polaris Partners, and Third Rock Ventures, with participation from Partners Innovation Fund.

Kevin Bitterman, PhD, a principal with Polaris, will serve as Editas' interim president. Rounding out the leadership team are Alexandra Glucksmann, PhD, interim COO and former founding employee and SVP of research and development at Cerulean Pharma; and Lou Tartaglia, PhD, interim CSO and partner with Third Rock.

Members of Editas' Board of Directors include another partner with Third Rock, Alexis Borisy; Douglas Cole, MD, general partner with Flagship; and Terry McGuire, co-founder and general partner of Polaris.

Amicus Therapeutics (www.amicusrx.com, Cranbury, NJ) bought back full rights to the Fabry disease compound migalastat HCl—overhauling a 3-year collaboration with GlaxoSmithKline—as part of a far-reaching restructuring intended to reposition the company as a top-tier developer of enzyme replacement therapies (ERTs) and save itself \$4 million annually.

As part of the restructuring, Amicus also cut its workforce by 14% to 91 employees and acquired Callidus Biopharma, an ERT developer whose lead preclinical compound has shown promise against Pompe disease, in an up-to-\$130 million deal. Amicus said its restructuring was intended to cut costs and align resources with its biologics business strategy. The company will shut down its San Diego research lab and consolidate all operations at its Cranbury headquarters.

The company also said it acquired global rights from GSK to develop and commercialize migalastat HCl, both as a monotherapy and in combination with ERT for Fabry disease. Amicus will pay nothing upfront, but agreed to make GSK eligible for unspecified future payments tied to regulatory and commercial milestones, plus royalty payments.

In addition, GSK agreed to take a \$3 million stake in Amicus through an equity investment in a concurrent private placement in public equity (PIPE) transaction.

For the Fabry ERT, GSK is eligible to receive single-digit royalties on net sales in eight undisclosed major markets outside the United States. For migalastat HCl monotherapy, GSK can receive post-approval and sales-based milestone payments, as well as tiered royalties in the mid-teens in eight undisclosed major markets outside the United States.

The new agreement between Amicus and GSK replaces a prior version of their agreement inked in July 2012, under which the companies were to codevelop all current and future formulations of migalastat HCl for Fabry disease, including a combination of migalastat HCl with a GSK investigational ERT for Fabry. Amicus won commercial rights

to all Fabry products in the United States; GSK won such rights for the rest of world and increased its ownership in Amicus with an \$18.6 million investment in common stock priced at \$6.30 per share, bringing GSK's total ownership stake in Amicus to 19.9%.

The companies began collaborating in 2010 when GSK paid Amicus \$60 million in upfront and equity money and committed itself to an additional \$170 million toward migalastat HCl development costs as well as milestones payments.

In December 2012, the collaboration met with a Phase III failure after acknowledging that migalastat HCl, also known as Amigal, failed to meet its primary efficacy endpoint in one of two pivotal trials, Study 011. Results showed a higher, but not statistically significant, percentage of patients achieving a 50% or greater reduction in GL3 in the kidneys of Fabry patients via migalastat HCl (41%) versus placebo (28%) in biopsies after 6 months.

In June, the U.S. Food and Drug Administration (FDA; www.fda.gov) refused to commit to using 12-month biopsy results as a possible route to approval of migalastat HCl, while directing the company to await results from the other Phase III trial (Study 012), which is ongoing and compares the compound to the current standard of treatment of ERT.

"This transaction is very important for Amicus and for our future. It delivers what we believe to be immediate and significant value to our shareholders while allowing us to maintain a strong relationship with GSK, our largest shareholder," John F. Crowley, Amicus' chairman and CEO, said in a Nov. 20 press release coissued by Amicus and GSK (Amicus Therapeutics, 2013a).

Amicus also said it will acquire Callidus, a move which will bolster its ERT pipeline with a next-generation Pompe ERT—a recombinant human acid-alpha glucosidase (rhGAA)—in late preclinical development, and complementary enzyme-targeting technologies.

Amicus said it will pay Callidus shareholders \$15 million in stock; up to \$10 million in milestone payments through Phase II development of the Pompe program; and up to \$105 million for the achievement of late-stage development, regulatory, and approval milestones spread across three products.

