SANGAMO BIOSCIENCES INC
Form 10-K
February 24, 2014
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UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

Form 10-K

x **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the fiscal year ended December 31, 2013

or

¨ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the transition period from to

Commission file number: 0-30171

SANGAMO BIOSCIENCES, INC.

(Exact name of registrant as specified in its charter)

Delaware	**68-0359556**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**
501 Canal Boulevard, Richmond, California	**94804**
(Address of principal executive offices)	**(Zip Code)**

(510) 970-6000

(Registrant s telephone number, including area code)

None

(Former name, former address and former fiscal year, if changed since last report)

Securities registered pursuant to Section 12(b) of the Act:

Title of Each Class	**Name of Each Exchange on Which Registered**
Common Stock, $0.01 par value per share	**NASDAQ Global Select Market**

Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ¨ No x

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Exchange Act. Yes ¨ No x

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes x No ¨

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes x No ¨

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant s knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ¨

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See definition of large accelerated filer, accelerated filer, and smaller reporting company in Rule 12b-2 of the Exchange Act.

Large accelerated filer ¨	Accelerated filer x
Non-accelerated filer ¨ (Do not check if a smaller reporting company)	Smaller reporting company ¨

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes ¨ No x

The aggregate market value of the voting stock held by non-affiliates of the registrant based upon the closing sale price of the common stock on June 30, 2013 (the last business day of the registrant s most recently completed second fiscal quarter), as reported on the NASDAQ Global Select Market was $405,023,312. For purposes of this calculation, directors and executive officers of the registrant have been deemed affiliates. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

Indicate the number of shares outstanding of each of the issuer s classes of common stock, as of the latest practicable date.

Class	**Outstanding at February 1, 2014**
Common Stock, $0.01 par value per share	62,736,879 shares

DOCUMENTS INCORPORATED BY REFERENCE

Document	**Parts Into Which Incorporated**
Proxy Statement for the 2014 Annual Meeting of Stockholders	Part III

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SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

Some statements contained in this report are forward-looking with respect to our operations, research, development and commercialization activities, clinical trials, operating results and financial condition. These statements involve known and unknown risks, uncertainties and other factors which may cause our actual results, performance or achievements to be materially different from any future results, performances or achievements expressed or implied by the forward-looking statements. Forward-looking statements include, but are not limited to, statements about:

- our strategy;
- product development and commercialization of our products;
- clinical trials;
- partnering, acquisition and other strategic transactions;
- revenues from existing and new collaborations;
- our research and development and other expenses;
- sufficiency of our cash resources;
- our operational and legal risks; and
- our plans, objectives, expectations and intentions and any other statements that are not historical facts.

In some cases, you can identify forward-looking statements by terms such as: anticipates, believes, continues, could, estimates, expects, intends, may, plans, seeks, should and will. These statements reflect our current vie to future events and are based on assumptions and subject to risks and uncertainties. Given these risks and uncertainties, you should not place undue reliance on these forward-looking statements. We discuss many of these risks in greater detail under the headings Risk Factors and Management s Discussion and Analysis of Financial Results of Operations in this Form 10-K. Sangamo undertakes no obligation to publicly release any revisions to forward-looking statements to reflect events or circumstances arising after the date of this report. Readers are cautioned not to place undue reliance on the forward-looking statements, which speak only as of the date of this Annual Report on Form 10-K.

ZFP Therapeutic® is a registered trademark of Sangamo BioSciences, Inc. This report also contains trademarks and trade names that are the property of their respective owners.

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PART I

ITEM 1 BUSINESS

Overview

We are a clinical stage biopharmaceutical company focused on the research, development and commercialization of engineered DNA-binding proteins for the development of novel therapeutic strategies for unmet medical needs. Our current mission is to develop ZFP Therapeutics®, or human therapeutics based on our proprietary ZFP technology, through early stage clinical testing, strategically partner with biopharmaceutical companies at points of value inflection and have the partner execute late-stage clinical trials and commercial development. In the long-term, our goal is to integrate marketing and development operations and to capture the value of late-stage and commercial ZFP Therapeutic products for ourselves.

We, and our licensed partners, are the leaders in the research, development and commercialization of zinc finger DNA-binding proteins (ZFPs), a naturally occurring class of proteins. We have used our knowledge and expertise to develop a proprietary technology platform. ZFPs can be engineered to make ZFP nucleases (ZFNs), proteins that can be used to modify DNA sequences in a variety of ways and ZFP transcription factors (ZFP TFs), proteins that can be used to turn genes on or off. As ZFPs act at the DNA level, they have broad potential applications in several areas including human therapeutics, plant agriculture and research reagents, as well as production of transgenic animals and cell-line engineering.

The main focus for our company is the development of novel human therapeutics and we are building a pipeline of ZFP Therapeutics. Our lead ZFP Therapeutic, SB-728-T, a ZFN-modified autologous T-cell product for the treatment of HIV/AIDS, is the first therapeutic application of our ZFN technology and is being evaluated in ongoing clinical trials, a Phase 2 study (SB-728-902, Cohort 5) and a Phase 1/2 study (SB-728-1101) in HIV-infected subjects. We expect to present data from this program at appropriate scientific and medical meetings in 2014.

On January 8, 2014, we established a collaborative partnership with Biogen Idec Inc. (Biogen) to research, develop and commercialize our preclinical ZFP Therapeutic development program, in hemoglobinopathies, and targeting sickle cell disease (SCD) and beta-thalassemia. We also have a collaborative partnership with Shire International GmbH, formerly Shire AG, (Shire) to research, develop and commercialize certain of our preclinical ZFP Therapeutic development programs, including programs in hemophilia, Huntington s disease (HD) and other monogenic diseases. We have proprietary preclinical programs in several lysosomal storage disorders (LSDs). In addition, we have research stage programs in other monogenic diseases, including certain immunodeficiencies, as well as central nervous system (CNS) disorders and cancer immunotherapy.

We believe the potential commercial applications of ZFPs are broad-based and we have entered into strategic partnerships in fields outside human therapeutics to facilitate the sale or licensing of our ZFP platform as follows:

- We have a license agreement with the research reagent company Sigma-Aldrich Corporation (Sigma). Sigma has the exclusive rights to develop and market high value laboratory research reagents based upon our ZFP technology as well as ZFP-modified cell lines for commercial production of protein pharmaceuticals and ZFP-engineered transgenic animals. Sigma is marketing ZFN-derived gene editing tools under the trademark

CompoZr ®.

We have a license agreement with Dow AgroSciences, LLC (DAS), a wholly owned subsidiary of Dow Chemical Corporation. Under the agreement, we have provided DAS with access to our ZFP technology and the exclusive rights to use it to modify the genomes or alter protein expression of plant cells, plants, or plant cell cultures. DAS markets our ZFN technology under the trademark EXZACT™ Precision Technology. We have retained rights to use plants or plant-derived products to deliver ZFP TFs or ZFNs into human or animals for diagnostic, therapeutic or prophylactic purposes.

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On October 1, 2013, we acquired Ceregene, Inc. (Ceregene), a privately held biotechnology company focused on the development of adeno-associated virus (AAV) gene therapies. The acquired assets include all of Ceregene s therapeutic programs, including CERE-110, an AAV expressing nerve growth factor (NGF) for the treatment of Alzheimer s disease (AD) that is currently in a Phase 2 clinical trial, certain intellectual property rights relating to the manufacturing of AAV, certain toxicology data and safety and efficacy data from Ceregene s human clinical trials. We believe that these additional assets provide valuable reference materials for us in the preparation and filing of Investigative New Drug (IND) applications for our *in vivo* ZFP Therapeutics, particularly those that target the brain.

We have a substantial intellectual property position in the design, selection, composition and use of engineered ZFPs to support our commercial activities. As of February 7, 2014, we either owned outright or have exclusively licensed the commercial rights to approximately 462 patents issued in the United States and foreign national jurisdictions, and we have 536 patent applications owned and licensed pending worldwide, including patents acquired from Ceregene. We continue to license and file new patent applications that strengthen our core and accessory patent portfolio. We believe that our intellectual property position is a critical element in our ability to research, develop and commercialize products and services based on ZFP technology across our chosen applications.

DNA, Genes, and Proteins

DNA is present in all cells except mature red blood cells, and encodes the inherited characteristics of all living organisms. A cell s DNA is organized in chromosomes as thousands of individual units called genes. Genes encode proteins, which are assembled through the process of transcription whereby DNA is transcribed into ribonucleic acid (RNA) and, subsequently, translation whereby RNA is translated into protein (Figure 1). Proteins are involved in virtually all cell functions. DNA, RNA and proteins comprise many of the targets for pharmaceutical drug discovery and therapeutic intervention.

Figure 1:

Schematic of the relationship between the human genome, DNA, RNA and protein

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The human body is composed of specialized cells that perform different functions and are thus organized into tissues and organs. All somatic cells in an individual s body contain the same set of genes. However, only a fraction of these genes are turned on, or expressed, in an individual human cell at any given time. Genes are regulated (i.e. turned on or turned off) in response to a wide variety of stimuli and developmental signals. Distinct sets of genes are expressed in different cell types. It is this pattern of gene expression that determines the structure, biological function and health of all cells, tissues and organisms. The aberrant expression of certain genes can lead to disease. Similarly, a mistake in the DNA sequence of a gene can result in corresponding error in the protein encoded by the gene, which may have serious consequences for the cell and its function. A number of disorders have been identified that are caused by the inheritance of a single defective gene. These so-called monogenic diseases include hemophilia, HD, SCD and LSDs.

Zinc finger DNA-binding proteins (ZFPs) are Transcription Factors

Transcription factors are proteins that bind to DNA and regulate gene expression. A transcription factor recognizes and binds to a specific DNA sequence within or near a particular gene and causes expression of that gene to be turned on (activated) or turned off (repressed). ZFPs are the largest class of naturally occurring transcription factors in organisms from yeast to humans. In higher organisms, naturally occurring transcription factors typically comprise two principal domains: the first is a DNA-binding domain, (designated in Figure 2 as the Recognition Domain) which recognizes a target DNA sequence and thereby directs the transcription factor to the proper chromosomal location; the second is a functional domain that causes the target gene to be activated or repressed. Sangamo has added to these naturally occurring functional domains to include domains enabling genome modification at the site determined by the DNA-binding domain.

Figure 2:

Schematic of the two-domain structure of a ZFP Therapeutic

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Engineered ZFP Nucleases (ZFNs) can be designed for Gene Modification and Engineered Zinc Finger Protein Transcription Factors (ZFP TFs) for Gene Regulation

Consistent with the two-domain structure of natural ZFP transcription factors, we take a modular approach to the design of the proteins that we engineer. The ZFP portion, the DNA-recognition domain, is typically composed of three or more zinc fingers. Each individual finger recognizes and binds to a three-four base pair sequence of DNA and multiple fingers can be linked together to recognize longer stretches of DNA, thereby improving specificity. By modifying the amino acids of a ZFP, we can engineer novel ZFPs capable of recognizing pre-selected DNA sequences within, or near, virtually any gene. We use the engineered ZFP DNA-binding domain linked to a functional domain. The ZFP DNA-binding domain brings the functional domain into the proximity of the gene of interest. Our ability to use our highly specific ZFP technology to precisely target a DNA sequence in a gene of interest provides us with a range of gene editing and gene regulation functions that can be applied in many different cell types.

Our engineered ZFPs can be attached to a cleavage domain of a restriction endonuclease, an enzyme that cuts DNA, creating a zinc finger nuclease or ZFN. The ZFN is able to recognize its intended gene target through its engineered ZFP DNA-binding domain. When a pair of such ZFNs is bound to the DNA in the correct orientation and spacing, the DNA sequence is cut between the ZFP binding sites. DNA binding by both ZFNs is necessary for cleavage, and both domains of the restriction endonuclease must be present in the correct orientation to interact with each other, in order to mediate DNA cleavage. This break in the DNA triggers a natural process of DNA repair in the cell. The repair process can be harnessed to achieve one of several outcomes that may be therapeutically useful (Figure 3). If cells are simply treated with ZFNs alone the repair process joins the two ends of the broken DNA together and frequently results in the loss of a small amount of genetic material at the site of the break. This disrupts the original DNA sequence and can result in the generation of a shortened or non-functional protein, effectively knocking out the protein. We believe that ZFN-mediated gene modification may be used to disrupt a gene that is involved in disease pathology such as disruption, or knock out, of the CCR5 gene to treat HIV infection. We are also using ZFN-mediated gene disruption of the *BCL11A* gene in HSCs as a potentially curative treatment for SCD and beta-thalassemia in our collaboration with Biogen.

In contrast, if cells are treated with ZFNs in the presence of an additional DNA sequence that encodes the correct gene sequence (referred to as a donor DNA), the cell can use the donor as a template to correct the cell s gene as it repairs the break resulting in ZFN-mediated gene correction. ZFN-mediated gene correction enables a corrected gene to be expressed in its natural chromosomal context and may provide a novel approach for the precise repair of DNA sequence mutations responsible for monogenic diseases such as X-linked severe combined immunodeficiency (X-linked SCID). In addition, by making the donor sequence a gene-sized segment of DNA, a new copy of a gene can also be precisely added into the genome at a specific location. The ability to place a gene-sized segment of DNA specifically into a pre-determined location in the genome broadens the range of mutations of a gene that can be corrected in a single step and eliminates the insertional mutagenesis concerns associated with traditional gene replacement approaches, in which the insertion of a new corrective copy of the gene typically occurs at random locations in the genome. Our In Vivo Protein Replacement Platform (IVPRP), in which our ZFN technology is used to insert a gene encoding a therapeutic protein into a safe harbor site such as the *Albumin* gene, is an approach that we are investigating for the potential long-term treatment of hemophilia and LSDs.

We can also create ZFP TFs which are capable of controlling or regulating the expression of a target gene in the desired manner (Figure 3). For instance, attaching an activation domain to a ZFP will cause a target gene to be turned on. Alternatively, a repression domain causes the gene to be turned off. We have a preclinical ZFP Therapeutic program for HD in which we are evaluating a ZFP TF designed to differentially down regulate the mutated

disease-causing *Huntingtin* (HTT) gene, while leaving expression of the normal gene unchanged.

