AmpliPhi Biosciences Corp
Form 10-K/A
September 12, 2014

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K/A

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

For the Fiscal Year Ended December 31, 2013

Commission File Number 000-23930

AMPLIPHI BIOSCIENCES CORPORATION

(Exact name of registrant as specified in its charter)

Washington	**91-1549568**
(State or other jurisdiction of incorporation and organization)	(I.R.S. Employer Identification No.)

4870 Sadler Road, Suite 300

Glen Allen, Virginia 23060

(Address of principal executive offices, including zip code)

(804) 205-5069

(Registrant's telephone number)

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

Securities registered pursuant to Section 12(g) of the Act:
Common Stock, par value $0.01 per share
(Title of class)

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 ¨ No x

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 definitions of "large accelerated filer," "accelerated filer," and "smaller reporting company" in Rule 12b-2 of the Exchange Act.

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

As of June 30, 2013, the aggregate market value of voting stock held by non-affiliates of the Registrant, based on the closing price of the Common Stock on June 28, 2013 as reported on the OTC Pink market, was approximately $10,122,521. Shares of Common Stock held by each officer and director and by each person who owns 5% or more of the outstanding Common Stock have been excluded from this computation in that such persons may be deemed to be affiliates. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

As of March 24, 2014, the Registrant had outstanding 182,535,562 shares of Common Stock.

Documents incorporated by reference: Portions of the Registrant's proxy statement to be filed pursuant to Regulation 14A within 120 days after Registrant's fiscal year end of December 31, 2013 are incorporated herein by reference into Items 10, 11, 12, 13 and 14 of Part III of this annual report.

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AMPLIPHI BIOSCIENCES CORPORATION

EXPLANATORY NOTE REGARDING AMENDMENT AND RESTATEMENT

Unless the context otherwise requires, we use the terms "AmpliPhi Biosciences," "AmpliPhi," "we," "us," "the Company" and "our" in this report to refer to AmpliPhi Biosciences Corporation and its subsidiaries.

This Annual Report on Form 10-K for the fiscal year ended December 31, 2013, includes restatement of the following previously filed consolidated financial statements and data (and related disclosures): (1) our consolidated balance sheet as of December 31, 2013, and our consolidated statements of operations and comprehensive loss, consolidated statement of stockholders' equity (deficit), and consolidated statement of cash flows for the fiscal year ended December 31, 2013; (2) our consolidated balance sheet as of December 31, 2012, and our consolidated statements of operations and comprehensive loss, consolidated statement of stockholders' equity (deficit), and consolidated statement of cash flows for the fiscal year ended December 31, 2012; and (3) our management's discussion and analysis of financial condition and results of operations as of and for our fiscal years ended December 31, 2013 and 2012, contained in Part II, Item 7 of this Annual Report on Form 10-K. All the aforementioned periods are collectively referenced as "Affected Periods".

The Company's previously issued December 31, 2013 financial statements have been restated to remove deemed dividends booked on the issuance of preferred shares and to recognize the increase in derivative expense due to adding several features to the valuation model used to measure the compound derivatives and changing from a Black-Scholes valuation model to a Monte Carlo valuation model. Additional paid in capital and accumulated deficit have been reduced by $8,464,000 after removing the deemed dividends. Loss on derivative liabilities increased by $1,755,000 to $42,317,000 due to the change in the valuation model.

The Company also contracted a valuation team to review the purchase price allocation of Biocontrol. As a result, in process research and development (IPR&D) was restated and a new intangible asset, patents, was recognized. For the Biocontrol acquisition, $493,000 of IPR&D was reclassified to patents. In addition, amortization expense for patents of $31,000 was recognized in both 2012 and 2013.

As a result of these corrections, the Company's net loss in 2013 increased $1,787,000 to $57,648,000. The net loss per share decreased by $0.07 per share to $(0.57) per share which also reflects the removal of the deemed dividends.

For more information regarding the restatement, please refer to Part II, Item 7, "Management's Discussion and Analysis of Financial Condition and Results of Operations"; Note 14, "Correction of Errors" in Part II, Item 8; and Part II, Item 9A, "Controls and Procedures."