According to Amicus, the Pompe ERT has shown superior uptake and activity compared to Lumizyme[®] in preclinical studies and may be further improved by incorporating Amicus' pharmacological chaperone AT2220 as a stabilizer designed to enhance tissue uptake and reduce the ERT's immunogenicity. Callidus' enzyme-targeting technology is also applicable to multiple ERTs—and, Amicus reasons, complement its CHART[™] platform for the development of bio-betters for multiple lysosomal storage diseases.

"With the addition of Callidus' Pompe program, we can move a next-generation Pompe ERT into the clinic in early 2015, approximately 12 months faster than our internal Pompe program. Even more significantly, we believe that the Callidus ERT for Pompe is a highly innovative and potentially superior ERT due to its carbohydrate structure, which should provide for greater uptake of the ERT into target muscle cells in Pompe patients," Crowley said in a separate Amicus announcement, also on Nov. 20 (Amicus Therapeutics, 2013b).

He said Amicus will advance the next-generation ERT as quickly as possible instead of the planned Phase II study of AT2220 co-administered with ERT.

As part of the restructuring, Amicus said Callidus' founder and CSO Hung Do, PhD, has been appointed Amicus' SVP of discovery biology, while Amicus' current CSO, David J. Lockhart, PhD, will step down from his position but continue as a member of the company's Scientific Advisory Board.

Amicus also secured about \$40 million in equity and expected debt financing toward the restructuring transactions. Of that total, \$15 million was raised in a private placement of 7.5 million shares of common stock priced at \$2.00 per share, plus warrants to buy another 1.6 million shares at \$2.50/share between July 1, 2014, and June 30, 2015. Redmile Group and GSK took part in the private placement. The remaining \$25 million in debt financing is expected to close in coming weeks at a cost of capital of less than 10%, with no warrant coverage, Amicus said.

Oxford BioMedica (www.oxfordbiomedica.co.uk; Oxford, United Kingdom) has resumed recruitment into the RetinoStat® Phase I, StarGen™ Phase I/IIa, and UshStat® Phase I/IIa studies using existing clinical trial material, following approvals from the FDA and from France's Agence Nationale de Sécurité du Médicament (ANSM; <http://ansm.sante.fr>).

Back in June, the company voluntarily paused recruitment for those studies as a precautionary measure while it investigated what it called very low concentrations of a potential impurity in its clinical trial material, namely, raw material from an unidentified third party. Oxford BioMedica has since carried out characterization studies that identified the impurity as highly fragmented DNA derived from fetal bovine serum (FBS).

"In light of these findings, Oxford BioMedica remains convinced of the safety, integrity and quality of its LentiVector® platform products and no safety concerns relating to any of the ocular products have been identified in any preclinical and clinical data generated to date," the company stated in an Oct. 17 press release (Oxford BioMedica, 2013).

Oxford BioMedica said it will ensure the quality and integrity of its lentiviral vector products and work with FDA and ANSM to define specifications for future batches of clinical trial material. The company's tech platform consists of the LentiVector gene delivery system, which targets diseases of the central nervous system and the eye, as well as a unique tumor antigen (5T4) that is a target for anti-cancer therapy.

FDA and ANSM agreed to allow Oxford BioMedica to resume recruitment into its ocular clinical trials using existing clinical trial material. Those trials include:

- RetinoStat, in which two anti-angiogenic genes, endostatin and angiostatin, are delivered directly to the retina with the goals of preserving and improving the vision of patients through anti-angiogenesis, which blocks the formation of new blood vessels. Based on preclinical data, the company anticipates that RetinoStat may require only a single administration, giving the product a significant advantage in the market over currently available treatments requiring more frequent, repeated administration.

- StarGen, which uses the LentiVector platform technology to deliver a corrected version of the ABCA4 gene. Based on preclinical data, it is anticipated that a single application of StarGen™ to the retina could potentially either provide long-term or permanent correction. There are currently no approved treatments available for Stargardt disease.
- UshStat uses LentiVector to deliver a corrected version of the MYO7A gene to address the vision loss associated with Usher syndrome type 1B, for which there are currently no approved treatments. Based on preclinical data, it is anticipated that a single application of UshStat to the retina could provide long-term or potentially permanent stabilization of vision.

The FDA finalized its "Guidance for Industry: Pre-clinical Assessment of Investigational Cellular and Gene Therapy Products" in November 2013, a year to the month that the agency released a draft guidance for comment (Food and Drug Administration, 2013).