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Figure 3:

ZFP Therapeutics can be designed to accomplish a range of functions in gene editing and gene regulation.

To date, we have designed, engineered and assembled several thousand ZFPs and have tested many of these proteins for their affinity, or tightness of binding, to their DNA target, as well as their specificity, or preference for their intended DNA target. We have developed methods for the design, selection and assembly of ZFPs capable of binding to a wide spectrum of DNA sequences and genes. We have linked ZFPs to numerous functional domains to create gene-specific ZFP TFs and have demonstrated the ability of these ZFP TFs to regulate hundreds of genes in dozens of different cell types and in whole organisms, including mice, rats, rabbits, pigs, fruit flies, worms, zebrafish and yeast, and in plant species including canola and maize. We and our collaborators have published data in peer-reviewed scientific journals on the transcriptional function of ZFP TFs, successful and highly-specific gene modification using ZFNs and the resulting changes in the behavior of the target cell, tissue or organism. ZFNs are currently being used to generate transgenic animals and cell lines that have specific genetic modifications that make them useful models of human disease. These high value biologic tools are being used by academics, and biotechnology and pharmaceutical companies for medical research and drug development. We have ongoing clinical trials to evaluate the safety and efficacy of ZFNs in humans.

We have several strategies for the application of our ZFP Therapeutics depending on the disease or indication. We can deliver these therapeutic proteins *ex vivo* (outside the body) to isolated cells of the blood, such as T-cells, in the case of our clinical HIV program, and HSCs for our preclinical programs in HIV and monogenic blood diseases such as SCD and beta-thalassemia. We are also developing ZFP Therapeutics in which we deliver our therapeutic proteins *in vivo*, either systemically (directly into the blood stream) as in our hemophilia and LSD programs, or directly into a specific tissue such as the brain as in our HD program.

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ZFP Therapeutics Provide the Opportunity to Develop a New Class of Human Therapeutics

With our ability to generate gene-specific ZFNs for the disruption or addition/correction of target genes and DNA sequences and ZFP TFs for the activation or repression of genes and with multiple strategies for administration, we are focused on developing a new class of highly differentiated human therapeutics. We believe that as more genes are linked to specific diseases, the clinical breadth and scope of our ZFP Therapeutic applications may be substantial.

We believe that our ZFP technology provides a unique and proprietary basis for a broad new class of drugs that have differential competitive advantages over small-molecule drugs, protein pharmaceuticals and RNA-based and conventional gene therapy approaches, enabling us to pursue the development of therapies for a broad range of unmet medical needs.

For example, ZFP Therapeutics can:

Provide novel activities such as gene modification and regulation of gene expression to address drug targets. Engineered ZFNs enable the disruption, correction or targeted addition of a gene sequence and ZFP TFs enable not only repression of the expression of a therapeutically relevant gene but also its activation in a cell. This gives our technology a degree of flexibility not seen in other drug platforms. Our ZFN gene editing technology, which requires only brief cellular expression of ZFNs, allows the permanent correction of a mutation in a defective gene in a highly specific fashion. This provides a novel therapeutic and potentially life-long clinical benefit in the treatment of monogenic diseases, such as hemophilia and SCD. In contrast, direct modification of genes cannot be achieved using antisense RNA, or siRNA, which act by interfering with the expression of cellular RNA, or conventional small molecules, antibodies, or other protein pharmaceuticals that primarily act to block or antagonize the action of a protein.

Provide therapeutic solutions for targets that cannot be effectively addressed by existing drug modalities. ZFNs and ZFP TFs act through a mechanism that is unique among biological drugs: direct modification or regulation of the disease-related or therapeutic gene as opposed to the RNA or protein target encoded by that gene. Following the genomics revolution of the 1990s, the sequencing and publication of the human genome, pharmaceutical and biotechnology companies have validated and characterized many new drug targets. Many of these targets have a direct role in disease processes but cannot be bound or modulated for therapeutic purposes by small molecules. Alternative therapeutic approaches may be required to modulate the biological activity of these so-called non-druggable targets. This may create a significant clinical and commercial opportunity for the therapeutic modification or regulation of disease-associated genes using engineered ZFNs or ZFP TFs. Thus, a target which may be intractable to treatment using a small molecule or monoclonal antibody can be modified, turned on or turned off at the DNA level using ZFP technology.

Provide high specificity and selectivity for targets. ZFP Therapeutics can be designed to act with high specificity and we have published such data (*Proc. Natl. Acad. Sci (2003) vol:100, 11997-12002; J Neurosci. (2010) 30(49):16469-74; Nat Biotechnol. (2008) 26(7):808-16 and Nature (2011)478(7369):391-4*). In addition, as there are only two copies of each gene, there are generally only two

targets per cell for a ZFP Therapeutic, which means that ZFNs and ZFP TFs need to be available in the cell in very low concentrations. In contrast, drugs that act on protein and RNA targets that are naturally present in higher cellular concentrations need to be administered in higher concentrations. Many small molecule and RNA-based approaches either affect multiple targets demonstrating so-called off-target effects or are toxic in the concentrations required to be therapeutically effective.

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THERAPEUTIC PRODUCT DEVELOPMENT

ZFP Therapeutic Product Development Programs

Figure 4:

Sangamo s Therapeutic Pipeline

Clinical Stage Programs

Product Candidate	Targeted Indication	Stage of Development	Protocol	Milestones
SB-728-T	HIV/AIDS	Phase 2	SB-728-902, Cohort 5 (CCR5 delta-32 heterozygotes)	Trial initiated in January 2012. Enrollment completed, in long-term follow-up. Data presented in 2013.
		Phase 1/2	SB-728-1101	Trial initiated in January 2012. Data presented in 2013. Six additional subjects to be enrolled at higher Cytoxan doses, further 12 subjects will be enrolled at optimum Cytoxan dose. Data expected in 2014.
		Phase 1	SB-728-902, Cohorts 1-3	Enrollment completed, in long-term follow-up.
		Phase 1	SB-728-T*	Enrollment completed, in long-term follow-up.
CERE-110 (AAV-NGF)	Alzheimer s disease	Phase 2		Direct delivery to the brain of AAV expressing NGF. All subjects treated, in two year follow-up. Data expected in 2015.

Table 1: Summary of our ongoing clinical trials.

(*Investigator sponsored trial)

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Human Immunodeficiency Virus (HIV) and Acquired Immunodeficiency Syndrome (AIDS)

HIV infection results in the death of immune system cells, particularly CD4+ T-cells, and thus leads to AIDS, a condition in which the body s immune system is depleted to such a degree that the patient is unable to fight off common infections. Ultimately, these patients succumb to opportunistic infections or cancers. According to UNAIDS/WHO, over 2.5 million people were newly infected with HIV in 2011. An estimated 1.7 million people died of AIDS in the same year. There are now over 34 million people living with HIV and AIDS worldwide. The United States Centers for Disease Control and Prevention (CDC) estimates that, in 2009 in the United States alone, there were 1.2 million people living with HIV/AIDS. Approximately 50,000 new infections occurred each year between 2006 and 2009, and more than 21,000 people with AIDS died in 2009.

Current Treatments and Unmet Medical Need

Currently, there are over 30 antiretroviral drugs approved by the U.S. Food and Drug Administration (FDA) to treat people infected with HIV. These drugs fall into four major classes: reverse transcriptase inhibitors, protease inhibitors, integrase inhibitors and entry and fusion inhibitors. This latter class also includes a small molecule antagonist of the CCR5 receptor, Selzentry® (maraviroc). This drug is being used in combination with other antiretroviral agents for treatment-experienced adult patients infected with CCR5-tropic HIV-1 strains that are resistant to multiple antiretroviral agents. The drug carries a black box warning of liver toxicity.

As HIV reproduces, variants of the virus emerge, including some that are resistant to antiretroviral drugs. Therefore, doctors recommend that people infected with HIV take a combination of antiretroviral drugs known as highly active antiretroviral therapy, or ART. This strategy typically combines drugs from at least three different classes of antiretroviral drugs. Currently available drugs do not cure HIV infection or AIDS. They can suppress the virus, even to undetectable levels, but they cannot eliminate HIV from the body. Hence, people with HIV need to take antiretroviral drugs continuously. The drugs are expensive and can have significant side effects over time. There is no therapeutic approach available which protects CD4+ T-cells, reduces viral load and does not require daily dosing.

Sangamo s Therapeutic Approach

Our therapeutic approach aims to use our ZFN-mediated gene editing technology to replicate a naturally occurring human mutation which renders individuals largely resistant to infection with the most common strain of HIV. CCR5 is a co-receptor for HIV entry into T-cells and if CCR5 is not expressed on their surface HIV infects them with lower efficiency. A population of individuals that is immune to HIV infection, despite multiple exposures to the virus, has been identified and extensively studied. The majority of these individuals have a natural mutation, CCR5 delta-32, resulting in the expression of a shortened, or truncated, and non-functional CCR5 protein. This mutation appears to have no observable deleterious effect. Individuals who carry the CCR5 delta-32 mutation on only one of their two CCR5 gene copies (heterozygotes), tend to take longer to develop AIDS and are classified as so-called long-term non-progressors. In addition, a study published in *Blood* in December 2010 reported an effective cure when an AIDS patient with leukemia received a bone marrow transplant from a matched donor with this CCR5 delta-32 mutation. This approach transferred the HSCs residing in the bone marrow from the delta-32 donor, and provided a self-renewable and potentially lifelong source of HIV-resistant immune cells. After transplantation, the AIDS patient was able to discontinue all anti-HIV drug treatments, CD4 counts increased and viral load dropped to an undetectable level, demonstrating effective transplantation of protection from HIV infection.

We are using our ZFN-mediated gene disruption technology to disrupt the CCR5 gene in cells of a patient s immune system to make these cells permanently resistant to HIV infection. The aim is to provide a population of HIV-resistant cells that can fight HIV and opportunistic infections mimicking the situation in individuals that carry the natural mutation. In December 2008, in collaboration with scientists at the University of Pennsylvania, an IND was filed for a Phase 1 trial of our CCR5 ZFP Therapeutic, SB-728-T. This single-dose, investigator-sponsored trial began enrolling subjects in February 2009, at the University of Pennsylvania. In September 2009,

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we filed an IND application and initiated a dose-escalation Phase 1 clinical trial (SB-728-902) of SB-728-T. Both Phase 1 studies were in HIV-infected individuals who were on ART. The studies were designed primarily to evaluate the safety and tolerability of this ZFP Therapeutic approach; however, subjects CD4 T-cell counts, levels of CCR5-modified T-cells and viral burden were also monitored. Preliminary data from both trials were presented in the first quarter of 2011 and demonstrated that the approach was well-tolerated in these subjects. In addition, we observed durable engraftment and persistence of SB-728-T, the ability of these cells to traffic to the gut mucosa and improvements in the overall CD4 T-cell count and the CD4:CD8 ratio in multiple subjects. Data from the study carried out at the University of Pennsylvania demonstrated that the treatment was well tolerated and that ZFN-modified cells show long-term engraftment and have a survival advantage over non-modified cells during an ART treatment interruption (TI).

In January 2012, we announced the initiation of two new studies (SB-728-1101 and SB-728-902, Cohort 5), based on data from our Phase 1 trials that demonstrated a correlation between the estimated numbers of circulating engrafted cells in which both copies of the CCR5 gene were modified (biallelic modification) and the reduction in viral load in treated subjects that underwent a TI. Using different approaches, both studies aim to increase the engraftment of cells that have undergone biallelic modification in SB-728-T-treated subjects and to evaluate the effect of increasing the numbers of these cells on the immune system and on viral load during a TI. Ten CCR5 delta-32 heterozygote subjects have been accrued and treated on the SB-728-902, Cohort 5 study and twelve subjects have been accrued and treated on the SB-728-1101 study, a trial which evaluated the effect of increasing doses of Cytoxan conditioning prior to SB-728-T administration on engraftment of cells that have undergone biallelic ZFN modification. Data presented at scientific meetings in 2013 further supported a correlation between the estimated numbers of engrafted biallelically modified cells and the reduction in viral load with one subject in the SB-728-902 study demonstrating a prolonged control of viral load at or below the limits of detection during TI. An additional six subjects are being enrolled into SB-728-1101 for evaluation of the effect of higher doses of Cytoxan and a further twelve subjects will be treated at the optimum Cytoxan dose. We expect to present data from the SB-728-1101 study in 2014.

We also have a preclinical stage program to investigate this approach to treating HIV in HSCs. Together with our collaborators at City of Hope Medical Center and the University of Southern California, we have funding for this program from a four-year $14.5 million Disease Team Research Award granted by the California Institute for Regenerative Medicine (CIRM), a State of California entity, in October 2009. We have received $5.2 million in funding through December 31, 2013, which is our total prescribed amount under the agreement. In 2014, we expect to file an IND application based on this work.

Clinical Development Programs Acquired from Ceregene

CERE-110 (AAV-NGF), a gene therapy approach designed to deliver NGF directly to the brain using an AAV vector for the treatment of AD, was developed by Ceregene. The program and ongoing Phase 2 clinical trial were assets that we acquired from Ceregene in October 2013. In November 2013, we released preliminary data from a Phase 1 dose escalation study of CERE-110 demonstrating that surgical delivery of CERE-110 to the brain results in the long-term expression of bioactive NGF, the therapeutic protein. Clinicians also observed apparent stabilization of brain cell metabolic activity in treated subjects, as determined by PET-scans measuring glucose use, which may reflect a slowing of cell deterioration. The treatment was well-tolerated at all dose levels. The Phase 2 clinical trial is fully accrued and is being carried out in collaboration with the Alzheimer s Disease Cooperative Study (ADCS) based at the University of California San Diego (UCSD) and funded by a grant from the National Institute on Aging (NIA). Forty-nine (49) patients with mild to moderate AD have been treated with a single administration of CERE-110 at ten clinical sites throughout the U.S. Approximately half of the patients received CERE-110 while the other half received

an appropriate sham surgery control treatment. Patients are being followed for a minimum of two years with respect to safety, brain imaging as well as standard tests used in Alzheimer s clinical trials to measure cognitive function and quality of life. Enrollment was completed in March 2013 and we expect to present data in 2015.

