Curative therapeutics take the stage

Regenerative medicine and advanced technologies make up a diverse group of therapeutics. As curative strategies for treating disease, they have the potential to alter the standard of care for many indications. With associated risks now tempered, investors and big pharma are showing interest.

BY MELANIE BRAZIL

Regenerative medicine and advanced technologies include gene therapy *in vivo* and *ex vivo*, gene-modified cell therapies, stem cells, tissue engineering and biomaterials, as well as emerging platforms for gene editing. The excitement in the field can be gauged by the huge amounts of money flooding into the space (**Table 1**).

Over the past decade, all of the big players have become increasingly involved in the curative-therapeutics space. Dealmaking was very strong throughout 2014, and this trend appears set to continue through 2015 as pharma aligns with expertise in the field.

"Ties to innovation are close to the prospects of clinical success and subsequent investment, and there is cause for optimism. The science in the field of regenerative medicine is hitting the make-or-break point over the next 2 years. If trials go well, we could see things take off like they have in the CAR-T [chimeric antigen receptor T cell] or oligonucleotide space," explained Anthony Sun, partner at Aisling Capital.

Gene therapy

Pfizer has taken steps to enter the gene therapy field by appointing Michael Linden, a gene therapy expert, to a 2-year secondment within Pfizer's Rare Disease Unit. The company has also made an agreement with Spark Therapeutics to develop SPK-FIX, a bio-engineered adeno-associated virus (AAV) vector for the treatment of hemophilia B. Phase 1/2 clinical trials were expected to start in the first half of 2015. According to the terms of the deal, Spark Therapeutics will get $20 million up front, with up to $260 million more tied to developmental milestones. Pfizer will be responsible for any pivotal studies and regulatory submissions. Spark Therapeutics could receive double-digit royalties on the basis of global product sales.

The Sanofi subsidiary Genzyme and the Cambridge (MA)-based gene therapy startup Voyager Therapeutics recently announced a broad collaboration for a range of neurobiological diseases. Voyager Therapeutics started only a year ago, headed by former Lilly executive and Third Rock partner Steve Paul, with a $45 million Series A funding round provided by Third Rock. The company uses gene therapy and microRNA tools using proprietary AAV vectors. Genzyme is paying $65 million in cash and has a $30 million equity investment in Voyager Therapeutics, and there are other potential contributions of up to $845 million in development and sales milestones and for international rights to gene therapies for Parkinson's disease, Friedreich's ataxia and Huntington's disease (US rights only). If any products reach market, Voyager Therapeutics will receive royalties. The company's candidate therapy for Parkinson's disease is in phase 1b.

GlaxoSmithKline (GSK) plans to file an application for approval of its own adenosine deaminase–severe combined immunodeficiency (ADA-SCID) program by the European Medicines Agency (EMA) in the next few months and is in active discussions with the US Food and Drug Administration (FDA) for filing in the United States. The therapeutic, which uses a gammaretrovirus integrating vector, is based on research licensed from Italy's San Raffaele Telethon Institute for Gene Therapy. Previously, the gammaretroviruses used in X-linked SCID and Wiscott-Aldrich Syndrome (WAS) led to leukemia. However, infusion of gammaretroviral ADA-transduced hematopoietic stem cells has not resulted in leukemia, or even clonal expansion, in about 20 ADA-SCID patients for more than 8 years after treatment and is considered safe. GSK is also developing two *ex vivo* stem cell gene therapy programs with self-inactivating lentiviral vectors for WAS and metachromatic leukodystrophy.

bluebird bio has two clinical-stage gene therapy programs in development: one for childhood cerebral adrenoleukodystrophy, and one for β-thalassemia. Its LentiGlobin BB305 gene therapy for β-thalassemia, which works by genetic modification of autologous CD34 cells, has recently received 'breakthrough designation' from the FDA. The company's market cap increased from $800 million to $4 billion over the past year.

In 2014, the area drew in $3 billion in financing, a sign that it is clearly overcoming forebodings of the past. The early development of this field did indeed result in unforeseen events because of limitations associated with the vectors themselves. Today, however, the biology is better understood, there are approved therapies on the market, and the future looks promising, albeit with new challenges to be addressed.

Richard Lawn, consulting professor at Stanford University's Cardiovascular Institute and Cardiogen Sciences, is confident about the current state of vector development. "The field is exploding because scientists have created lentiviral and AAV vectors, which are much safer and more efficacious than first-generation gene therapy."