The document is intended to provide sponsors and individuals involved in the design and implementation of pre-clinical studies with recommendations on the substance and scope of preclinical information needed to support clinical trials for investigational products reviewed by FDA's Center for Biologics Evaluation and Research (CBER)/Office of Cellular, Tissue and Gene Therapies (OCTGT).

The final guidance consists of four main sections: Pre-clinical study considerations, recommendations for investigational cell therapy products, recommendations for investigational gene therapy products, and recommendations for investigational therapeutic vaccines. Product areas covered by the guidance include cellular therapy, gene therapy, therapeutic vaccination, xenotransplantation, and certain biologic-device combination products that are reviewed by OCTGT.

"The diverse biology and clinical indications and the rapid and fluid state of the evolving scientific research into these product areas pose unique scientific challenges in terms of regulatory review," the guidance states (Food and Drug Administration, 2013, page 3).

Because the intrinsic material composition and putative mechanisms of action of cellular and gene therapy (CGT) products differ from small molecular weight drugs, and macromolecular biologic drugs such as therapeutic proteins, FDA contends that "traditional, standardized approaches for preclinical toxicity testing, which were developed for drug development and device testing, are often not appropriate for evaluating the safety of CGT products" (Food and Drug Administration, 2013, page 1).

According to the FDA, the guidance is designed to clarify current expectations regarding preclinical information that would support an investigational new drug application (IND) and a biologics license application (BLA) for these products. The guidance supersedes recommendations in Section VIII of the March 1998 guidance entitled "Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy."

"We have revised our recommendations to reflect our current knowledge gained through advancements in the field and through experience gained through OCTGT's review of CGT products," the finalized guidance states (Food and Drug Administration, 2013, page 3).

FDA also recommends that CGT product developers engage in “early and ongoing communication with OCTGT pharmacology/toxicology staff during product development.”

“These communications help to ensure that regulatory expectations related to safety, demonstration of potential activity, and understanding of possible MOA(s) are addressed,” the guidance added.

The new guidance does not apply to human cells, tissues, and cellular and tissue-based products regulated solely under section 361 of the PHS Act (42 U.S.C. 264) as described under 21 CFR Par 1271, nor to therapeutic biological products for which the Center for Drug Evaluation and Research (CDER) has regulatory responsibility. In addition, the guidance does not apply to those biological products regulated by the Office of Vaccines Research and Review (such as prophylactic vaccines) or to those biological products overseen by the Office of Blood Research and Review.

A 30-month-old girl from Mississippi remains free of active HIV infection a year after the end of antiretroviral treatment (ART) that began unusually early, when she was just 30 hours old, according to an updated case report, “Absence of Detectable HIV-1 Viremia after Treatment Cessation in an Infant,” published Oct. 23 in the *New England Journal of Medicine* (Persaud *et al.*, 2013).

“This case suggests that very early ART may interfere with either the quantities or qualities of persistent reservoirs of replication-competent virus,” the research team concluded in its report. “The absence of rebound viremia, the undetectable replication-competent virus, the almost-complete disappearance of cell-associated HIV-1 DNA, and the absence of HIV-1-specific immune responses while the child was not receiving ART suggest that replication-competent HIV-1 reservoirs may not have been established or were markedly abated, if not extinguished.”

While early findings were presented in March 2013 during a scientific meeting in Atlanta, the newly published report adds details and confirms what researchers say is the first documented case of HIV remission in a child.

“Our findings suggest that this child’s remission is not a mere fluke but the likely result of aggressive and very early therapy that may have prevented the virus from taking a hold in the child’s immune cells,” said Deborah Persaud, MD, lead author of the *NEJM* report and a virologist and pediatric HIV expert at the Johns Hopkins Children’s Center, in a JHMI press release (Science Daily, 2013).

Dr. Persaud worked with immunologist Katherine Luzuriaga, MD, of the University of Massachusetts Medical School, and pediatrician Hannah Gay, MD, of the University of Mississippi Medical Center, who identified and treated the baby and continues to see the child.

“We’re thrilled that the child remains off medication and has no detectable virus replicating,” Dr. Gay said. “We’ve continued to follow the child, obviously, and she continues to do very well. There is no sign of the return of HIV, and we will continue to follow her for the long term.”