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ZFP Therapeutic Pre-Clinical Stage Programs

Programs Partnered with Shire

Hemophilia

Hemophilia, a rare bleeding disorder in which the blood does not clot normally, is an example of a monogenic disease (a disease that is caused by a genetic defect in a single gene). There are several types of hemophilia caused by mutations in genes that encode factors which help the blood clot and stop bleeding when blood vessels are injured. Individuals with hemophilia experience bleeding episodes after injuries and spontaneous bleeding episodes that often leads to joint disease such as arthritis. The most prevalent form of the disease, hemophilia A, is caused by a defect in clotting Factor VIII, while defects in clotting Factor IX lead to hemophilia B. The most severe forms of hemophilia affect males. According to the National Hemophilia Foundation, hemophilia A occurs in about one in every 5,000 male births in the US with approximately 25,000 males currently affected in the US, and hemophilia B in about 1 in every 25,000 male births with approximately 5,000 males currently affected. The standard treatment for individuals with hemophilia is replacement of the defective clotting factor with regular infusion of recombinant clotting factors or plasma concentrates. These therapies are expensive, carry the risk of transmission of blood-borne diseases such as hepatitis and other viral infections and sometimes stimulate the body to produce antibodies against the factors that inhibit the benefits of treatment. In these situations, other clotting factors such as Factor VII and X may be used to treat patients.

In collaboration with Shire, we are working on four gene targets, clotting factors VII, VIII, IX and X to develop ZFP Therapeutics to treat hemophilia. Using our ZFN technology we are pursuing two approaches in the development of these therapeutics: correction of the disease-causing mutation in the endogenous copy of the Factor VIII or IX gene and addition of a new correct copy of the Factor VIII or IX gene into a safe-harbor site, the Albumin gene or locus, using our In Vivo Protein Replacement Platform (IVPRP). We have published data demonstrating functional correction of the human factor IX gene in the liver by direct intravenous delivery of ZFNs in a mouse model of the disease. We have ongoing preclinical studies to develop therapies for hemophilia A and B which will provide a permanent correction that would reduce or eliminate the need for infusions of clotting factor products. Our goal is to submit IND applications for these ZFP Therapeutics in 2014.

Huntington s disease

Huntington s disease (HD) is an inherited, progressive neurologic disease for which there is no treatment or cure. The disease is caused by a particular type of mutation in a single gene, the HTT gene. Most patients inherit one normal and one defective or mutant copy of the HTT gene, which is enough to cause HD. The mutation is characterized by expansion of a repeated stretch of DNA sequence within the gene called a CAG repeat. A normal copy of the HTT gene usually has 10 to 29 of these CAG repeats but a defective copy has many more generally greater than 39 repeats. While the protein produced by the normal copy of the gene appears to be essential for development (mice lacking the gene do not survive to birth), the product of the mutated gene is damaging to nerve cells. Symptoms, which include deterioration of muscle control, cognition and memory, usually develop between 35 and 44 years of age. It is known that the greater the number of CAG repeats, the earlier the onset. HD is usually fatal within 10 to 20 years after the onset of symptoms. The disease has a high prevalence for an inherited disorder, affecting approximately 30,000 people (one in 10,000) in the US. An additional 150,000 people in the U.S. carry a 50% risk of developing the disease.

Research in animal models of the disease has shown that lowering the levels of the defective HTT protein can prevent, or even reverse, disease progression. However, to date most HTT-lowering methods decrease levels of both the normal and mutant forms of HTT, raising potential safety concerns given the importance of normal HTT protein. In collaboration with Shire, we are developing ZFP TFs that can selectively repress the expression of the mutant disease-causing form of HTT while leaving expression levels of the normal gene unchanged. Preclinical studies in animal models of the disease are ongoing and our goal is to file an IND application for a ZFP Therapeutic for HD in 2015.

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Programs Partnered with Biogen

Hemoglobinopathies: Sickle cell disease and Beta-thalassemia

Mutations in the genes encoding globin, the oxygen carrying protein of red blood cells, lead to hemoglobinopathies such as sickle cell disease (SCD) and beta-thalassemia. The mutation that gives rise to SCD causes the red blood cells to form an abnormal sickle or crescent shape. The cells are fragile and deliver less oxygen to the body s tissues. They can also get stuck more easily in small blood vessels and break into pieces that can interrupt healthy blood flow which further decrease the amount of oxygen flowing to body tissues. Almost all patients with SCD have painful episodes (called crises), which can last from hours to days. Current standard of care is to manage and control symptoms, and to limit the number of crises. Treatments include blood transfusions, iron-chelation therapy and administration of hydroxyurea, pain medications and antibiotics. As of 2011, the CDC estimates that there are 90,000 to 100,000 Americans living with SCD which occurs in approximately 1 out of every 500 African-American births and 1 out of every 36,000 Hispanic-American births.

There are several forms of beta-thalassemia. Broadly, the disorder results in excessive destruction of red blood cells leading to life-threatening anemia, enlarged spleen, liver and heart, and bone abnormalities. Beta-thalassemia major is a severe form of thalassemia that requires regular, often monthly, blood transfusions and subsequent iron-chelation therapy to treat iron overload. The CDC estimates that 1,000 people have beta-thalassemia major in the United States, and an unknown number carry the genetic trait and can pass it on to their children. Thalassemia is most common among people of Mediterranean descent and is also found among people from the Arabian Peninsula, Iran, Africa, Southeast Asia and Southern China.

We are developing ZFP Therapeutics for both SCD and beta-thalassemia based on the use of our ZFN gene editing technology in a patient s own (autologous) bone marrow stem cells. Our ZFN genome editing technology enables multiple approaches to the correction of SCD and beta-thalassemia. Both diseases manifest in the months after birth, when patients switch from producing functional fetal gamma-globin to a mutant form of adult beta-globin, which results in their condition. Naturally occurring increased levels of therapeutic fetal hemoglobin have been shown to reduce the severity of both SCD and beta-thalassemia disorders. In HSCs, our genome editing technology can be used to precisely disrupt key transcriptional regulators, such as *BCL11A*, to reverse the switch from expression of the mutant adult beta-globin back to the production of functional fetal gamma-globin. Alternatively, the technology can be used to precisely insert a new corrected beta-globin gene to replace the defective copy.

A bone marrow transplant (BMT), of HSCs from a matched related donor (allogeneic BMT) is curative for both diseases. However, this therapy is limited due to the scarcity of matched donors and the significant risk of Graft versus Host Disease (GvHD) after transplantation of the foreign cells. By performing genome editing in HSCs that are isolated from and subsequently returned to the same patient (i.e. an autologous HSC transplant), our approach eliminates both the need for a matched donor and the risk of acute and chronic GvHD. The ultimate goal of this approach is to develop a one-time curative treatment for SCD and beta-thalassemia.

In May 2013, CIRM granted us a $6.4 million Strategic Partnership Award to develop this potentially curative ZFP Therapeutic for beta-thalassemia. The four-year grant provides matching funds for preclinical studies that will support an IND application and a Phase 1 clinical trial in transfusion-dependent beta-thalassemia patients, which will be carried out at Children s Hospital & Research Center Oakland, and City of Hope. We are in currently in preclinical development in collaboration with Biogen and our goal is to file an IND application for beta-thalassemia in 2014 and for SCD in 2015.

Proprietary Research Programs

Lysosomal Storage Disorders

Lysosomal storage disorders (LSDs) are a heterogeneous group of inherited disorders including Fabry disease, Gaucher disease, Pompe disease and Hurler syndrome. They are caused by defects in genes that encode

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proteins known as enzymes, which break down and eliminate unwanted substances in the cells of the body. These enzymes are found in structures called lysosomes which act as recycling sites in cells, breaking down unwanted material into simple products for the cell to use to build new materials. A defect in a lysosomal enzyme leads to the accumulation of toxic levels of the substance that the enzyme would normally eliminate and resulting cell damage which can lead to serious health problems. There are nearly 50 of these disorders altogether and they may affect different parts of the body, including the skeleton, brain, skin, heart and CNS. While their individual incidence tends to be rare, this group as a whole has a prevalence of more than 1:5,000 live births according to the National Institute of Neurological Disorders and Stroke.

There is no cure for LSDs, and treatments have not yet been developed for many of these diseases. For certain disorders, including Gaucher and Fabry, enzyme replacement therapies (ERTs) are available. However, these require frequent administration, are costly and there is a risk that over time patients develop an immunogenic response to the administered protein lessening its efficacy.

We are developing a genetic approach to enzyme replacement for several LSDs based on systemic delivery of our ZFN gene editing technology to the liver to enable production of the corrective enzyme by the body. We are in preclinical development with several product candidates and our goal is to file two IND applications for such product candidates in 2015.

ZFP Therapeutic Research Programs

We have research stage programs in other monogenic diseases, in CNS disorders and in cancer immunotherapy.

CORPORATE RELATIONSHIPS

We have established collaborative and strategic partnerships for our ZFP Therapeutic programs and in non-therapeutic areas. We will continue to pursue further partnerships when appropriate with selected pharmaceutical, biotechnology and chemical companies to fund internal research and development activities and to assist in product development and commercialization. We are applying our ZFP technology platform to several commercial applications in which our products provide us and our strategic partners and collaborators with potential technical, competitive and economic advantages.

Therapeutic Collaborations

Collaboration and License Agreement with Shire International GmbH (formerly Shire AG) in Human Therapeutics and Diagnostics

In January 2012, we entered into a collaboration and license agreement with Shire, pursuant to which we are collaborating to research, develop and commercialize human therapeutics and diagnostics based on our ZFP technology. Under the agreement, the two companies may develop potential human therapeutic or diagnostic products for seven gene targets. The initial four gene targets are blood clotting Factors VII, VIII, IX and X, and products developed for such initial gene targets would be used for treating or diagnosing hemophilia. In June 2012, Shire selected a fifth gene target for the development of a ZFP therapeutic for treating HD. Shire has the right, subject to certain limitations, to designate two additional gene targets. Pursuant to the agreement, we have granted Shire an exclusive, world-wide, royalty-bearing license, with the right to grant sublicenses, to use our ZFP technology for the purpose of developing and commercializing human therapeutic and diagnostic products for the gene targets.

The initial research term of the agreement is six years and is subject to extensions upon mutual agreement and under other specified circumstances. We are responsible for all research activities through the submission of an IND or European Clinical Trial Application (CTA), while Shire is responsible for clinical development and

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commercialization of products generated from the research program from and after the acceptance of an IND or CTA for the product. Shire reimburses us for our internal and external research program-related costs.

Under the agreement, we received an upfront license fee of $13.0 million. In addition, for each gene target, we are eligible to receive $33.5 million in payments upon the achievement of specified research, regulatory, clinical development milestones, as well as $180 million in payments upon the achievement of specified commercialization and sales milestones. The total amount of potential milestone payments for each of the seven gene targets, assuming the achievement of all specified milestones in the Agreement, is $213.5 million. The milestone payments for each gene target through the acceptance of an IND or CTA submission total $8.5 million. We will also receive royalty payments that are a tiered double-digit percentage of net sales of products developed under the collaboration. To date, we have not received any payments from Shire related to milestone or royalty payments.

The agreement may be terminated by (i) us or Shire, in whole or in part, for the uncured material breach of the other party, (ii) us or Shire for the bankruptcy or other insolvency proceeding of the other party and (iii) Shire, in its entirety, beginning 24 months after the effective date of the agreement upon 90 days advance written notice. In addition, Shire may terminate the agreement with respect to an individual gene target at any time, and under certain circumstances may designate a replacement gene target for a terminated gene target. As a result, actual future milestone payments could be lower than the amounts stated above.

Collaboration and License Agreement with Biogen Idec Inc. in Human Therapeutics and Diagnostics

In January 2014, we entered into an exclusive worldwide collaboration and license agreement with Biogen focused on the development of therapeutics for hemoglobinopathies, and targeting beta-thalassemia and SCD. Under the agreement, the two companies will jointly conduct two research programs: the beta-thalassemia program and the SCD program. In the beta-thalassemia program, we are responsible for all discovery, research and development activities through the first human clinical trial. In the SCD program, both parties are responsible for research and development activities through the submission of an IND application for ZFP therapeutics intended to treat SCD. Biogen will reimburse us for our internal and external program-related costs.

Under both programs, Biogen is responsible for subsequent worldwide clinical development, manufacturing and commercialization of licensed products developed under the agreement. At the end of specified research terms for each program or under certain specified circumstances, Biogen retains the right to step in and take over any of our remaining activities. Furthermore, we have an option to co-promote in the United States any licensed product to treat beta-thalassemia and SCD developed under the agreement, and Biogen will compensate us for such co-promotion activities. Subject to the terms of the agreement, we have granted Biogen an exclusive, royalty-bearing license, with the right to grant sublicenses, to use certain ZFP and other technology controlled by Sangamo for the purpose of researching, developing, manufacturing and commercializing licensed products developed under the agreement. We have also granted Biogen a non-exclusive, worldwide, royalty-free, fully paid license, with the right to grant sublicenses, of our interest in certain other intellectual property developed pursuant to the agreement.

Under the agreement, we will receive an upfront license fee of $20.0 million and are eligible to receive development milestone payments upon the achievement of specified regulatory, clinical development and commercialization milestones. The total amount of potential regulatory, clinical development, commercialization and sales milestone payments, assuming the achievement of all specified milestones in the agreement, is $293.8 million, including Phase 1 milestone payments of $7.5 million for each of the beta-thalassemia and SCD programs. In addition, we will also receive royalty payments for each licensed product that are a tiered double-digit percentage of annual net sales of each

product.