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This report and certain information incorporated herein by reference contain forward-looking statements, which are provided under the "safe harbor" protection of the Private Securities Litigation Reform Act of 1995. These statements relate to future events or to our future financial performance and 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, performance or achievements expressed or implied by the forward-looking statements. Forward-looking statements include, but are not limited to, statements regarding:

- *our ability to manufacture, or otherwise secure the manufacture of, sufficient amounts of our product candidates for our preclinical studies and clinical trials;*
- *our clinical development plans, including planned clinical trials;*
- *our research and development plans, including our plans to initiate at least one new clinical study in the first half of 2015;*
- *our ability to select combinations of phages to formulate our product candidates;*
- *the safety and efficacy of our products and product candidates;*
- *the anticipated regulatory pathways for our product candidates;*

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- *our ability to successfully complete preclinical and clinical development of, and obtain regulatory approval of our product candidates and commercialize any approved products on our expected timeframes or at all;*
- *the content and timing of submissions to and decisions made by the FDA and other regulatory agencies;*
- *our ability to leverage the experience of our management team;*
- *our ability to attract and keep management and other key personnel;*
- *the capacities and performance of our suppliers, manufacturers, contract research organizations, or CROs, and other third parties over whom we have limited control;*
- *the actions of our competitors and success of competing drugs that are or may become available;*
- *our expectations with respect to future growth and investments in our infrastructure, and our ability to effectively manage any such growth;*
- *the size and potential growth of the markets for any of our product candidates, and our ability to capture share in or impact the size of those markets;*
- *the benefits of our products and product candidates;*
- *market and industry trends;*
- *the effects of government regulation and regulatory developments, and our ability and the ability of the third parties with whom we engage to comply with applicable regulatory requirements;*
- *our financial performance, including our net revenue, return rates and related estimates, cost of revenue, gross profit and gross margin, operating expenses, utilization of net operating losses, or NOLs, stock-based compensation expense, cash flows, expected uses of anticipated cash flow, funding requirements and market risk;*
- *our expectations regarding future planned expenditures;*
- *our expectations with respect to product pricing;*

- *our ability to effectively remediate any significant deficiencies or material weaknesses in our internal control over financial reporting;*

- *our ability to achieve and maintain effective internal control over financial reporting in accordance with Section 404 of the Sarbanes-Oxley Act;*

- *our ability to obtain, maintain and successfully enforce adequate patent and other intellectual property protection of any of our products and product candidates;*

- *our ability to operate our business without infringing the intellectual property rights of others; and*

- *our plans to potentially transact business outside the United States.*

In some cases, you can identify these statements by terms such as "anticipates," "believes," "could," "estimates," "expects," "intends," "may," "plans," "potential," "predicts," "projects," "should," "will," "would" or the negative of those terms, and similar expressions. These forward-looking statements reflect our management's beliefs and views with respect to future events and are based on estimates and assumptions as of the date of this Annual Report and are subject to risks and uncertainties. We discuss many of these risks in greater detail in the section entitled "Risk Factors." Moreover, we operate in a very competitive and rapidly changing environment. New risks emerge from time to time. It is not possible for our management to predict all risks, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements we may make. Given these uncertainties, you should not place undue reliance on these forward-looking statements.

This Annual Report on Form 10-K includes trademarks and registered trademarks of AmpliPhi Biosciences Corporation. Products or service names of other companies mentioned in this Annual Report on Form 10-K may be trademarks or registered trademarks of their respective owners.

As used in this Annual Report, unless the context requires otherwise, the "Company," "we," "us" and "our" refer to AmpliPhi Biosciences Corporation, a Washington corporation, or, where appropriate, Targeted Genetics Corporation or AmpliPhi Biosciences Corporation, a Delaware corporation to be formed in connection with the Company's planned reincorporation.

PART I

Item 1. BUSINESS.

Company History

We were incorporated under the laws of the State of Washington in March 1989 as a wholly owned subsidiary of Immunex Corporation and began operations as an independent company in 1992 as Targeted Genetics Corporation.

In January 2011, we completed the acquisition of Biocontrol Ltd, which we refer to as Biocontrol, an antimicrobial biotechnology company based in the United Kingdom, with the goal of developing their phage therapy programs using funding from the sale of our legacy gene therapy assets. On February 22, 2011, we changed our name to "AmpliPhi Biosciences Corporation."