Born to an HIV-infected mother, the girl showed a progressively diminishing presence of HIV-1 in her blood from the start of treatment until reaching undetectable levels 29 days after birth. She remained on antivirals until age 18 months, at which point the ART treatment was stopped. Ten months later, the young patient underwent repeated standard

HIV tests, which showed that levels of plasma HIV-1 RNA, proviral DNA in peripheral-blood mononuclear cells, and HIV-1 antibodies, as assessed via clinical assays, remained undetectable in the child through 30 months of age.

The girl is not among the tiny percentage of “elite controllers” or people with HIV whose immune systems allow them to naturally keep the virus in check without treatment. The absence of elite-controller immune system characteristics in the child indicates that early therapy, rather than natural immune mechanisms, led to the child’s remission,” according to the investigators.

Investigators said the girl’s experience offers evidence that HIV-infected infants can achieve viral remission if ART begins within hours or days of infection. A federally funded study set to begin in early 2014 will test the early-treatment method used with the Mississippi girl case to determine whether the approach can be used to treat all HIV-infected newborns.

Human Gene Therapy, a peer-reviewed journal published by **Mary Ann Liebert, Inc.**, will feature a series of “Perspectives” by top pioneers in cell and gene therapy in the 2014 issues of the journal. The series will celebrate *Human Gene Therapy*’s 25th anniversary next year.

According to Mary Collins, PhD, chair of the award selection committee, a blue-ribbon scientific panel was commissioned to identify the pioneers. “Identifying the pioneers who have made current successes in gene therapy possible was a really interesting process. The committee agreed that a mixture of virologists, technologists, and clinicians had made essential contributions,” Dr. Collins said in a press release announcing the winners (Mary Ann Liebert, Inc. publishers, 2013).

Winners of the 12 Pioneer Series Awards are:

- Robin R. Ali, PhD, UCL Institute of Ophthalmology; Jean Bennett, MD, PhD, Perelman School of Medicine, University of Pennsylvania; and William W. Hauswirth, PhD, University of Florida College of Medicine—nominated for *Gene therapy for eye disorders*
- Malcolm K. Brenner, MD, PhD, Baylor College of Medicine—nominated for *Cancer gene therapy using gene modified T cells*
- Frederic D. Bushman, PhD, Perelman School of Medicine, University of Pennsylvania; and Christof von Kalle, MD, PhD, National Center for Tumor Diseases, Heidelberg—nominated for *Vector integration and tumorigenesis*
- Marina Cavazzana, MD, PhD, Paris Descartes University; and Adrian J. Thrasher, MD, PhD, UCL Institute of Child Health—nominated for *Basic and clinical gene therapy for immunodeficiency disorders*
- Ronald G. Crystal, MD, Weill Cornell Medical College, Cornell University—nominated for *Adenoviral vectors/role in translation of gene therapy to clinic*
- Zelig Eshhar, PhD, Department of Immunology, The Weizmann Institute of Science; and Carl H. June, MD, Perelman School of Medicine, University of Pennsylvania—nominated for *CARs for cancer gene therapy/ lentiviral gene therapy clinical trials*
- Joseph C. Glorioso III, PhD, University of Pittsburgh, School of Medicine—nominated for *Development of HSV as a vector for gene therapy*

- Katherine A. High, MD, Children's Hospital of Philadelphia; Amit C. Nathwani, PhD, UCL Cancer Institute; Andrew M. Davidoff, MD, St. Jude Children's Research Hospital; and Arthur W. Nienhuis, MD, St. Jude Children's Research Hospital—Nominated for *Basic and clinical gene therapy for hemophilia*
- A. Dusty Miller, PhD, Fred Hutchinson Cancer Research Center, University of Washington; and Richard C. Mulligan, PhD, Harvard Gene Therapy Initiative, Harvard Institute of Medicine—nominated for *Retroviral vectors*
- Luigi M. Naldini, MD, PhD, San Raffaele Telethon Institute for Gene Therapy—nominated for *Basic and clinical lentiviral vector development and translational gene therapy*
- R. Jude Samulski, PhD, Gene Therapy Center, University of North Carolina at Chapel Hill—nominated for *Basic AAV vector technology*
- James M. Wilson, MD, PhD, Gene Therapy Program, Perelman School of Medicine, University of Pennsylvania, and editor-in-chief, *Human Gene Therapy*—nominated for *Basic and clinical AAV vector development*

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—Alex Philippidis