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The Agreement may be terminated by (i) us or Biogen for the uncured material breach of the other party, (ii) us or Biogen for the bankruptcy or other insolvency proceeding of the other party; (iii) Biogen, upon 180 days advance written notice to us and (iv) Biogen, for certain safety reasons upon written notice to, and after consultation with, us. As a result actual future milestone payments could be lower than the amounts stated above.

The Agreement will become effective upon the satisfaction of certain customary conditions.

Strategic Partnerships in Non Therapeutic Applications of the Technology

Agreement with Sigma-Aldrich Corporation in Laboratory Research Reagents, Transgenic Animal and Commercial Protein Production Cell-line Engineering

In July 2007, we entered into a license agreement with Sigma. Under the license agreement, we agreed to provide Sigma with access to our proprietary ZFP technology and the exclusive right to use the technology to develop and commercialize research reagents products and services in the research field, excluding certain agricultural research uses that we previously licensed to DAS. Under the agreement, we and Sigma agreed to conduct a three-year research program to develop laboratory research reagents using our ZFP technology during which time we assisted Sigma in connection with its efforts to market and sell services employing our technology in the research field. We transferred the ZFP manufacturing technology to Sigma.

In October 2009, we expanded the license agreement with Sigma. In addition to the original terms of the license agreement, Sigma received exclusive rights to develop and distribute ZFP-modified cell lines for commercial production of protein pharmaceuticals and certain ZFP-engineered transgenic animals for commercial applications. Under the terms of the agreement, Sigma made an upfront cash payment of $20.0 million, consisting of a $4.9 million purchase of 636,133 shares of our common stock, valued at $4.9 million, and a $15.1 million upfront license fee. Under the terms of the agreement, we are eligible to receive commercial license fees of $5.0 million based on a percentage of net sales and sublicensing revenue and thereafter a reduced royalty rate of 10.5% of net sales and sublicensing revenue. During the term of the license agreement, Sigma is obligated to pay us minimum annual payments, a share of certain revenues received by Sigma from sublicensees and royalty payments on the sale of licensed products and services. Sigma also has the right to sublicense the ZFP technology for research applications and we will receive 50% of any sublicensing revenues in the first two years and 25% of any sublicensing revenues thereafter. We retain the sole right to use and license our ZFP technology for GMP production purposes, for the production of materials used in or administered to humans, and for any other industrial commercial use. In addition, upon the achievement of certain cumulative commercial milestones Sigma will make milestone payments to us up to an aggregate of $25.0 million. The agreements may be terminated by Sigma at any time with a 90-day notice or by either party upon an uncured material breach of the other party. As a result, actual future milestone payments could be lower than the amounts stated above. In the event of any termination, all rights to use our ZFP technology will revert to us, and Sigma will no longer be permitted to practice our ZFP technology or to develop or, except in limited circumstances, commercialize any products derived from our ZFP technology.

Other Programs and Partners in Transgenic Animal and Commercial Protein Production Cell-line Engineering

Prior to our agreement with Sigma, we marketed our ZFP TF and ZFN technology and intellectual property in products and areas outside ZFP Therapeutics directly to the pharmaceutical and biotechnology industry. We established agreements in cell line engineering for pharmaceutical protein production with Genentech and in the development of transgenic animals with Open Monoclonal Technology, Inc. (OMT) and F. Hoffmann-La Roche Ltd

and Hoffmann-La Roche Inc. (collectively, Roche).

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Genentech has continuing obligations to pay us an annual technology access fee and, for each product developed by Genentech containing a protein expressed by the modified cell line created using our ZFN technology, aggregate milestone payments of up to $5.4 million upon achievement of specified milestones relating to the development and commercialization of such products.

For any given OMT product, OMT has the right to buy out its future royalty payment obligations under the license agreement by paying a lump sum fee to us. Roche will pay milestone payments upon the achievement of certain clinical development milestones relating to products produced under such commercial license, and low-single-digit royalties on sales of such products. The aggregate milestone payments for therapeutic products will not exceed $5.75 million, but the diagnostics milestone payments are not similarly capped. Under the research and license agreement, on a product-by-product basis, Roche has the right to buy out its future royalty payment obligations by paying specified fixed amounts.

Agreement with Dow AgroSciences in Plant Agriculture

We and our collaborators have shown that ZFNs and ZFP TFs can be used to regulate and modify genes in plants. The ability to regulate gene expression with engineered ZFP TFs may lead to the creation of new plants that increase crop yields, lower production costs and are more resistant to herbicides, pesticides, and plant pathogens, which could permit the development of branded agricultural products with unique nutritional and processing characteristics. In addition, ZFNs may be used to facilitate the efficient and reproducible generation of transgenic plants.

In October 2005, we entered into an exclusive commercial license with DAS. Under this agreement, we provided DAS with access to our proprietary ZFP technology and the exclusive right to use the technology to modify the genomes or alter the nucleic acid or protein expression of plant cells, plants, or plant cell cultures. We have retained rights to use plants or plant-derived products to deliver ZFNs and ZFP TFs into humans or animals for diagnostic, therapeutic, or prophylactic purposes. Our agreement with DAS provided for an initial three-year research term. In June 2008, DAS exercised its option under the agreement to obtain a commercial license to sell products incorporating or derived from plant cells generated using our ZFP technology, including agricultural crops, industrial products and plant-derived biopharmaceuticals.

We agreed to supply DAS and its sublicensees with ZFNs and ZFP TFs for both research and commercial use over the initial three year period of the agreement and have amended and extended this provision. The agreement also provides for minimum sublicense fees each year due to us every October, provided the agreement is not terminated by DAS. Annual fees range from $250,000 to $3.0 million and total $25.3 million over 11 years. Furthermore, DAS has the right to sublicense our ZFP technology to third parties for use in plant cells, plants, or plant cell cultures, and we will be entitled to 25% of any cash consideration received by DAS under such sublicenses. We do not have any performance obligations with respect to the sublicensing activities to be conducted by DAS. DAS has the right to terminate the agreement at any time; accordingly, our actual sublicense fees over the term of the agreement could be lower than $25.3 million. In addition, each party may terminate the agreement upon an uncured material breach of the agreement by the other party. In the event of any termination of the agreement, all rights to use our ZFP technology will revert to us, and DAS will no longer be permitted to practice our ZFP technology or to develop or, except in limited circumstances, commercialize any products derived from our ZFP technology.

Funding from Research Foundations

California Institute for Regenerative Medicine

In October 2009, CIRM granted a $14.5 million Disease Team Research Award to develop an HIV therapy based on the application of ZFN gene editing technology in HSCs. The four year grant supports an innovative research project conducted by a multidisciplinary team of investigators, including investigators from the University of Southern California, City of Hope National Medical Center and Sangamo BioSciences.

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Through December 31, 2013, we have received total funding of $5.2 million, which is the total amount awarded to us as prescribed in the agreement. The award is intended to substantially fund our research and development efforts related to the agreement. The State of California has the right to receive, subject to the terms and conditions of the agreement, payments from us or our collaborators, resulting from sales of a commercial product resulting from research and development efforts supported by the grant, not to exceed two times the amount we receive in funding under the agreement with CIRM.

In May 2013, CIRM granted us a $6.4 million Strategic Partnership Award to develop a potentially curative ZFP Therapeutic for beta-thalassemia based on the application of our ZFN gene editing technology in HSCs. The four year grant provides matching funds for preclinical work that will support an IND application and a Phase 1 clinical trial in transfusion-dependent beta-thalassemia patients which will be carried out at Children s Hospital & Research Center Oakland, and City of Hope in collaboration with our partner in this program, Biogen. The State of California has the right to receive, subject to the terms and conditions of the agreement between us and CIRM, payment from us, or our collaborators, from sales of a commercial product resulting from research and development efforts supported by grants, in accordance with Title 17, California Code of Regulations, Section 100600.

ACQUISITION OF CEREGENE

On October 1, 2013, we acquired Ceregene, a privately held biotechnology company focused on the development of AAV gene therapies, pursuant to an Agreement and Plan of Merger (the Merger Agreement). The acquired assets include all of Ceregene s therapeutic programs, including CERE-110, an AAV-NGF for the treatment of AD that is currently in a Phase 2 clinical trial. In addition to the clinical assets acquired, we acquired certain intellectual property rights relating to the manufacturing of AAV, and certain toxicology data and safety and efficacy data from Ceregene s human clinical trials, which will be used in the preparation and filing of IND applications for our *in vivo* ZFP Therapeutics, particularly those that target the brain.

Under the Merger Agreement, the aggregate consideration paid by us at closing consisted of 100,000 shares of our common stock, with an approximate fair value of $1.2 million. In addition, we may be required to make contingent earn-out payments to the stockholders of Ceregene as follows:

- If we grant a third-party license to develop and commercialize Ceregene s CERE-110 for the treatment of AD or CERE-120 for the treatment of Parkinson s diseases or HD (the Earn-Out Products), we are required to pay a double-digit percentage of any upfront and milestone payments we receive for such license, subject to certain reductions based on expenses incurred by us in the development of the Earn-Out Products; and

- If we commercialize any Earn-Out Product ourselves, we are required to pay, for each Earn-Out Product, royalty-like payments as a percentage of net sales that range in the low double-digits depending upon the amount of net sales, subject to certain reductions by us.

INTELLECTUAL PROPERTY AND TECHNOLOGY LICENSES

Patents and licenses are important to our business. Our strategy is to file or license patent applications to protect technology, inventions and improvements to inventions that we consider important for the development of our technology. We seek patent protection and licenses that relate to our technology and candidates in our pipeline and/or

may be important to our future. We have filed numerous patents and patent applications with the United States Patent and Trademark Office (USPTO) and foreign jurisdictions. This proprietary intellectual property includes methods relating to the design of zinc finger and TALE (Transcription activator-like effector) proteins, therapeutic applications of genome editing technology, enabling technologies related to our platform and the use of genome editing across a variety of applications. We rely on a combination of patent, copyright, trademark, proprietary know how, continuing technological innovations, trade secret laws, as well as confidentiality agreements, materials transfer agreements, research agreements and licensing agreements, to establish and protect our proprietary rights.

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Technology Licenses

We have licensed intellectual property directed to the design, selection, and use of ZFPs, ZFNs and ZFP TFs for gene modification and regulation from the Massachusetts Institute of Technology, Johnson & Johnson, The Scripps Research Institute, The Johns Hopkins University, Harvard University, the Medical Research Council, the California Institute of Technology, City of Hope and the University of Utah. These licenses grant us rights to make, use and sell ZFPs, ZFNs and ZFP TFs under 13 families of patent filings. As of February 7, 2014, these patent filings have resulted in 19 issued U.S. patents and 46 granted foreign patents, with 6 currently pending U.S. patent applications and 26 pending applications in foreign patent offices.

We believe that these in-licensed patents and patent applications include several of the early and important patent filings directed at the design, selection, composition and use of ZFPs, ZFNs and ZFP TFs, particularly the agreements with Johns Hopkins University, the Massachusetts Institute of Technology, Johnson & Johnson and The Scripps Research Institute.

We have licensed intellectual property directed to the composition of two AAV vectors (AAV5 and AAV6) from the National Institute of Health and the University of Washington, respectively. The AAV5 license from the National Institute of Health is a nonexclusive license that will expire in 2021. The AAV6 license from the University of Washington is also a non-exclusive license and will expire in 2017. Additionally, Sangamo has licensed intellectual property from the National Institutes of Health (NIH) relating to methods of production of production of AAV. This license will expire in 2021.

Johns Hopkins University

We entered into a license agreement with the Johns Hopkins University, or JHU, on June 29, 1995, as subsequently amended, whereby JHU granted us a worldwide exclusive license to technology and patents relating to nuclease and gene targeting technology for all fields of use, including the right to sublicense. Under the license agreement, we are obligated to pay low single-digit royalties on licensed product sales, a low single-digit percentage of license fees received from sublicensees and a high single-digit or low teens percentage of sublicense royalties received from sublicensees for sales of products. We are subject to an annual minimum royalty, which we currently pay. The license agreement expires upon the expiration of the last patent covered by the license agreement. Although many of the JHU in-licensed patents have now expired, based on currently issued patents, the license agreement will terminate on or about August 14, 2014. JHU may terminate the license agreement upon a material default by us that remains uncured following written notice. We may terminate the license agreement at any time upon six months written notice.

Massachusetts Institute of Technology

We entered into a patent license agreement with the Massachusetts Institute of Technology, or MIT, on May 9, 1996, as subsequently amended, whereby MIT granted us a worldwide exclusive license to technology and patents relating to the design, selection and use of ZFPs for all fields of use, including the right to sublicense. Under the patent license agreement, we are obligated to pay an annual license fee, low single-digit royalties of product sales, an up-front sublicense and annual sublicense fees, a percentage of its sublicense revenues, and milestone payments upon achievement of certain commercial development milestones. The aggregate milestone payments under the patent license agreement are $450,000, of which $150,000 has been paid. The patent license agreement expires upon the expiration of the last patent covered by the patent license agreement. Based on currently issued patents and currently filed patent applications, the patent license agreement will terminate on or about September 23, 2025. MIT may

terminate the license agreement upon a material default by us that remains uncured following written notice. We may terminate the license agreement at any time upon six months written notice.

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Johnson & Johnson

We entered into a sublicense agreement with Johnson & Johnson on May 9, 1996, whereby Johnson & Johnson granted us a worldwide exclusive sublicense to technology and patents for the research, development and commercialization of human and animal therapeutic and diagnostic products using engineered ZFPs, including the right to sublicense. These patents were originally exclusively licensed by Johnson & Johnson from The Scripps Research Institute. Under the sublicense agreement, we will pay low single-digit royalty payments based upon sales of license products by us or our sublicensees and a milestone payment upon the achievement of a commercial development milestone. The sublicense agreement expires upon the expiration of the last patent covered by the sublicense agreement. Based on currently issued patents and currently filed patent applications, the sublicense agreement will terminate on or about June 5, 2018. Johnson & Johnson has the right to terminate the sublicense agreement upon a breach or default by us that remains uncured following written notice of such default. We may terminate the sublicense agreement at any time upon sixty days written notice.