Industry veteran and CEO of Voyager Therapeutics Steve Paul said, "We are ready to go now with the vectors in hand. However, as good as these vectors are, we and others are really just beginning studies to phenotypically screen thousands, if not millions, of capsid variants to find even better vectors to deliver genes to a given tissue or even cell type, for example, brain, spinal cord, liver, heart, lung, etc. Using this data we can apply more rational approaches to establishing structure-activity relationships and to further optimize these vectors for a given disease application. We should have much better vectors in just a few years."

Genome editing

Genome editing uses DNA nucleases or 'molecular scissors' to create specific breaks in genes and allows the endogenous repair mechanisms of the cell, together with an introduced corrective template, to repair the induced break (**Fig. 1**). The families of nucleases include zinc finger nucleases, transcription activator–like effector nucleases, meganucleases and the CRISPR-Cas9 system.

In January 2015, AstraZeneca indicated its intention to enter the gene-editing field with CRISPR by forging partnerships with The Wellcome Trust Sanger Institute UK, The Innovative Genomics Institute, Thermo Fisher Scientific and both the Broad Institute and the Whitehead Institute in Massachusetts. In this method, a plasmid containing Cas9 and specifically designed CRISPRs is inserted into the genome at a specific location, allowing the genome to be cut at that location to silence, enhance or change genes. Startups in the field include Intellia, Editas and CRISPR Therapeutics. There is disagreement among the scientists within the companies over where the intellectual property belongs.

Clinically, the most advanced in the genome-editing space is Sangamo BioSciences, which uses zinc finger technology for genome editing and raised $50 million through its initial public offering (IPO) and additional funds in follow-on financing, most recently $94 million in March 2014. The company's lead program in HIV is an autologous zinc finger–modified T cell product that is currently in phase 2 trials in HIV-infected subjects. It works by introducing a mutation into CCR5, the T cell surface receptor that is used by HIV-1 for cell entry. Sangamo BioSciences

Table 1: Total financing, 2013–2014.

	2013	2014	% change
Gene and gene-modified cell therapy	$491 million	$3 billion	+510%
Cell therapy	$2 billion	$2.6 billion	+30%
April 2014 Tissue engineering	$708 million	$687 million	–3%

Data source: Alliance for Regenerative Medicine.