In November 2012, we completed the acquisition of Special Phage Holdings Pty Ltd, a company based in Australia, which we refer to as SPH, pursuant to our offer to acquire all outstanding shares of SPH from its shareholders under the terms of a Shareholder Sale Agreement and a Managers Warranty Deed. SPH was formed in 2004 to address the rapidly escalating problem of antibiotic resistance through the development of a series of bacteriophage-based treatments.

We intend to reincorporate as AmpliPhi Biosciences Corporation in the State of Delaware.

Company Overview

We are a biotechnology company focused on the discovery, development and commercialization of novel phage therapeutics. Our proprietary pipeline is based on the use of bacteriophages, a family of viruses that infect only bacteria. Phages have powerful and highly selective mechanisms of action that permit them to target and kill specific bacterial pathogens, including the so-called multi-drug-resistant (MDR) or "Superbug" strains.

We believe that we are a leading developer of phage-based therapeutics. We are combining our proprietary approach and expertise in identifying, characterizing and developing naturally occurring bacteriophages with that of our collaboration partners in bacteriophage biology, drug engineering, development and manufacturing, to develop second-generation bacteriophage products. We believe that phages represent a promising means to treat bacterial infections, especially those that have developed resistance to current medicines.

The extensive use of antibiotics, since their discovery in the 1940s, has resulted in drug resistance among many disease-causing bacteria. Resistance to antibiotics, according to the Centers for Disease Control (CDC), threatens to reverse the medical advances of the last half-century. Examples of clinically important microbes that are rapidly developing resistance to available antimicrobials include bacteria that cause skin, bone, lung and bloodstream infections (e.g., *S. aureus* and MRSA), pneumonia and lung infections in the community, hospital and cystic fibrosis (e.g., *A. baumanii*, *P. aeruginosa*, and *K. pneumoniae*), meningitis (e.g., *S. pneumonia*), urinary tract and gastrointestinal infections (e.g., *E. coli* and *C. difficile*). As a phage kills bacteria in ways entirely unlike the mechanisms used by antibiotics, MDR bacteria are not resistant to a phage in the same manner. Furthermore, as new resistant bacteria emerge, it should be possible to identify new phages that will still have efficacy.

Our lead program is AmpliPhage-002, for the treatment of *S. aureus* infections (including methicillin-resistant MRSA). We also have two other product candidates in development: AmpliPhage-001 for the treatment of *P. aeruginosa* lung infections in CF patients, and AmpliPhage-004 for the treatment of *C. difficile* infections.

We are developing these phage product candidates using our proprietary discovery and development platform, which is designed for rapid identification, characterization and manufacturing of multiple phage therapies. Each product candidate combines several carefully chosen phages which target a specific disease-causing bacterial pathogen such as MRSA, *P. aeruginosa and C. difficile* . We believe that our understanding of unique regulatory and development requirements of bacteriophage biology combined with the scientific expertise of our collaboration partners will enable the rapid advancement of phage treatments through the clinic and eventually to the market.

In March 2013, we entered into an Exclusive Channel Collaboration (ECC) with Intrexon Corporation, which we refer to as Intrexon, directed towards the research, development and commercialization of new bacteriophage-based therapies to target specific antibiotic-resistant infections, including for use in the treatment of bacterial infections associated with acute and chronic wounds, the treatment of acute and chronic *P. aeruginosa* lung infections, and the treatment of infections of *C. difficile*.

In April 2013, we entered into a collaboration agreement, which we refer to as the April Collaboration Agreement, and on September 5, 2013, we entered into a license agreement, which we refer to as the Leicester License Agreement, with the University of Leicester to develop a phage therapy that targets and kills all toxin types of *C. difficile*. Pursuant to the Leicester License Agreement, we may be obligated to pay the University of Leicester a royalty in the single digits and an aggregate of up to £575,000 million in milestone payments. We also entered into a collaboration agreement on August 1, 2013, which we refer to as the August Collaboration Agreement, with the University of Leicester and the University of Glasgow, whereby the University of Glasgow will carry out certain animal model development work. Pursuant to the August Collaboration Agreement, we may be obligated to pay up to a total of approximately £205,000 in milestone payments.

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In June 2013, we entered a cooperative research and development agreement (CRADA) with the United States Army Reserve Medical Corps (USAMRMC) and the Walter Reed Army Institute of Research (WRAIR) focusing on developing bacteriophage therapeutics to treat *S. aureus*, *E. coli* and *P. aeruginosa* infections.