The Scripps Research Institute

We entered into a license agreement with The Scripps Research Institute on March 14, 2000, as subsequently amended, whereby The Scripps Research Institute granted us a worldwide exclusive license to technology and patents for the research, development and commercialization of products and services using engineered ZFPs, excluding the use of these engineered ZFPs in plant agriculture, therapeutics and diagnostics. Under the license agreement, we are required to pay a low-single digit royalty on sales of licensed products by us and our sublicensees, subject to an annual minimum. The license agreement expires upon the expiration of the last patent covered by the license agreement. Based on currently issued patents and currently filed patent applications, the license agreement will terminate on or about June 5, 2018. Each party may terminate the license agreement upon a material default by the other party that remains uncured following written notice.

Sangamo Intellectual Property

In addition to our in-licensed patent portfolio, as of February 7, 2014, we had 133 families of Sangamo-owned or co-owned patent filings, including 107 issued U.S. patents, 290 granted foreign patents, 122 pending U.S. patent applications and 382 pending foreign patent applications. These patent filings are directed to the design, composition and use of ZFPs, ZFNs, ZFP TFs and TALE proteins. Sangamo s acquisition of Ceregene s patent estate has also brought patent filings relating to AAV, needle technology and specific methods of treating diseases of the CNS and ocular diseases. In this acquisition, Sangamo acquired 7 patent families, comprising 8 issued U.S. patents, 23 issued foreign patents, 3 pending U.S. Patent applications and 13 pending foreign patent applications.

The earliest patents in our portfolio are set to begin expiring in 2015, with the majority of our currently issued patents expiring between 2019 and 2021. However, these patents in our estate may be subject to Patent Term Adjustment (due to delays in patent prosecution by the USPTO), Patent Term Extension (due to review of a patented product by a regulatory agency) or terminal disclaimer. Additionally, patents that may be issued from our pending applications will extend the patent exclusivity of our patent estate. Accordingly, all dates given above for patent expirations are estimates and the actual dates of expirations may differ.

We believe that our licensed patents and patent applications, as well as the issued Sangamo patents and pending Sangamo patent applications, in the aggregate, will provide us with a substantial intellectual property position in our commercial development of ZFP technology. In this regard, patents issued to us, applied for by us, or exclusively and

non-exclusively licensed to us, cover the following types of inventions, processes and products:

ZFP and ZFN design, engineering and compositions: includes DNA target site selection and zinc finger binding domain design (see newly issued US8617807, US8383766 and 8524874) and nuclease domain design, target site arrays, ZFP libraries databases and methods of construction, as well as methods to increase zinc finger binding specificity, linker designs and methods of making modified plant zinc finger proteins;

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ZFP targeted regulation of endogenous genes: methods relating to activation and inhibition of endogenous cellular genes, identification of accessible regions within chromatin, and regulation of endogenous plant genes;

ZFP Therapeutics: Treatment of Huntington s Disease (see US Patent Publication US 20130253040), cancer therapeutics, treatment of head and neck cancer, glioblastoma, pain (see newly issued 8466267), modulation of cardiac contractility and methods to regulate the glucocorticoid receptor, treatments for HIV (see US8268618 and US patent publication US20120294838);

ZFN Therapeutics: Treatments for HIV (see newly issued US8524221 and US8569253), SCD and beta-thalassemia , In Vivo Protein Replacement Platform for treatment of hemophilia and lysosomal storage diseases (see patent publication US 20130177983 and 20140017212), genome editing (see newly issued US8524500, US8349810 and US8409861), models for Parkinson s Disease (see US patent publication US20120192301), regulation of the expression of PD1 to block PD1-dependent immune suppression in both chronic infectious diseases and malignancies (see newly issued US8563314);

Non-Therapeutic Applications of ZFPs: Methods for linking genes and phenotypes, identification of genes, analysis of gene regulation, structure and biological function, methods of agricultural biotechnology (see newly issued US8399218 and US8592645), methods of altering cellular differentiation state, and methods of introducing exogenous nucleic acids of interest into a safe harbor locus;

Non-Therapeutic Applications of ZFNs: Methods for identification of regulatory DNA sequences, prediction of patient response to drug therapeutics, and development of cell lines for improved protein production , (see newly issued US8597912);

TALE protein methods of design and use (see newly issued US8586526 and US8623618); and

Methods of use with stem cells (see published US patent application US20120252122).

We have been advised that certain aspects of our technology can give us and our collaborators independence from third party patent claims to gene sequences. In general, under United States patent law, a patent may be obtained for any new and useful process, machine, manufacture, or composition of matter. An underlying theme of United States patent law, as related to biotechnology, is that the sequence of a gene, as it exists in the chromosome, is not new, even when newly discovered, unless it is isolated or modified from its normal chromosomal context. As a result, patent courts have held that a DNA sequence must be purified, isolated or modified to be patentable. Accordingly, U.S. patent claims to DNA sequences can cover only isolated, purified or modified nucleic acid sequences (e.g., a purified DNA fragment or a DNA sequence inserted into a vector). We have been advised that U.S. patent claims to DNA sequences do not, and cannot, cover gene sequences as they exist in their natural chromosomal environment, and international patent law is even more stringent than U.S. patent law in this regard. Most current methods for over-expression of a gene or protein involve the introduction into a cell of a vector containing a DNA encoding the protein to be over-expressed. Since such a vector contains isolated sequences which encode the protein, it would be

covered by any patent claims to those sequences. In contrast, our methods for over-expression utilize ZFP TFs that target endogenous genes as they exist in the chromosome. As a result, our gene regulation methods do not require the use of isolated DNA sequences encoding the protein to be over-expressed and, our counsel has advised us, do not infringe patent claims to such sequences. Notwithstanding this advice, we realize that others could take a contrary position that could result in litigation. While we believe that we would prevail in any such litigation, the uncertainties involved in litigation generally make it impossible to provide assurance as to the ultimate outcome of such matters. See *Risk Factors Because it is difficult and costly to protect our proprietary rights, and third parties have filed patent applications that are similar to ours, we cannot ensure the proprietary protection of our technologies and products.*

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The patent positions of pharmaceutical and biotechnology firms, including our patent position, are uncertain and involve complex legal and factual questions for which important legal tenets are largely unresolved. Patent applications may not result in the issuance of patents and the coverage claimed in a patent application may be significantly reduced before a patent is issued. Although we have filed for patents on some aspects of our technology, we cannot provide assurances that patents will be issued as a result of these pending applications or that any patent that has been or may be issued will be upheld. The laws of some foreign countries may not protect our proprietary rights to the same extent as do the laws of the United States. Our issued US patent US8153399 is currently the subject of a re-examination procedure. We do not know what the outcome of this procedure will be. The claims of this patent may be amended such that claim scope is reduced or the patent may be revoked as a result of this procedure.

In the future, third parties may assert patent, copyright trademark, and other intellectual property rights to technologies that are important to our business. Any claims asserting that our products infringe or may infringe proprietary rights of third parties, if determined adversely to us, could significantly harm our business. See *Risk Factors Because it is difficult and costly to protect our proprietary rights, and third parties have filed patent applications that are similar to ours, we cannot ensure the proprietary protection of our technologies and products.*

Estimated Licensing and Other Contingent Expenses

If we are successful in the development and commercialization of our products, we will be obligated by our license agreements to make sublicensing, milestone and royalty payments to some or all of the licensors mentioned above, including payments due pursuant to the acquisition of Ceregene. We plan to continue to license and generate intellectual property internally covering the design, selection, composition and use of ZFPs; the genes encoding these proteins; the application of ZFPs, ZFNs, and ZFP TFs in ZFP Therapeutics; and non-therapeutic applications of the technology including applications in research and plant agriculture, and intellectual property relating to TALE design and use.

COMPETITION

We, and our licensed partners, are the leaders in the research, development, and commercialization of DNA binding proteins for gene modification and regulation of gene expression. We are aware of several companies focused on other methods for and modifying genes and regulating gene expression and a limited number of commercial and academic groups pursuing the development of ZFP gene regulation and gene modification technology. The field of applied gene regulation and gene modification is highly competitive and we expect competition to persist and intensify in the future from a number of different sources, including pharmaceutical, agricultural, and biotechnology companies; academic and research institutions; and government agencies that will seek to develop ZFPs as well as technologies that will compete with our ZFP technology platform, such as TALE proteins and the CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats)/Cas9 system.

Accordingly, our competitors may succeed in obtaining patent protection, receiving FDA approval, or commercializing ZFP Therapeutics or other competitive products before us. If we commence commercial product sales, we may be competing against companies with greater marketing and manufacturing capabilities, areas in which we have limited or no experience. In addition, any product candidate that we successfully develop may compete with existing products that have long histories of safe and effective use.

Although we are in the clinical development phase of operations and have no current therapeutic product sales, we believe the following companies, products and/or technologies may potentially be competitive with our technology or

our products under development:

Small molecules in development from both in-house drug discovery programs of pharmaceutical companies such as Pfizer, Inc., GlaxoSmithKline (GSK), Novartis, Merck & Co., Inc., as well as from

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biotechnology companies with expertise and capabilities in small molecule discovery and development such as Gilead and Genzyme.

Monoclonal antibody companies and product candidates from certain biotechnology firms such as Genentech, Inc. and Amgen.

Protein pharmaceuticals under development at pharmaceutical and biotechnology companies such as Pfizer, Baxter, Bayer, Novo Nordisk, Genzyme, Shire, BioMarin, Biogen and numerous other pharmaceutical and biotechnology firms.

Gene therapy companies developing gene-based products in clinical trials. uniQure s product for lipoprotein lipase deficiency (LPLD) was recently approved in Europe but no other products have yet been approved. Our competitors in this category may include but not be limited to uniQure, bluebird bio, RegenX, Asklepios, Spark and Lentigen Corporation.

Cell therapy companies developing cell-based products. Our competitors in this category may include Dendreon and Adaptimmune.

Nuclease technologies, under development for therapeutic applications of genome modification including companies such as Editas developing the CRISPR/Cas9 system, Cellectis SA developing TALE nucleases and Cellectis SA and Precision BioSciences, Inc. that are developing meganucleases.

Antisense therapeutics and RNA interference technology, including RNAi and microRNA, which are technologies that may compete with ZFP Therapeutics in the development of novel therapeutic products acting through the regulation of gene expression. These technologies are being developed by several companies including Alnylam Pharmaceuticals, Inc., Isis Pharmaceuticals, Inc., Genzyme (a Sanofi Company) and Regulus Therapeutics, LLC.

We expect to face intense competition from other companies for collaborative arrangements with pharmaceutical and biotechnology companies; for establishing relationships with academic and research institutions; and for licenses to proprietary technology. These competitors, either alone or with their collaborative partners, may succeed in developing technologies or products that are more effective or less costly than ours.

Our ability to compete successfully will depend, in part, on our ability to:

develop safe, efficacious and commercially attractive proprietary products;

obtain access to gene transfer technology on commercially reasonable terms;

obtain required regulatory approvals;

attract and retain qualified scientific and product development personnel;

enter into collaborative and strategic partnerships with others, including our competitors, to develop our technology and product candidates;

obtain and enforce patents, licenses or other proprietary protection for our products and technologies;

formulate, manufacture, market and sell any product that we develop; and

develop and maintain products that reach the market first and are technologically superior to or are of lower cost than other products in the market.

GOVERNMENT REGULATION

The research, testing manufacturing and marketing of human therapeutics are extensively regulated in the United States and the rest of the world.

Before marketing in the United States, any therapeutic or pharmaceutical products we develop must undergo rigorous preclinical testing (generally conducted in animals) and clinical trials in humans and an extensive

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regulatory clearance process implemented by the U.S. Food and Drug Administration (FDA) under the federal Food, Drug and Cosmetic Act. The FDA regulates, among other things, the development, testing, manufacture, safety, efficacy, record keeping, labeling, storage, approval, advertising, promotion, sale and distribution of biopharmaceutical products. The regulatory review and approval process, which includes preclinical testing and clinical trials of each product candidate, is lengthy, expensive and uncertain. Securing FDA approval requires the submission of extensive preclinical and clinical data and supporting information including manufacturing information and stability data to the FDA for each indication to establish a product candidate s safety and efficacy. The approval process takes many years, requires the expenditure of substantial resources, involves post-marketing surveillance and may involve ongoing requirements for post-marketing studies.

Before commencing clinical investigations in humans in the United States, we must carry out preclinical testing. In addition, our proposed clinical studies require review from the Recombinant DNA Advisory Committee (RAC), which is the advisory board to the NIH, focusing on clinical trials involving gene transfer. We typically submit a proposed clinical protocol and other product-related information to the RAC three to six months prior to the expected IND application filing date.

Preclinical tests include laboratory and animal studies to evaluate product characteristics, potential safety and efficacy. The results of these studies must be submitted to the FDA as part of an IND Application, which must be reviewed by the FDA before proposed clinical testing in humans can begin. The FDA has 30 days to comment on the application and if the agency has no comments, we or our clinical partner may begin clinical trials.

Clinical trials are lengthy and are typically conducted in three sequential phases, but the phases may overlap or be combined. At each stage of testing, the proposed clinical protocol must be reviewed by the FDA and reviewed and approved by an independent ethics committee or institutional review board of each participating center before it can begin. Phase 1 usually involves the initial introduction of the investigational drug into small numbers of healthy volunteers or patients to evaluate certain factors, including its safety and dose tolerance. Phase 2 usually involves trials in a limited patient population to evaluate dosage tolerance and appropriate dosage, identify possible adverse effects and safety risks, and evaluate preliminary efficacy of the drug for specific indications. Phase 3 trials usually further evaluate clinical efficacy and test further for safety by using the drug in its final form in an expanded patient population. Phase 2 and 3 trials must be registered in a government database of clinical trials. Later clinical trials may fail to support the findings of earlier trials, which can delay, limit or prevent regulatory approvals. We filed a Phase 1 clinical protocol for review by the RAC in the fourth quarter of 2004, an IND application in January 2005, and Phase 2 protocols for review by the FDA in 2006, 2007 and 2009 for our first product candidate, SB-509, for the potential treatment of diabetic neuropathy. In addition, in 2008 we filed an IND application for SB-509 for the treatment of ALS. We have also filed a Phase 1 clinical protocol for review by the RAC for our HIV (SB-728-T) program. In October 2010 and January 2012 we initiated Phase 1/2 clinical trials and a Phase 2 trial of this ZFP Therapeutic in subjects infected with HIV.