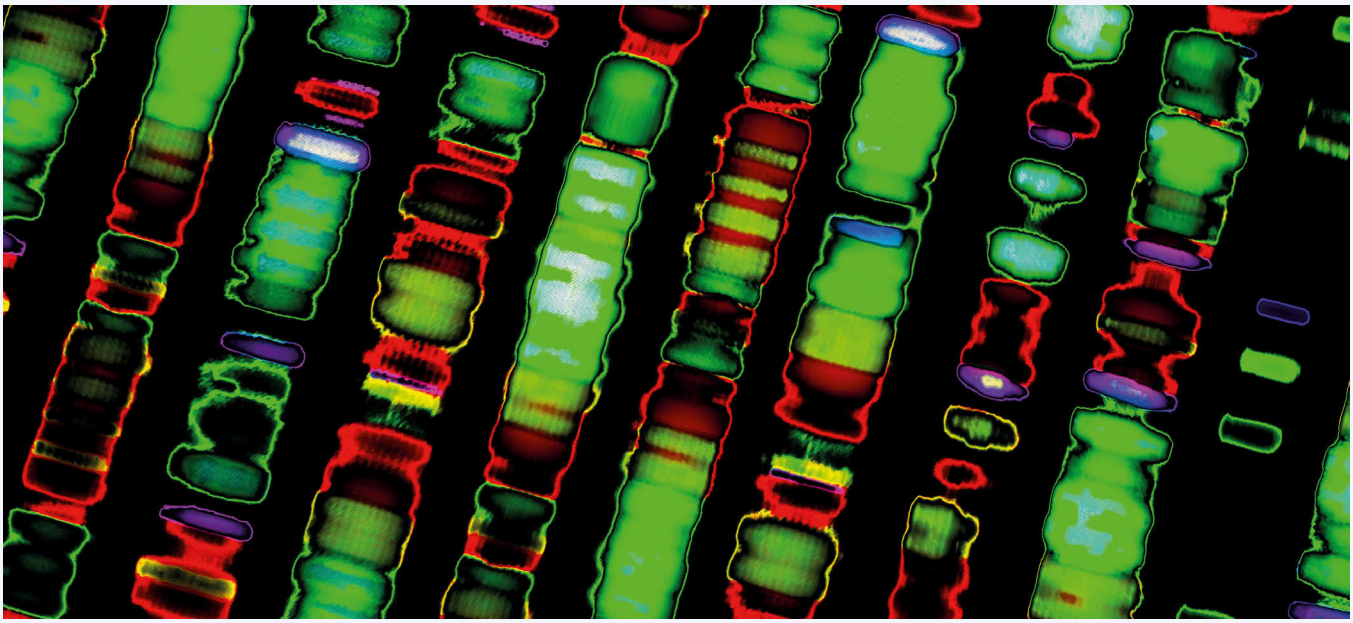

Figure 1: DNA sequence. Genome editing is among the curative therapeutic strategies attracting investment. Programmable nucleases can also be used to correct genetic mutations to treat diseases

has a partnership with Biogen to develop gene therapies to treat β-thalassemia and sickle cell disease. Sangamo BioSciences can receive up to $320 million per indication, as well as double-digit royalties on product sales. Sangamo BioSciences also has a partnership with Shire to develop therapies for hemophilia and Huntington's disease. Shire will pay Sangamo BioSciences $13 million up front, plus research, regulatory, development and commercial milestone payments and royalties on product sales.

Tissue engineering and cell therapy

In the past few years, regenerative medicine and advanced technologies has become a dynamic and rapidly changing field, owing to numerous positive clinical trial results. Many new companies have emerged, and programs are moving from academia to the corporate world. A number of successful IPOs have taken place over the past couple of years, including those of bluebird bio, Cellectis and uniQure (**Table 2**). Other companies are forging partnerships, including Avalanche and Regeneron, Sangamo and Biogen, and Moderna, who has partnerships with Alexion and AstraZeneca (**Table 3**).

Regenerative medicine includes the tissue-engineering and cell-therapy space. Products may be scaffold or matrix material alone, cells or a combination of both used to create the desired effect and therapeutic model. Cells may be autologous (patient derived) or allogeneic (donor derived). Cardiology, orthopedics, skin and wound healing, diabetes and central nervous system disorders continue to be the commercial markets for products.

One company in big demand is Moderna Therapeutics, working on delivering synthetic mRNA to cells to cure all manner of disease. Moderna Therapeutics has a balance sheet of $950 million, which is highly unusual for a company without a drug in clinical trials. AstraZeneca, Alexion and Merck, together with private investors, are collaborating on more than 40 drugs in development.

Semma Therapeutics received $44 million in Series A funding to be used to bring a cell therapy for type 1 diabetes through proof of concept in humans. Scientific founder and Harvard professor Doug Melton showed the ability to generate an unlimited amount of glucose-responsive pancreatic β-cells, which are necessary for insulin production to regulate blood sugar. MPM Capital led the funding round ahead of ARCH Venture Partners, Fidelity Biosciences and Medtronic. Semma has also entered into an agreement with Novartis for an undisclosed amount.

TiGenix's ChondroCelect, a cell-based product for cartilage repair in the knee, has been approved in Europe. The company has other products in the pipeline for Crohn's disease, rheumatoid arthritis, sepsis and autoimmune disease.

A major initiative in the tissue-engineering space is the Armed Forces Institute for Regenerative Medicine (AFIRM), which specializes in the treatment of battlefield injuries and has provided more than $300 million in funding to a consortium of military and academic scientists to accelerate and develop therapies, including for wound healing, bone repair and regeneration and burn repair. AFIRM researchers have established a wide variety of partnerships with academic institutions and dozens of companies.

Blockbuster indications

Traditionally, gene therapy has been associated with the treatment of rare genetic diseases; however, it has the potential to treat a broader array of indications, such as HIV, retinal diseases, hemophilia, heart failure and cancer (**Fig. 2**). Early successes with gene therapy for these indications indicate that it could compete with and even disrupt current treatments.

Ophthalmic disease and hemophilia are indications that feature prominently in gene therapy indications. Eye diseases are well understood and are often caused by a single gene mutation, and there are good predictive animal models that enable rapid clinical testing. In this field, the FDA consistently applies four accepted endpoints–visual acuity, visual fields, contrast sensitivity and color vision and provides guidance on how much improvement is required for a therapy to be considered clinically relevant. Clearly defined endpoints help accelerate the approval process. In addition, the eye is well suited for the direct delivery of a therapeutic to a site that is immunoprivileged and has a small volume. In the clinic, both AAVs (Spark Therapeutics, AGTC, Avalanche Biotech, NightstarX and GenSight) and lentiviral vectors (Oxford Biomedica) have been used to successfully administer gene therapy to the eye. Although there are a few companies working in this space, there is not a great deal of overlap among disease targets, which will allow each company, if successful, to carve out its own niche.