We plan to initiate a Phase 1 study of AmpliPhage-002 in the first half of 2015 to demonstrate the safety of AmpliPhage-002 when administered to healthy volunteers colonized by *S. aureus*. The study population will be enriched to contain subjects with MRSA colonization. If that study is successful, we then intend to conduct a Phase 2 study in *S. aureus* for wound and skin infections.

The Need for New Anti-Infective Therapies

The rapid and continuous emergence of antibiotic-resistant bacteria has become a global crisis. While the numbers of novel anti-infective therapies in development are at historically low levels, antibiotic-resistant infections have dramatically increased. The CDC estimates that more than two million people in the United States acquire an antibiotic-resistant infection each year and more than 23,000 of these prove fatal. It is estimated that 50 – 70% of hospital-acquired infections are resistant to first-line anti-infective therapies. The cumulative annual cost for treating resistant bacterial infections in the United States alone is estimated to be $20 billion, while the global antibiotics market opportunity is estimated to be $40.3 billion by 2015.

The CDC's latest report on the matter, *Antibiotic Resistance Threats in the United States, 2013*, notes that there are "potentially catastrophic consequences of inaction" and ranks *C. difficile* as belonging to the highest tier of threat, "Urgent Threats." Despite the potential market opportunity, only two new antibacterial drug applications were approved between 2010 and 2012 compared to eighteen in the period between 1980 and 1984. One of the primary CDC recommendations is the development of new antibiotics to diversify treatment options.

Product Candidates

AmpliPhage-002: Wound and Skin Infections Caused by *S. aureus*

In conjunction with our CRADA with the USAMRMC, we are developing a phage product that is intended to effectively treat acute and chronic wound and skin infections caused by *S. aureus*, including infections caused by methicillin-resistant (MRSA) strains of the same bacterium. MRSA infections are one of the most common causes of hospital-acquired (nosocomial) infections and Global Data estimates the MRSA market for infections alone was more than $2.7 billion in 2007. This market is forecast to grow to more than $3.5 billion by 2019.

By screening our proprietary library of phage samples against a panel of *S. aureus* bacteria, we have selected a phage product mix that has demonstrated in *in vitro* studies greater than 85% efficacy with high overlap against a global diversity panel that includes some of the most virulent isolates of *S. aureus*, including MRSA strains identified by the U.S. Army.

We plan to initiate a Phase 1 study of AmpliPhage-002 in the first half of 2015 to demonstrate the safety of AmpliPhage-002 when administered to healthy volunteers colonized by *S. aureus*. The study population will be enriched to contain subjects with MRSA colonization. If that study is successful, we then intend to conduct a Phase 2 study in *S. aureus* for wound and skin infections.

After extensive financial and capability evaluation and a global search we have elected to proceed with cGMP manufacturing at a wholly owned facility that has been constructed in Ljubljana, Slovenia. We have been able to access and hire highly skilled process development and phage manufacturing expertise and believe that we now have control of our proprietary platform from phage identification through final product fill and finish. Our facility inclusive of laboratory and office space is approximately 4,000 sq. ft. and is expected to produce cGMP product by the end of 2014 for our currently planned and future studies. We believe that this facility should be sufficient to meet our product needs through Phase 3 and initial commercialization. Our current formulation for AmpliPhage-002 is intended for nasal delivery via a small spray device. We plan to further formulate our product for delivery to patients with wound and skin infections.

AmpliPhage-001: Lung Infections in Cystic Fibrosis (CF) Patients Caused by *P. aeruginosa*

According to Global Data in April 2013, the market for CF therapeutics was $1.2 billion in 2012 and forecasted to grow to $4.6 billion in 2017, with 65% of this market in the United States. One of our lead programs targets *P. aeruginosa*, the most prevalent bacterial infection that leads to the highest mortality in patients with CF with approximately 440 deaths per year in the United States. To develop our products, we have created a global “diversity” panel of relevant *P. aeruginosa* clinical isolates from CF clinics in the United States, Europe and Australia. Clinical isolates are bacteria isolated from patients. This diversity panel has been screened against our phage library that was isolated and characterized according to our proprietary discovery and development platform. We have demonstrated *in vitro* that we are able to effectively kill the targeted bacteria with a mixture of a few phages propagated in carefully selected bacterial hosts. Furthermore, our phage mix was selected to exhibit a high degree of overlap, defined as the number of bacteria targeted by more than one phage in the product. We believe that high overlap is an important factor in preventing bacteria from developing resistance to our phage products.