As part of the acquisition of Ceregene, we acquired and assumed sponsorship of two INDs on file at FDA for the use of AAV to deliver nerve growth factors. CERE-110 is an investigational agent using AAV delivery of human NGF to the brain for the treatment of Alzheimer s disease and is currently being evaluated in a fully enrolled Phase 2 clinical trial. CERE-120 uses AAV delivery of human neurturin to the brain for treatment of Parkinson s disease. Subjects are undergoing long-term follow-up observation after being treated in completed Phase 1 and 2 studies.

The results of the preclinical and clinical testing of a pharmaceutical product are submitted to the FDA in the form of a New Drug Application (NDA), or a Biologic License Application (BLA), for approval to commence commercial

sales. In responding to an NDA or a BLA, the FDA may grant marketing approval, grant conditional approval (such as an accelerated approval), request additional information or deny the application if the FDA determines that the application does not provide an adequate basis for approval. Most research and development projects fail to produce data sufficiently compelling to enable progression through all of the stages

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of development and to obtain FDA approval for commercial sale. See also *Our potential therapeutic products are subject to a lengthy and uncertain regulatory process, and we may encounter unanticipated toxicity or adverse events or fail to demonstrate efficacy, causing us to delay, suspend or terminate the development of a ZFP Therapeutic. If these potential products are not approved, we will not be able to commercialize those products*. under Risk Factors below in Part I, Item 1A of this Form 10-K.

Outside the United States, our ability to market a product is contingent upon receiving marketing authorization from the appropriate regulatory authorities. The requirements governing the conduct of clinical trials, marketing authorization, pricing, and reimbursement vary widely from country to country. At present, foreign marketing authorizations are applied for at a national level; although, within the European Union (EU), a centralized registration procedure is available to companies wishing to market an Advanced Therapies product in more than one EU member state. If the regulatory authority is presented with adequate evidence of safety, quality, and efficacy, they will grant a marketing authorization. This foreign regulatory approval process involves all of the risks associated with FDA clearance discussed above.

We have hired personnel with expertise in preclinical and clinical development of therapeutic programs, clinical manufacturing and regulatory affairs to assist us in developing our programs and obtaining appropriate regulatory approvals as required. We also intend to work with collaborators who have experience in clinical development to assist us in obtaining regulatory approvals for collaborative products. *See Risk Factors Our potential therapeutic products are subject to a lengthy and uncertain regulatory process, and if these potential products are not approved, we will not be able to commercialize those products and Regulatory approval, if granted, may be limited to specific uses or geographic areas which could limit our ability to generate revenues.*

EMPLOYEES

As of February 1, 2014, we had 85 full-time employees, all of whom are located at our headquarters in Richmond, California. None of our employees are represented by a collective bargaining organization or covered by a collective bargaining agreement, nor have we experienced work stoppages. We believe that our relations with our employees are good.

AVAILABLE INFORMATION

We were incorporated in June 1995 in the state of Delaware.

Sangamo can be found on the internet at http://www.sangamo.com. We make available free of charge, on or through our internet site, our annual, quarterly, and current reports and any amendments to those reports filed or furnished pursuant to Section 13(a) of the Exchange Act as soon as reasonably practicable after we electronically file such material with, or furnish it to, the SEC. Information contained in our internet site is not part of, nor incorporated by reference into, this report.

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ITEM 1A RISK FACTORS

This Form 10-K contains forward-looking information based on our current expectations. Because our actual results may differ materially from any forward-looking statements made by or on our behalf, this section includes a discussion of important factors that could affect our actual future results, including, but not limited to, our revenues, expenses, net loss and loss per share.

Risks Relating to Development, Commercialization and Regulatory Approval of our Products and Technology

ZFP Therapeutics have undergone limited testing in humans and our ZFP Therapeutics may fail safety studies in clinical trials.

We are conducting an on-going Phase 2 clinical trial and an on-going Phase 1/2 clinical trial of our ZFP Therapeutics for the treatment of HIV/AIDS. Preliminary data from these studies demonstrated that, to date, treatment of aviremic HIV-infected subjects with SB-728-T has been well-tolerated. In addition, we have previously completed enrollment and the treatment phase of a Phase 1 and several Phase 2 clinical trials of our ZFP Therapeutic, SB-509, for diabetic neuropathy and ALS and the drug was well tolerated in these studies. However, if one of our ZFP Therapeutic fails one of its safety studies, it could reduce our ability to attract new investors and corporate partners.

All of these studies are designed primarily to evaluate the safety and tolerability of this ZFP Therapeutic approach. Our clinical studies are a highly visible test of our ZFP Therapeutics, and our investors assess the value of our technology primarily based on the continued progress of ZFP Therapeutic products into and through clinical trials. If clinical trials of our ZFP Therapeutic products were halted due to safety concerns, this would negatively affect our operations and the value of our stock.

Our progress in early Phase 1 and Phase 2 trials may not be indicative of long-term efficacy in late stage clinical trials.

The results in early phases of clinical testing are based upon limited numbers of patients and a limited follow-up period. Typically, our Phase 1 clinical trials for indications of safety enroll less than 25 patients. Our Phase 2 and late-stage clinical trials generally enroll a larger number of patients. Accordingly, any positive data obtained in early Phase 1 and Phase 2 trials may not be indicative of long-term efficacy in late-stage clinical trials. In September 2011, we announced preliminary data from our Phase 1 clinical program to develop SB-728-T for the treatment of HIV/AIDS. The data demonstrated a statistically significant relationship between SB-728-T and the reduction of HIV viral load. In January 2012, we initiated a Phase 2 clinical study (SB-728-902, Cohort 5) and a Phase 1/2 clinical study (SB-728-1101) for the treatment of HIV/AIDS. In December 2013, we presented data from all cohorts of these two clinical trials. Three of seven evaluable subjects in Cohort 5 showed a decrease of greater than one log in their viral load during a sixteen week treatment interruption (TI) with one subject achieving a transiently undetectable viral load during the TI period and one subject achieving a viral load during TI at or below the limit of detection for a prolonged period (20 weeks as of December 2013) In subjects in which viral load decreased, a measurable anti-HIV immune response was also observed. Additional data were presented from the Company s Phase 1 study (SB-728-902, Cohorts 1-3) that demonstrated a long-term decrease in the peripheral blood mononuclear cell (PBMC) HIV reservoir using a sensitive test for integrated HIV DNA in nine of nine subjects over a 36 month period (median decrease 0.9 logs). Additional subjects have been enrolled into the SB-728-1101 study to define the optimum dose of Cytoxan required to safely enhance engraftment and an additional 12 subjects will be enrolled to further test this dose. However, there is no guarantee that these and other future studies of SB-728-T in later stage trials involving larger patient groups may

produce positive or similar results as those obtained in earlier trials.

In addition, the initial results from the Phase 1 clinical trial of our ZFP Therapeutic product, SB-509, became available in the first half of 2006 and the complete data set was presented in June 2008. The primary end point of the trial was clinical and laboratory safety; however, we collected some preliminary efficacy data that

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showed trends of clinical improvement in some subjects. Notwithstanding this preliminary efficacy data, the top-line data from our Phase 2b clinical study for SB-509-901 did not meet the key primary or secondary endpoints for the study and as a result we discontinued development of our SB-509 program in October 2011.

A number of companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late stage clinical trials even after achieving promising results in earlier stage clinical trials. If a larger population of patients does not experience positive results, or if these results are not reproducible, our products may not receive approval from the FDA. Failure to confirm favorable results from earlier trials by demonstrating the safety and effectiveness of our ZFP Therapeutic products in late stage clinical trials with larger patient populations could have a material adverse effect on our business that would cause our stock price to decline significantly.

Our potential therapeutic products are subject to a lengthy and uncertain regulatory process, and we may encounter unanticipated toxicity or adverse events or fail to demonstrate efficacy, causing us to delay, suspend or terminate the development of a ZFP Therapeutic. If these potential products are not approved, we will not be able to commercialize those products.

The FDA must approve any human therapeutic product before it can be marketed in the United States. The process for receiving regulatory approval is long and uncertain, and a potential product may not withstand the rigors of testing under the regulatory approval processes.

Before commencing clinical trials in humans, we must submit an IND application to the FDA. The FDA has 30 days to comment on the application and if the agency has no comments, we or our commercial partner may begin clinical trials. While we have stated our intention to file additional IND applications during the next several years, this is only a statement of intent, and we may not be able to do so because the associated product candidates may not meet the necessary preclinical requirements. In addition, there can be no assurance that, once filed, an IND application will result in the actual initiation of clinical trials. Clinical trials are subject to oversight by institutional review boards and the FDA. In addition, our proposed clinical studies require review from the Recombinant DNA Advisory Committee (RAC), which is the advisory board to the National Institutes of Health (NIH), focusing on clinical trials involving gene transfer. We will typically submit a proposed clinical protocol and other product-related information to the RAC three to six months prior to the expected IND application filing date.

Clinical trials:

- must be conducted in conformance with the FDA s good clinical practices, within the guidelines of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and other applicable regulations;

- must meet requirements for Institutional Review Board (IRB) oversight;

- must follow Institutional Biosafety Committee (IBC) and NIH RAC guidelines where applicable;

must meet requirements for informed consent;

are subject to continuing FDA oversight;

may require oversight by a Data Safety Monitoring Board (DSMB);

may require large numbers of test subjects; and

may be suspended by a commercial partner, the FDA, or us at any time if it is believed that the subjects participating in these trials are being exposed to unacceptable health risks or if the FDA finds deficiencies in the IND application or the conduct of these trials.

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We have limited experience in conducting clinical trials.

We have ongoing Phase 1/2 and 2 trials of a ZFP Therapeutic for HIV/AIDS and an ongoing Phase 2 trial to evaluate the safety and efficacy of AAV-NGF for Alzheimers disease. However, the FDA will require additional clinical testing which involves significantly greater resources, commitments and expertise and so it is likely that we would need to enter into a collaborative relationship with a pharmaceutical company that could assume responsibility for late-stage development and commercialization.

We have limited experience in conducting advanced clinical trials and may not possess the necessary resources and expertise to complete such trials. We have entered into collaborative agreements with Shire and Biogen to provide funding and assistance in the development of our ZFP Therapeutics through the clinical trial process. Under the agreement with Shire, we are responsible for all activities through submission of IND Applications and European CTAs and Shire is responsible for clinical development and commercialization of products arising from the alliance. Under the Agreement with Biogen, we are responsible for all research and development through the first human clinical trial for the treatment of beta-thalassemia and both parties are responsible for research and development through the submission of IND for ZFP Therapeutics to treat sickle cell disease (SCD). However, there is no guarantee that we will be able to enter into future collaborative relationships with third parties that can provide us with the funding and expertise for later stage trials.

While we have stated that we intend to file IND applications for several ZFP Therapeutic programs over the next two years, we may encounter difficulties that may delay, suspend or scale back our efforts.

We have previously announced a strategy for our ZFP Therapeutic programs that enables the potential filing of eight IND applications by the end of 2015. The preparation and submission of IND applications requires us to conduct rigorous and time-consuming preclinical testing, studies, and documentation relating to, among other things, the toxicity, safety, manufacturing, chemistry and clinical protocol of new ZFP Therapeutic products. We may experience unforeseen difficulties that could delay or otherwise prevent us from executing this strategy successfully. For example, we may encounter problems in the manufacturing of our ZFP Therapeutic products and fail to demonstrate consistency in the formulation of the drug. Our pre-clinical tests may produce negative or inconclusive results, which may lead us to decide, or regulators may require us, to conduct additional preclinical testing. If we cannot obtain positive results in preclinical testing, we may decide to abandon the projects altogether. Furthermore, the filing of several IND applications involves significant cost and labor, and we may not have sufficient resources and personnel to complete the filing of all intended IND applications, which may force us to scale back the number of IND applications or forego potential IND applications that we believe are promising. Any delay, suspension or reduction of our efforts to pursue our pre-clinical and IND strategy could have a material adverse effect on our business and cause our stock price to decline.

We may not be able to find acceptable patients or may experience delays in enrolling patients for our clinical trials.

We may experience difficulties or delays in recruiting and enrolling a sufficient number of patients to participate in our clinical trials due to a variety of reasons, including competition from other clinical trial programs for the same indication, failure of patients to meet our enrollment criteria and premature withdraws of patients prior to the completion of clinical trials. The FDA and institutional review boards may also require large numbers of patients, and the FDA may require that we repeat a clinical trial. Any delay resulting from our failure to enroll a sufficient number of patients on a timely basis may have a material adverse affect on our business.

As we cannot predict whether or when we will obtain regulatory approval to commercialize our product candidates, we cannot predict the timing of any future revenue from these product candidates.

We cannot commercialize any of our ZFP Therapeutics to generate revenue until the appropriate regulatory authorities have reviewed and approved the applications for the product candidates. We cannot ensure that the regulatory agencies will complete their review processes in a timely manner or that we will obtain regulatory

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approval for any product candidate that we or our collaborators develop. Satisfaction of regulatory requirements typically takes many years, is dependent upon the type, complexity and novelty of the product and requires the expenditure of substantial resources. Regulatory approval processes outside the United States include all of the risks associated with the FDA approval process. In addition, we may experience delays or rejections based upon additional government regulation from future legislation or administrative action or changes in FDA policy during the period of product development, clinical trials and FDA regulatory review.

Regulatory approval, if granted, will be limited to specific uses or geographic areas, which could limit our ability to generate revenues.