Current hemophilia drugs represent markets of around $6.5 billion for hemophilia A and $1.5 billion for hemophilia B—markets that are currently dominated by expensive therapies. Researchers have successfully used AAVs to deliver the gene-encoding factor IX (the clotting factor deficient in people with hemophilia B) to liver cells. After treatment with gene therapy, most patients had fewer bleeding incidents. A number of companies and institutions are involved in hemophilia

platforms in the clinic: St. Jude Children's Hospital–University College London, Spark Therapeutics–CHOP and AsklepiosBio-Baxter. Although hemophilia represents a global market of around $8 billion, there is a higher degree of overlap among the competing programs, and it remains to be seen whether there is room for multiple products in this category.

In May 2014, Regeneron and Avalanche announced a broad collaboration to develop proprietary AAV-based gene therapy products for ophthalmic diseases. Avalanche receives an up-front cash payment and up to $640 million on achievement of certain development and regulatory milestones. Eight therapeutic targets are covered, and Regeneron will have exclusive worldwide rights for each product that goes into clinical development. Avalanche has the option to share in costs and profits for two therapeutic targets. Regeneron gets a time-limited right of first negotiation for Avalanche's vascular endothelial growth factor gene therapy product for wet age-related macular degeneration upon completion of the ongoing phase 2a trial.

Pricing models—annuities?

Two gene therapy products are currently commercially available: Gendicine (Shenzhen SiBiono GeneTech), a recombinant adenovirus engineered to express p53 for use in patients with p53 mutant tumors that was approved in China in 2003 for head and neck cancer, and Glybera (alipogene tiparvovec; uniQure–Chiesi Farmacutici), a human lipoprotein lipase (LPL) gene therapy approved by EMA in 2012 for use in patients with LPL deficiency, which can cause severe pancreatitis.

Since Glybera's approval, the treatment has been cleared for reimbursement in Germany for

Table 2: IPO and follow-on proceeds and recent rounds of funding for advanced therapeutics.

Company	IPO/follow-on proceeds	Date
Cellectis	$228 million	March 2015
Bone Therapeutics	$35 million	February 2015
Intrexon	$116.4 million	January 2015
Avalanche	$162.8 million	January 2015
Lysogene	$22 million	May 2014
Audentes	$30 million	July 2014
Applied Genetic Technologies	$50 million	April 2014
AAVLife	$12 million	April 2014
CRISPR Therapeutics	$25 million	April 2014
Avalanche Biotechnologies	$55 million	April 2014
Sangamo	$94 million	Secondary offering, March 2014
NightstarX	$20 million	March 2014
Voyager Therapeutics	$45 million	February 2014
UniQure	$92 million	February 2014
Celladon	$51 million	January 2014
bluebird bio	$116 million	June 2013
Inovio	$59 million	Secondary offering, March 2014
Moderna	$110 million	November 2013
Editas	$43 million	November 2013
Dimension Therapeutics	>$10 million	November 2013 and 2014
Spark Therapeutics	$123 million	October 2013 and May 2014
GenSight Biologics	$42 million	April 2013
Hemera Biosciences	$3.8 million	March 2013

BOX 1: REGULATORY ACTION RAMPS UP

Regenerative medicine presents a regulatory challenge because a product may be considered a biologic, a medical device or a combination of the two. The FDA's Office of Combination Products determines the primary method of action and therefore the appropriate regulatory pathway. Although a company's reimbursement and regulatory strategies will preferably be aligned, it is possible to have a product regulated as a medical device and reimbursed as a cell therapy within one country and multiple reimbursement categories from each country in which the product is sold.