In collaboration with Institut Pasteur (Paris, France) and Brompton Clinic, Imperial College (London, United Kingdom), we have demonstrated in the preclinical studies described below that phages can effectively treat infections in animal models of acute *P. aeruginosa* lung infections. The graphic below shows the three groups from a study conducted at the Institute Pasteur. Each group consisted of eight mice. Group 1 was treated with Placebo, or PBS, Group 2 was treated with an antibiotic (note the model was optimized for this antibiotic) and Group 3 was treated with an AmpliPhi phage mix. The colored regions, measured by light, intensity, or luminescence, demonstrate where the *P. aeruginosa* infection is active and the bacteria are actively replicating. By the 24 th hour, the surviving untreated animals (Group 1) are sacrificed as the infection has spread and in some cases has already proved lethal whereas the two treatment groups (Group 2, antibiotic and Group 3, phage) demonstrate effective reduction of the active infection.

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Average luminescence for each group is shown below:

Bacterial counts and the number of bacteriophage infection units detected by assay, or phage titers, were measured in these animals after 24 hours, and the results demonstrated that our phage mix effectively lowered the bacterial counts, or CFU, in the mouse lung to levels comparable to antibiotic treatment (PBS vs. antibiotic, p=0.0003; PBS vs. bacteriophage, p=0.0003). Furthermore, it was evident that phage replicated to high levels in the infected lung. These results are shown in the graphics below.

In a separate *in vivo* study of acute *P. aeruginosa* infection of the mouse lung conducted at the Brompton Clinic, results demonstrated that our phage mix reduced CFU levels upon simultaneous intranasal administration (six mice in each of the treatment and control groups) and also when administered 24 hours post-bacterial infection (seven mice in the treatment group and eight mice in the control group) using Pa01, a standard strain of *P. aeruginosa*. These results are depicted in the graphics below.

Importantly, a preclinical study conducted at the Institut Pasteur in mice (12 mice in each of the treatment and control groups) demonstrated the ability of our phage mix to reach the lung within two hours of being delivered by oral administration. The phage levels increased between two and six hours post-treatment, and the results were statistically significant (p-value <0.001). A p-value is a statistical measure of the probability that the difference in two values could have occurred by chance. The smaller the p-value, the greater the confidence that the results are significant. These results demonstrate that when orally administered in mice, phages not only reached the lungs but were also able to infect and multiply in target bacteria.

We were granted an advisory meeting with United Kingdom Medicines and Healthcare products Regulatory Agency, (MHRA) in the first quarter of 2014 to discuss our plans and intent to move the CF program into additional preclinical testing in preparation for a Phase 1/2 study in CF patients. We also sought advice and comment that our planned Chemistry Manufacturing and Controls (CMC) plans were acceptable to the MHRA. The MHRA concurred with our approach and plans as presented, including a first in man dose ranging clinical study in CF patients. Subject to the availability of adequate financing, we expect to continue product selection and formulation work. Upon final product selection, we plan to manufacture the AmpliPhage-001 product in our facility in Ljubljana, Slovenia.

We believe that successful proof of concept in this lung indication could lead to other acute and chronic lung infection markets, such as Ventilator Associated Bacterial Pneumonia (VABP) and Chronic Obstructive Pulmonary Disease (COPD). The bacteria we are currently targeting are predominant pathogens in both of these indications.

AmpliPhage-004: Gastrointestinal (GI) Infection Caused by *C. difficile Infection (CDI)*

From 2000 through 2007, deaths in the United States from *C. difficile* infection increased over 400%. Over 90% of such deaths occur in hospitalized or confined patients over the age of 65. Global Data estimates that the major European Union and United States markets for CDI therapies grew to more than $314 million in 2011 and they are expected to grow to more than $500 million by 2019.

According to the CDC, almost 250,000 people each year require hospitalization for *C. difficile* infections, and at least 14,000 people die each year in the United States from *C. difficile* infections. We are actively working with researchers at the University of Leicester and the University of Glasgow to develop a phage therapy that targets and kills all toxin types of *C. difficile*. We believe that orally delivered phages are well suited to treat CDI. Within this collaboration, researchers at the University of Leicester have discovered phages that have been shown to be effective against clinically-relevant strains of *C. difficile* isolated from around the world. Since current therapies against *C. difficile* are considered less than optimal, we believe that there is a significant market opportunity for our product in treating this disease.