Regulatory approval will be limited to the indicated use for which we can market a product. Further, once regulatory approval for a product is obtained, the product and its manufacturer are subject to continual review. Discovery of previously unknown problems with a product or manufacturer may result in restrictions on the product, manufacturer, and manufacturing facility, including withdrawal of the product from the market. In Japan and Europe, regulatory agencies also set or approve prices.

Even if regulatory clearance of a product is granted, this clearance is limited to those specific states and conditions for which the product is useful, as demonstrated through clinical trials. We cannot ensure that any ZFP Therapeutic product developed by us, alone or with others, will prove to be safe and effective in clinical trials and will meet all of the applicable regulatory requirements needed to receive marketing clearance in a given country.

Outside the United States, our ability to market a product is contingent upon receiving a marketing authorization from appropriate regulatory authorities; therefore we cannot predict whether or when we would be permitted to commercialize our product. These foreign regulatory approval processes include all of the risks associated with FDA clearance described above.

Commercialization of our technologies will depend, in part, on strategic partnering with other companies. If we are not able to find partners in the future or our partners do not diligently pursue product development efforts, we may not be able to develop our technologies or products, which could slow our growth and decrease the value of our stock.

We expect to rely, to some extent, on our strategic partners to provide funding in support of our research and to perform independent research and preclinical and clinical testing. Our technology is broad based, and we do not currently possess the resources necessary to fully develop and commercialize potential products that may result from our technologies or the resources or capabilities to complete the lengthy marketing approval processes that may be required for the products. Therefore, we plan to rely on strategic partnerships to help us develop and commercialize ZFP Therapeutic products. If we are unable to find partners or if the partners we find, such as Shire and Biogen, are unable or unwilling to advance our programs, or if they do not diligently pursue product approval, this may slow our progress and defer our revenues. Our partners may sublicense or abandon development programs or we may have disagreements with our partners, which would cause associated product development to slow or cease. There can be no assurance that we will be able to establish further strategic collaborations for ZFP Therapeutic product development. We may require significant time to secure collaborations or partners because we need to effectively market the benefits of our technology to these future collaborators and partners, which may direct the attention and resources of our research and development personnel and management away from our primary business operations. Further, each collaboration or partnering arrangement will involve the negotiation of terms that may be unique to each collaborator or partner. These business development efforts may not result in a collaboration or partnership.

The loss of partnering agreements would not only delay or terminate the potential development or commercialization of products we may derive from our technologies, but it may also delay or terminate our ability to test ZFP Therapeutic candidates for specific genes. If any partner fails to conduct the collaborative activities successfully and in a timely manner, the preclinical or clinical development or commercialization of the affected product candidates or research programs could be delayed or terminated.

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Under typical partnering agreements we would expect to receive revenue for the research and development of a ZFP Therapeutic product based on achievement of specific milestones, as well as royalties based on a percentage of sales of the commercialized products. Achieving these milestones will depend, in part, on the efforts of our partner as well as our own. If we, or any partner, fail to meet specific milestones, then the partnership may be terminated, which could reduce our revenues. For more information on risks relating to our third party collaborative agreements, see Risks Relating to our Collaborative Relationships.

We may be unable to license gene transfer technologies that we may need to commercialize our ZFP technology.

In order to regulate or modify a gene in a cell, the ZFP must be efficiently delivered to the cell. We have licensed certain gene transfer technologies for our ZFP in research. We are evaluating these systems and other technologies that may need to be used in the delivery of ZFP into cells for *in vitro* and *in vivo* applications, including ZFP Therapeutics. However, we may not be able to license the gene transfer technologies required to develop and commercialize our ZFP Therapeutics. We have not developed our own gene transfer technologies, and we rely on our ability to enter into license agreements to provide us with rights to the necessary gene transfer technology. Our approach has been to license appropriate technology as required. The inability to obtain a license to use gene transfer technologies with entities which own such technology on reasonable commercial terms, if at all, could delay or prevent the preclinical evaluation, drug development collaborations, clinical testing, and/or commercialization of our therapeutic product candidates.

Our gene regulation and gene modification technology is relatively new, and if we are unable to use this technology in all our intended applications, it would limit our revenue opportunities.

Our technology involves a relatively new approach to gene regulation and gene modification. Although we have generated ZFPs for thousands of gene sequences, we have not created ZFPs for all gene sequences and may not be able do so, which could limit the usefulness of our technology. In addition, while we have demonstrated the function of engineered ZFNs and ZFP TFs in mammalian cells, yeast, insects, plants and animals, we have not yet demonstrated clinical benefit of this technology in humans, and the failure to do so could restrict our ability to develop commercially viable products. If we, and our collaborators or strategic partners, are unable to extend our results to new commercially important genes, experimental animal models, and human clinical studies, we may be unable to use our technology in all its intended applications.

The expected value and utility of our ZFNs and ZFP TFs is in part based on our belief that the targeted modification of genes or specific regulation of gene expression may enable us to develop a new therapeutic approach as well as to help scientists better understand the role of genes in disease, and to aid their efforts in drug discovery and development. We also believe that ZFP-mediated targeted gene editing and gene regulation will have utility in agricultural applications. There is only a limited understanding of the role of specific genes in all these fields. Life sciences companies have developed or commercialized only a few products in any of these fields based on results from genomic research or the ability to regulate gene expression. We, our collaborators or our strategic partners, may not be able to use our technology to identify and validate drug targets or to develop commercial products in the intended markets.

Effective delivery of ZFNs and ZFP TFs into the appropriate target cells and tissues is critical to the success of the therapeutic applications of our ZFP technology. In order to have a meaningful therapeutic effect, the ZFP Therapeutic must be delivered to sufficient numbers of cells in the targeted tissue. The ZFN or ZFP TF must be present in that tissue for sufficient time to effect either modification of a therapeutically relevant gene or regulation of its expression.

In our current clinical and preclinical programs, we administer our ZFP Therapeutics as a nucleic acid that encodes the ZFN or ZFP TF. We use different formulations to deliver the ZFP Therapeutic depending on the required duration of expression, the targeted tissue and the indication that we intend to treat. However, there can be no assurances that we will be able to effectively deliver our ZFNs and ZFP TFs to produce a beneficial therapeutic effect.

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We are conducting proprietary research to discover ZFP Therapeutic product candidates. These programs increase our financial risk of product failure, may significantly increase our research expenditures, and may involve conflicts with future collaborators and strategic partners.

Our proprietary research programs consist of research which is funded solely by us or by grant funding and in which we retain exclusive rights to therapeutic products generated by such research. This is in contrast to certain of our research programs that may be funded by corporate partners and in which we may share rights to any resulting products. Conducting proprietary research programs may not generate corresponding revenue and may create conflicts with our collaborators or strategic partners over rights to our intellectual property with respect to our proprietary research activities. Any conflict with our collaborators or strategic partners could reduce our ability to enter into future collaborations or partnering agreements and negatively impact our relationship with existing collaborators and partners which could reduce our revenue and delay or terminate our product development. As we continue to focus our strategy on proprietary research and therapeutic development, we expect to experience greater business risks, expend significantly greater funds and require substantial commitments of time from our management and staff.

Even if our technology proves to be effective, it still may not lead to commercially viable products.

Even if our collaborators or strategic partners are successful in using our ZFP technology in drug discovery, protein production, therapeutic development, or plant agriculture, they may not be able to commercialize the resulting products or may decide to use other methods competitive with our technology. To date, no company has received marketing approval or has developed or commercialized any therapeutic or agricultural products based on our technology. Should our technology fail to provide safe, effective, useful, or commercially viable approaches to the discovery and development of these products, this would significantly limit our business and future growth and would adversely affect our value.

Even if our product development efforts are successful and even if the requisite regulatory approvals are obtained, our ZFP Therapeutics may not gain market acceptance among physicians, patients, healthcare payers and the medical community.

A number of additional factors may limit the market acceptance of our ZFP Therapeutic products including the following:

- rate of adoption by healthcare practitioners;
- rate of a product s acceptance by the target population;
- timing of market entry relative to competitive products;
- availability of alternative therapies;

price of our product relative to alternative therapies;

availability of third-party reimbursement;

extent of marketing efforts by us and third-party distributors or agents retained by us; and

side effects or unfavorable publicity concerning our products or similar products.

Therefore, even after we have obtained the required regulatory approval for our ZFP Therapeutic products, we may not be able to commercialize these products successfully if we cannot achieve an adequate level of market acceptance.

We do not currently have the infrastructure or capability to manufacture, market and sell therapeutic products on a commercial scale.

In order for us to commercialize our therapeutic products directly, we would need to develop, or obtain through outsourcing arrangements, the capability to manufacture, market and sell our products on a commercial scale. Currently we do not have the ability nor the financial resources to establish the infrastructure and

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organizations needed to execute these functions, including such infrastructure needed for the commercialization of any product from our HIV/AIDS or Alzheimer s disease program, which can be complex and costly. If we are unable to establish adequate manufacturing, sales, marketing and distribution capabilities, we will not be able to directly commercialize our therapeutics products, which would limit our future growth.

We may not be able to fully realize the expected benefits from the acquisition of Ceregene, Inc., and the operation of the new business of Ceregene, Inc. may subject us to additional risks.

On October 1, 2013, we acquired Ceregene, including all of its therapeutic programs and related intellectual property and other assets. Although we expect to realize strategic, operational and financial benefits as a result of the acquisition, we cannot be certain whether, and to what extent, such benefits will be achieved in the future. In particular, the success of the acquisition will depend on our ability to efficiently and successfully integrate Ceregene s business, including the prosecution of its CERE-110 Phase 2 clinical trial, and to apply Ceregene s technology to advance our ZFP Therapeutics. There is no guarantee that any existing and future clinical trials of Ceregene s product candidates, including CERE-110 for the treatment of AD, will produce positive results, and failure to do so may adversely affect our ability to validate the AAV delivery technology and apply such technology to our ZFP products as well as negatively impact our stock price. In April 2013, Ceregene reported that its top line data for the CERE-120 Phase 2b clinical trial for Parkinson s disease did not demonstrate statistically significant efficacy in the primary endpoint. In November 2013, we presented early positive data from Phase 1 clinical trial of CERE-110 demonstrating that the drug was well-tolerated and resulted in appropriate delivery of the therapeutics. However, even if we obtain positive data from such clinical trials, there is no guarantee that the AAV delivery technology can be applied to our ZFP Therapeutics safely and effectively.

The acquisition of Ceregene also subjects us to additional operational and financial risks, including the following:

- additional costs that we may need to incur in order to conduct and complete Ceregene s therapeutic programs, including the CERE-110 Phase 2 clinical trial, and to comply with new regulatory requirements;
- difficulties acquiring and developing the necessary expertise to continue the development of AAV technologies and other acquired assets of Ceregene;
- difficulties in coordinating research and development activities;
- uncertainties in the business relationships with our collaborators and suppliers due to the acquisition; and
- lack of previous experiences in conducting Phase 2 trials of a gene therapy based on AAV vector delivery system.

In addition, the market price of our common stock may decline as a result of the merger if the integration of Ceregene is unsuccessful, takes longer than expected or fails to achieve the expected benefits to the extent anticipated by financial analysts or investors, or the effect of the acquisition on our financial results is otherwise not consistent with

the expectations of financial analysts or investors.

Risks Relating to our Industry

If our competitors develop, acquire, or market technologies or products that are more effective than ours, this would reduce or eliminate our commercial opportunity.

Any products that we or our collaborators or strategic partners develop by using our ZFP technology platform will enter into highly competitive markets. Even if we are able to generate ZFP Therapeutics that are safe and effective for their intended use, competing technologies may prove to be more effective or less

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expensive, which, to the extent these competing technologies achieve market acceptance, will limit our revenue opportunities. In some cases, competing technologies have proven to be effective and less expensive. Competing technologies may include other methods of regulating gene expression or modifying genes. ZFNs and ZFP TFs have broad application in the life sciences industry and compete with a broad array of new technologies and approaches being applied to genetic research by many companies. Competing proprietary technologies with our product development focus include but are not limited to:

For ZFP Therapeutics:

- small molecule drugs;
- monoclonal antibodies;
- recombinant proteins;
- gene therapy/cDNAs;
- antisense;
- siRNA and microRNA approaches, exon skipping;
- CRISPR/Cas9 technology;
- TALE proteins; and
- meganucleases.

For our Non-Therapeutic Applications:

- For protein production: gene amplification, meganucleases, TALE technology, insulator technology, mini-chromosomes and CRISPR/Cas9 technology;

For target validation: antisense, siRNA, TALE technology and CRISPR/Cas9 technology;

For plant agriculture: recombination approaches, mutagenesis approaches, meganucleases, TALE technology, CRISPR/Cas9 technology, mini-chromosomes; and

For transgenic animals: somatic nuclear transfer, embryonic stem cell, TALE, CRISPR/Cas9 technology and transposase technologies.

In addition to possessing competing technologies, our competitors include pharmaceutical and biotechnology companies with:

substantially greater capital resources than ours;

larger research and development staffs and facilities than ours; and

greater experience in product development and in obtaining regulatory approvals and patent protection.

These organizations also compete with us to:

attract qualified personnel;

attract parties for acquisitions, joint ventures or other collaborations; and

license the proprietary technologies of academic and research institutions that are competitive with our technology, which may preclude us from pursuing similar opportunities.

Accordingly, our competitors may succeed in obtaining patent protection or commercializing products before us. In addition, any products that we develop may compete with existing products or services that are well established in the marketplace.

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Adverse public perception in the field of gene therapy may negatively impact regulatory approval of, or demand for, our potential products.

Our potential therapeutic products are delivered to patients as gene-based drugs, or gene therapy. The clinical and commercial success of our potential products will depend in part on public acceptance of the use of gene therapy for the prevention or treatment of human diseases. Public attitudes may be influenced by claims that gene therapy is unsafe, and, consequently, our products may not gain the acceptance of the public or the medical community. Negative public reaction to gene therapy in general could result in greater government regulation and stricter labeling requirements of gene therapy products, including any of our products, and could cause a decrease in the demand for any products we may develop.

Laws or public sentiment may limit the production of genetically modified agricultural products, and these laws could reduce our partner s ability to sell such products.