Gene therapy typically targets extremely rare orphan diseases, so clinical trials are necessarily small and might not use a control group or blinding procedures before phase 3 trials. EMA can grant marketing authorization under 'exceptional circumstances', recognizing the potential benefit of a product in light of incomplete information about a disease (typically owing to the small patient population) as well as the risks associated with the therapy. EMA recognized the benefit that uniQure's Glybera offered in a high-risk patient population and approved it under exceptional circumstances, but follow-up data are required to determine long-term safety and efficacy. Similarly, the FDA has established a 'breakthrough' designation, which identifies therapies for which the size of benefit is meaningful and apparent after just a small number of patients have been treated. In addition, the FDA has outlined strict guidelines for gene therapy clinical trials (based on the vector used) and for immediately reporting adverse events. In 2014, Celladon's Mydicar, for advanced heart failure, and Juno's JCAR015, which is used to treat leukemia, both received this designation, and Humacyte's Humagraft for vascular access in advanced renal failure and Novartis–University of Pennsylvania's CAR-T program both received 'fast track' designation.

In November 2014, Japan's Pharmaceutical, Medical Device and Other Therapeutic Products Act (PMD) took effect, establishing a framework for expedited approval of regenerative medicine and advanced therapeutic products in Japan. The PMD grants conditional product approval, on the basis of existing results from phase 2 clinical trials that demonstrate probable efficacy and safety, allowing sales of each product candidate for up to 7 years, with continued performance evaluation and monitoring. At the same time, the Act on the Safety of Regenerative Medicine also became law, defining clear guidelines within three safety tiers for advanced technologies. These developments are likely to create a pathway allowing regenerative medicine therapeutics to get to patients faster, representing an early market opportunity for companies in this space.

On the basis of these changes, Mesoblast, with proprietary technology based on mesenchymal-lineage adult stem cells, announced its intention to seek expedited conditional approvals in Japan for its cell-therapy product candidates. The first clinical trial using induced pluripotent stem cells is under way, led by physicians at Kobe City Hospital. Cell-therapy company Athersys is also taking advantage of this change and in March 2015 announced a partnership with Chugai Pharma to develop and commercialize Athersys's proprietary cell therapy MultiStem for ischemic stroke, which is a priority disease area in Japan.

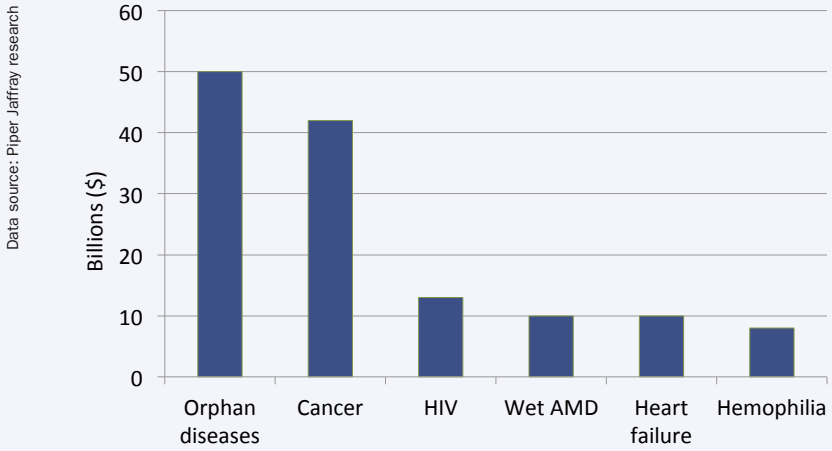

Figure 2: Global market potential for gene therapy indications.

€850,000 (~$1 million). For a one-time treatment, the cost is expected to be in the range of $1 million to $1.3 million, particularly because many of the therapies target orphan diseases with huge unmet need, and a cure will remove the need for expensive chronic medical care. Discussions with payers about reimbursement for Glybera are likely to set the stage for future gene therapy treatments for rare diseases.

However, there is obvious concern that health insurers will be unwilling to stump up that kind of cost, particularly for conditions affecting larger patient populations. Gilead Sciences felt pressure from insurers to cut the cost of their new $1,000-per-pill hepatitis C drug and recently announced that they are discounting the price by nearly 50%. One new idea for reimbursement where there is a larger patient population is an annuity model in which the payer makes regular payments until the patient dies ('cash for life') or needs retreatment ('cash until event'). With this model, the price would amortize over a certain time period, contingent on proof that the therapy was effective and safe. Payments would be stopped if testing showed that the therapy was no longer working. Proponents of the new model say that payment streams could eventually be packaged and sold to investors. Michael Werner, the executive director at ARM and a partner at Holland & Knight, said, "Right now, no one has figured out exactly how pricing will work, but ultimately payers will focus on quality, clinical benefit and cost efficiency. It's all about value to the patient."