Prior Clinical Development

In 2010, the Company’s wholly owned subsidiary, Biocontrol, reported a double-blind placebo-controlled, randomized Phase 1/2 clinical trial targeting chronic ear infections (otitis) caused by antibiotic-resistant *P. aeruginosa*. This was the first, and to date, we believe the only, regulated efficacy trial of bacteriophage therapy in humans that has been reported. Positive results were reported demonstrating decreasing levels of *P. aeruginosa* in the ear and improvement of clinical condition with a single input dose of 2.4 nanograms of bacteriophage preparation. While this was a small trial (n=24), changes from baseline at the end of the trial in the test group (n=12) were statistically significant for both clinical condition (p=0.001) and bacterial load (p=0.016). No significant changes were seen in the control group (n=12) compared to baseline at the end of the trial. Difference between test and control groups was statistically significant by analysis by covariance (ANCOVA) on day 21 for bacterial count (p=0.0365). These results will need to be validated in larger well-controlled trials.

Anti-Infective Therapeutics Market

The market opportunity for antibiotics is extremely large, with the market estimated to reach $40.3 billion in annual sales globally in 2015.

Almost one in every five deaths worldwide occurs as a result of infection and, according to the World Health Organization, or WHO, many bacterial infections will become difficult or impossible to cure as the efficacy of current antibiotic drugs wanes. Despite the advances in antimicrobial and vaccine development, infectious diseases still remain as the third-leading cause of death in the United States and the second-leading cause of death worldwide.

The number of new antibiotics approved by the FDA and other global regulatory authorities has declined consistently over the last two decades. According to the Infectious Diseases Society of America, as of early 2013, only two new antibiotics have been approved by the FDA since 2009 and only seven new antibiotics targeting multi-drug-resistant Gram-negative bacilli were in either Phase 2 or Phase 3 trials. This dramatic decrease in productivity is evidenced by only two classes of antibiotics oxazolidinones and cyclic lipopeptides having been developed and launched in the last 30 years. At the same time, the evolution of antibiotic-resistant bacteria has led to an increasing number of infections for which there are no current treatments available.

Hospital-acquired (nosocomial) infections are a major healthcare problem throughout the world, affecting developed countries as well as resource-poor countries. The WHO reports that hospital-acquired infections are among the major causes of death and increased morbidity among hospitalized patients and estimates that more than 1.4 million people per year worldwide suffer from infectious complications from a hospital stay.

A recent CDC report also cites that in the United States, between 5 and 10% of all patients admitted to a hospital will be affected by a hospital-acquired infection during their stay, typically requiring extended stays and additional care. There is also a significant risk of death from such infections. In the United States, the CDC estimates that approximately 99,000 people die from hospital-acquired infections each year. The Cystic Fibrosis Foundation estimates that *P. aeruginosa* accounts for 10% of all hospital-acquired infections.

Infections also occur in connection with Cystic Fibrosis (CF), which is a genetic disease affecting primarily Caucasians of northern European descent. According to the Cystic Fibrosis Foundation, there are approximately 50,000 cases of CF in North America and Europe. *P. aeruginosa* opportunistically infects the mucous membranes, primarily the lungs, of CF patients and quickly grows out of control, resulting in pneumonia. *P. aeruginosa* infections are notoriously resistant to known antibiotics, and treatment may be further complicated by the formation of biofilms. Biofilms are organized structures of microorganisms growing on solid surfaces (such as lung tissue) and often limit access of antibiotics to the covered tissues. Since phages attack bacteria in a manner independent of chemical antibiotic resistance mechanisms and can infect bacteria growing in biofilms, we believe that *P. aeruginosa* infection among CF patients represents a compelling indication to pursue. The availability of *Pseudomonas*-specific phages along with validated animal models of *P. aeruginosa* lung infections has contributed to the development of our bacteriophage program in CF.

Compounding the above situations is the alarming and continuing rise in the prevalence of antibiotic-resistant bacterial infections. This, coupled with the lack of new antibiotics in current discovery and development pipelines, has generated a significant clinical management problem worldwide, leading to increases in morbidity and mortality due to these antibiotic-resistant bacteria as well as increases in healthcare costs.