Genetically modified products are currently subject to public debate and heightened regulatory scrutiny, either of which could prevent or delay production of agricultural products. We have a research license and commercial option agreement with DAS through which we provide DAS with access to our proprietary ZFP technology and the exclusive right to use our ZFP technology to modify the genomes or alter the nucleic acid or protein expression of plant cells, plants or plant cell cultures. The field-testing, production and marketing of genetically modified plants and plant products are subject to federal, state, local and foreign governmental regulation. Regulatory agencies administering existing or future regulations or legislation may not allow production and marketing of our genetically modified products in a timely manner or under technically or commercially feasible conditions. In addition, regulatory action or private litigation could result in expenses, delays or other impediments to our product development programs or the commercialization of resulting products.

The FDA currently applies the same regulatory standards to foods developed through genetic engineering as those applied to foods developed through traditional plant breeding. Genetically engineered food products, however, will be subject to pre-market review if these products raise safety questions or are deemed to be food additives. Governmental authorities could also, for social or other purposes, limit the use of genetically modified products created with our gene regulation technology.

Even if the regulatory approval for genetically modified products developed under our agreement with DAS was obtained, our success will also depend on public acceptance of the use of genetically modified products including drugs, plants, and plant products. Claims that genetically modified products are unsafe for consumption or pose a danger to the environment may influence public attitudes. Our genetically modified products may not gain public acceptance. The subject of genetically modified organisms has received negative publicity in the United States and particularly in Europe, and such publicity has aroused public debate. The adverse publicity in Europe could lead to greater regulation and trade restrictions on imports of genetically altered products. Similar adverse public reaction or sentiment in the United States to genetic research and its resulting products could result in greater domestic regulation and could decrease the demand for our technology and products.

Risks Relating to our Finances

We have incurred significant operating losses since inception and anticipate that we will incur continued losses for the foreseeable future.

We have generated operating losses since we began operations in 1995. Our net losses for the years ended December 31, 2013, 2012 and 2011 were $26.6 million, $22.3 million and $35.8 million, respectively. The extent of our future losses and the timing of profitability are uncertain, and we expect to incur losses for the foreseeable future. We have been engaged in developing our ZFP technology since inception, which has and will continue to require significant research and development expenditures. To date, we have generated our funding from issuance of equity securities, revenues derived from strategic partnering agreements, other collaborations in non-

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therapeutic applications of our technology, federal government research grants and grants awarded by research foundations. As of December 31, 2013, we had an accumulated deficit of $302.1 million. From 2005 to date, we have generated an aggregate of approximately $231.4 million in net proceeds from the sale of our equity securities. We expect to continue to incur additional operating losses for the next several years as we continue to expand and extend our research and development activities into human therapeutic product development. If the time required to generate significant product revenues and achieve profitability is longer than we currently anticipate or if we are unable to generate liquidity through equity financing or other sources of funding, we may be forced to curtail or suspend our operations.

We may be unable to raise additional capital, which would harm our ability to develop our technology and products.

We have incurred significant operating losses and negative operating cash flows since inception and have not achieved profitability. We expect capital outlays and operating expenditures to increase over the next several years as we expand our infrastructure and research and ZFP Therapeutic product development activities. While we believe our financial resources will be adequate to sustain our current operations at least through 2015, we may need to seek additional sources of capital through equity or debt financing. In addition, as we focus our efforts on proprietary human therapeutics, we will need to seek FDA approval of potential products, a process that could cost in excess of hundreds of millions of dollars per product. Furthermore, we may experience difficulties in accessing the capital market due to external factors beyond our control such as volatility in the equity markets for emerging biotechnology companies and general economic and market conditions. We cannot be certain that we will be able to obtain financing on terms acceptable to us, or at all. Our failure to obtain adequate and timely funding will materially adversely affect our business and our ability to develop our technology and ZFP Therapeutic products. Furthermore, any sales of additional equity securities may result in dilutions to our stockholders and any debt financing may include business and financial covenants that restricts our operations.

We are at the development phase of operations and may not succeed or become profitable.

We began operations in 1995 and are in the early phases of ZFP Therapeutic product development, and we have incurred significant losses since inception. To date, our revenues have been generated from strategic partners, other collaborations in non-therapeutic applications of our technology, and federal government and research foundation grants. Our focus on higher-value therapeutic product development and related strategic partnerships requires us to incur substantial expenses associated with product development. In addition, the preclinical or clinical failure of any single product may have a significant effect on the actual or perceived value of our stock. Our business is subject to all of the risks inherent in the development of a new technology, which includes the need to:

- attract and retain qualified scientific and technical staff and management, particularly scientific staff with expertise to develop our early-stage technology into therapeutic products;

- obtain sufficient capital to support the expense of developing our technology platform and developing, testing and commercializing products;

develop a market for our products; and

successfully transition from a company with a research focus to a company capable of supporting commercial activities.

Risks Relating to our Relationships with Collaborators and Strategic Partners

If conflicts arise between us and our collaborators or strategic partners, these parties may act in their self-interest, which may limit our ability to implement our strategies.

If conflicts arise between our corporate or academic collaborators or strategic partners and us, the other party may act in its self-interest, which may limit our ability to implement our strategies. Some of our academic collaborators and strategic partners are conducting multiple product development efforts within each area that is

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the subject of the collaboration with us. Our collaborators or strategic partners, however, may develop, either alone or with others, products in related fields that are competitive with the products or potential products that are the subject of these collaborations. Competing products, either developed by the collaborators or strategic partners or to which the collaborators or strategic partners have rights, may result in the withdrawal of partner support for our product candidates.

Some of our collaborators or strategic partners could also become our competitors in the future. Our collaborators or strategic partners could develop competing products, preclude us from entering into collaborations with their competitors, fail to obtain timely regulatory approvals, terminate their agreements with us prematurely, or fail to devote sufficient resources to the development and commercialization of products. Any of these developments could harm our product development efforts.

Our collaborators and strategic partners may control aspects of our clinical trials, which could result in delays and other obstacles in the commercialization of our proposed products.

For some programs, we depend on third party collaborators and strategic partners to design and conduct our clinical trials. As a result, we may not be able to conduct these programs in the manner or on the time schedule we currently contemplate, which may negatively impact our business operations. In addition, if any of these collaborators or strategic partners withdraws support for our programs or proposed products or otherwise impair their development; our business could be negatively affected.

In January 2012, we entered into a research and collaborative agreement with Shire, pursuant to which we are engaging in a joint program with Shire to research, develop and commercialize human therapeutics and diagnostics for hemophilia, Huntington s disease and other monogenic diseases based on our ZFP technology. Under this agreement, we are responsible for all research activities through the submission of an IND or CTA, while Shire is responsible for clinical development and commercialization of products generated from the research program from and after the acceptance of an IND or CTA for the product. Under the agreement, we may be eligible to receive milestone payments upon the achievement of specified clinical development, commercialization and post-commercialization milestones. The total amount of potential milestone payments for each gene target, assuming the achievements of all specified milestones in the agreement, is $213.5 million. We may receive royalty payments based on specified percentages of net sales of products, if any.

In addition, in January 2014, we entered into a collaborative agreement with Biogen for the clinical development and commercialization of therapeutics based on our ZFP technology for hemoglobinopathies, including beta-thalassemia and SCD. Under the Agreement, we are responsible for all discovery, research and development activities through the first human clinical trial for the first ZFP therapeutic developed for the treatment of beta-thalassemia. In the SCD program, both parties are responsible for research and development activities through the submission of an IND. Under both programs, Biogen is responsible for subsequent clinical development, manufacturing and commercialization of licensed products developed under the Agreement. Under the agreement with Biogen, we may be eligible to receive payments upon the achievement of specified regulatory, clinical development, commercialization, and sales milestones of up to $293.8 million. We may also receive royalty payments based on specified percentage of annual net sales of products, if any.

Under these agreements with Biogen and Shire will have control and broad discretion over all or certain aspects of the clinical development and commercialization of any product developed under the agreements, and we will have little, if any, influence on how these programs will be conducted. Our lack of control over the clinical development in our

agreement with Biogen and Shire could cause delays or other difficulties in the development and commercialization of our product candidates, which may prevent us from receiving any milestone, royalty payments and other benefits under the agreement. In addition, under their respective agreement(s), Biogen and Shire have certain rights to terminate the agreements by providing us with advance notices, therefore the actual milestone payments that we may receive under these agreements may be lower than the full amounts stated above.

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Our collaborators or strategic partners may decide to adopt alternative technologies or may be unable to develop commercially viable products with our technology, which would negatively impact our revenues and our strategy to develop these products.

Our collaborators or strategic partners may adopt alternative technologies, which could decrease the marketability of ZFP technology. Additionally, because many of our collaborators or strategic partners are likely to be working on more than one development project, they could choose to shift their resources to projects other than those they are working on with us. If they do so, this would delay our ability to test our technology and would delay or terminate the development of potential products based on our ZFP technology. Further, our collaborators and strategic partners may elect not to develop products arising out of our collaborative and strategic partnering arrangements or to devote sufficient resources to the development, manufacturing, marketing or sale of these products. If any of these events occur, we may not be able to develop our technologies or commercialize our products.

If we do not successfully commercialize ZFP-based research reagents, ZFP-modified cell lines for commercial protein production, or ZFP-engineered transgenic animals under our license agreement with Sigma-Aldrich Corporation or ZFP-based agricultural products with Dow AgroSciences, or if Sigma-Aldrich Corporation or Dow AgroSciences terminates our agreements, our ability to generate revenue under these license agreements may be limited.

In July 2007, we entered into a license agreement with Sigma to collaborate in the application and development of ZFP-based products for use in the laboratory research reagents markets. The agreement provides Sigma with access to our ZFP technology and the exclusive right to use our ZFP technology to develop and commercialize products for use as research reagents and to offer services in related research fields. This relationship was expanded in October 2009 when we amended our license agreement with Sigma to provide Sigma with the exclusive rights to develop and distribute ZFP-modified cell lines for commercial production of protein pharmaceuticals and, certain ZFP-engineered transgenic animals for commercial applications. In June 2008, following a research period, DAS exercised its commercial license option under a license agreement with us relating to plant agriculture. This agreement provides DAS with the exclusive right to develop agricultural products using our ZFP technology in plant cells, plants, or plant cell cultures. Both companies also have the right to sublicense our technology in their respective areas. In addition to upfront payments, we may also receive additional license fees, shared sublicensing revenues, royalty payments and milestone payments depending on the success of the development and commercialization of the licensed products and services covered under both agreements. The commercial milestones and royalties are typically based upon net sales of licensed products.

We cannot be certain that we or our collaboration partners will succeed in the development of commercially viable products in these fields of use, and there is no guarantee that we or our collaboration partners will achieve the milestones set forth in the respective license agreements. To the extent we or our collaboration partners do not succeed in developing and commercializing products or if we or our collaboration partners fail to achieve such milestones, our revenues and benefits under the license agreements will be limited. In addition, the respective license agreements may be terminated by Sigma and DAS at any time by providing us with a 90-day notice. In the event Sigma or DAS decides to terminate the license agreements, our ability to generate revenue under such license agreements will cease.

Our collaborations with outside scientists may be subject to change, which could limit our access to their expertise.

We work with scientific advisors and collaborators at academic research institutions. These scientists are not our employees and may have other commitments that would limit their availability to us. Although our scientific advisors

generally agree not to do competing work, if a conflict of interest between their work for us and their work for another entity arises, we may lose their services. Although our scientific advisors and academic collaborators sign agreements not to disclose our confidential information, it is possible that some of our valuable proprietary knowledge may become publicly known through them, which may cause competitive harm to our business.

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Risks Relating to our Intellectual Property and Business Operation

Because it is difficult and costly to protect our proprietary rights, and third parties have filed patent applications that are similar to ours, we cannot ensure the proprietary protection of our technologies and products.

Our commercial success will depend in part on obtaining patent protection of our technology and successfully defending any of our patents that may be challenged. The patent positions of pharmaceutical and biotechnology companies can be highly uncertain and can involve complex legal and factual questions. No consistent policy regarding the breadth of claims allowed in biotechnology patents has emerged to date. Accordingly, we cannot predict the breadth of claims allowed in patents we own or license.

We are a party to various license agreements that give us rights under specified patents and patent applications. Our current licenses, as our future licenses frequently will, contain performance obligations. If we fail to meet those obligations, the licenses could be terminated. If we are unable to continue to license these technologies on commercially reasonable terms, or at all, we may be forced to delay or terminate our product development and research activities.

With respect to our present and any future sublicenses, since our rights derive from those granted to our sublicensor, we are subject to the risk that our sublicensor may fail to perform its obligations under the master license or fail to inform us of useful improvements in, or additions to, the underlying intellectual property owned by the original licensor.

We are unable to exercise the same degree of control over intellectual property that we license from third parties as we exercise over our internally developed intellectual property. We do not control the prosecution of certain of the patent applications that we license from third parties; therefore, the patent applications may not be prosecuted as we desire or in a timely manner.

The degree of future protection for our proprietary rights is uncertain, and we cannot ensure that:

- we or our licensors were the first to make the inventions covered by each of our pending patent applications;
- we or our licensors were the first to file patent applications for these inventions;
- the patents of others will not have an adverse effect on our ability to do business;
- others will not independently develop similar or alternative technologies or reverse engineer any of our products, processes or technologies;
- any of our pending patent applications will result in issued patents;

any patents issued or licensed to us or our collaborators or strategic partners will provide a basis for commercially viable products or will provide us with any competitive advantages;

any patents issued or licensed to us will not be challenged and invalidated by third parties; or

we will develop additional products, processes or technologies that are patentable.

Others have filed and in the future are likely to file patent applications that are similar to ours. We are aware that there are academic groups and other companies that are attempting to develop technology that is based on the use of zinc finger, TALE and other DNA-binding proteins, and that these groups and companies have filed patent applications. Several patents have been issued, although we have no current plans to use the associated inventions. If these or other patents issue, it is possible that the holder of any patent or patents granted on these applications may bring an infringement a