The concept of curative biologics delivers the promise of biotechnology, but there is probably a long road ahead to market, as history has shown. Curative approaches will certainly have a disruptive effect in the field, but reimbursement challenges are front and center in the industry. Efforts to show the value and comparative effectiveness of regenerative medicine therapies and to supply health economic data will be important as companies examine future revenue streams and valuations.

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Table 3: Selected gene therapy and regenerative medicine partnership deals.

Date	Companies/Deal type	Terms
April 2015	**uniQure** and **Bristol-Myers** Squibb entered into an exclusive collaboration to develop gene therapies for cardiovascular diseases.	BMS promised payments of approximately $100 million, including an upfront payment of $50 million, a $15 million payment for the selection of three targets, in addition to cardiovascular therapy S100A1, and an initial equity investment in uniQure of at least $32 million in total. uniQure could receive milestone payments, including up to $254 million for the lead S100A1 therapeutic and up to $217 million for each other gene therapy product potentially developed under the collaboration. uniQure is also eligible to receive royalties on product sales.
February 2015	**Voyager** and **Genzyme** entered a collaboration involving novel AAV gene therapies for severe CNS disorders.	The partnership covers programs for Parkinson's disease, Friedreich's ataxia and Huntington's disease. Genzyme can option to license several programs following completion of an initial proof-of-concept human clinical trial. Voyager retains U.S. rights to its lead product programs in Parkinson's disease and Friedreich's ataxia. Voyager will split U.S. profits with Genzyme for the Huntington's disease program. Genzyme promised an upfront payment of $100 million to Voyager, including $65 million in cash, a $30 million equity investment in Voyager and additional in-kind contributions. Milestone payments to Voyager could reach up to $745 million.
December 2014	**Spark Therapeutics** and **Pfizer** entered a collaboration to develop novel AAV vectors for hemophilia.	The deal builds a development program based on Spark's SPK-FIX, a Phase 1 trial program demonstrating proof of concept for a gene therapy to deliver and express a therapeutic gene in the liver. Spark received a $20 million upfront payment, and may receive up to an additional $260 million in milestones. Spark is also entitled to receive low-teen royalties on global sales by Pfizer.
June 2014	**Dimension Therapeutics** and **Bayer Healthcare** to develop a gene therapy for the treatment of hemophilia A.	Dimension received an upfront payment of $20 million and is eligible for milestone payments up to $232 million. Dimension is responsible for all pre-clinical development activities. Bayer will fund clinical trials and retain worldwide rights for the treatment of hemophilia A. Dimension is eligible to receive tiered royalties based on product sales.
March 2014	**Avalanche** and **Regeneron** partnered to develop ophthalmic gene therapy vectors and proprietary molecules.	Using Avalanche's AAV-based platform, Regeneron can explore eight distinct targets. Avalanche receives an upfront cash payment, contingent payments of up to $640 million based on certain milestones, plus a royalty on worldwide net sales of collaboration products. Regeneron retains worldwide rights for each product it moves forward in clinical development. Avalanche can exercise an option to share in development costs and profits for two therapeutic targets selected by Avalanche. Upon completion of the ongoing Phase 2a trial, Regeneron has a time-limited right of first negotiation for certain rights to AVA-101 for the treatment of wet, acute macular degeneration.
January 2014	**Alexion** and **Moderna** partner to discover and develop rare disease therapies using Moderna's mRNA platform.	Moderna received an up front payment of $100 million to provide Alexion with 10 product options for rare using the company's proprietary mRNA Therapeutics platform. Alexion will lead the discovery, development and commercialization of the treatments, while Moderna will retain responsibility for the design and manufacture of the messenger RNA against selected targets. Moderna may be entitled to drug development and commercial milestone payments, as well as high single to double digit royalties on commercial sales. In addition, Alexion made a $25 million preferred equity investment into Moderna.
January 2014	**Sangamo BioSciences** and **Biogen Idec** entered a development partnership involving hemoglobinopathies, sickle cell disease and β-thalassemia.	Biogen will expand its expertise in non-malignant hematology using Sangamo's proprietary zinc finger nuclease genome-editing technology. Sangamo is responsible for all R&D activities through the first clinical trial in β-thalassemia; Biogen will take on worldwide clinical development and commercialization. Sangamo receives an upfront payment of $20 million and reimbursement for its R&D program-related costs. Sangamo may also receive additional payments of ~$300 million based on the various milestones, as well as double digit royalties on product sales.