The first of these antibiotic-resistant infections to reach epidemic proportions was caused by the Gram-positive bacterium *S. aureus*. *S. aureus* resistance to a broad range of antibiotics has necessitated the use of expensive and potentially toxic “drugs of last resort”, most notably vancomycin. Antibiotic-resistant forms of *S. aureus*, usually termed MRSA (methicillin-resistant *S. aureus*), VISA (vancomycin-intermediate *S. aureus*), or VRSA (vancomycin-resistant *S. aureus*), can be extremely challenging to treat. Although several antibiotics targeting *S. aureus* have been developed, rapidly developing bacterial resistance has been noted for all of these including linezolid, daptomycin and tigecycline. On the basis of historical evidence, resistance to these existing products is likely to increase over time, and this picture is further complicated by the reduced efficacy of conventional antibiotics against *Staphylococcus* biofilms.

Typically *S. aureus* infection causes a variety of suppurative (pus-forming) infections and toxinoses in humans. It causes superficial skin lesions such as boils, styes and furuncles; more serious infections such as pneumonia, mastitis, phlebitis, meningitis and urinary tract infections; and deep-seated infections, such as osteomyelitis and endocarditis. *S. aureus* is the leading cause of wound infections, in particular, hospital-acquired (nosocomial) infection of surgical wounds and infections associated with indwelling medical devices. *S. aureus* is the leading pathogen in healthcare-associated infections in the United States as a whole, accounting for 30.4% of surgical site infections (SSI), and 15.6% of such infections overall.

Anti-Infective Treatments with Bacteriophages

Background

The dramatic rise in antibiotic resistance, the appearance of an increasing number of new "superbugs" and the lack of new antibiotics in the pipeline has prompted calls to action from many of the world's major health bodies such as the CDC and the WHO, who warn of an "antibiotic cliff" and a "post-antibiotic era." In 2009, the European Antimicrobial Resistance Surveillance System, or EARSS, concluded that "the loss of effective antimicrobial therapy increasingly threaten[s] the delivery of crucial health services in hospitals and in the community." This conclusion was reinforced by The Antimicrobial Availability Task Force, or AATF, of the Infectious Diseases Society of America, or IDSA, and the European Centre for Disease Prevention and Control, or ECDC, in conjunction with the European Medicine Agency, or EMA. Clearly, there is a pressing need to find alternative antibacterial therapies.

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Bacteriophage therapy has the potential to be an alternative method of treating bacterial infection. Phages are ubiquitous environmental viruses that grow only within bacteria. The name "bacteriophage" translates as "eaters of bacteria" and reflects the fact that as they grow, phages kill the bacterial host by multiplying inside and then bursting through the cell membrane in order to release the next generation of phages. Phages can differ substantially in morphology and each phage is active against a specific range of a given bacterial species. Phages were first discovered in 1915 at the Institut Pasteur and were shown to kill bacteria taken from patients suffering from dysentery. Furthermore, it was noted that phage numbers rose as patients recovered from infection, suggesting a direct association.

Life Cycle of a Bacteriophage

Until the discovery of effective antibiotics, phages were used as an effective means of combating bacterial infection. When broad-spectrum antibiotics came into common use in the early 1940s, phages were considered unnecessary, with antibiotics being seen for many years as the answer to bacterial disease. This attitude persisted until the development of the wide-ranging, and in some cases total, resistance to antibiotics seen within the last 10 years.

It is now clear that bacteria can adapt to resist chemical antibiotics. In addition, there is now strong pressure to limit the use of antibiotics for human and veterinary use. There is a real need for different approaches to the control of antibiotic-resistant bacterial infections. In the light of current knowledge, it is apparent that early work with phages was hindered by poor understanding of the biology of phages, leading to exaggerated claims that damaged the reputation of phage therapy. Several companies in the 1920s and 1930s began to produce and market bacteriophage preparations. Unfortunately, these were often marketed with promises of efficacy against diseases that are now known to have nothing to do with bacteria, and many preparations themselves failed to actually contain bacteriophages. These conditions made bacteriophage subject to understandable skepticism. Now, with the far greater understanding of phages and their function that is now available, it is possible to identify the bacteria that are causing disease and then target them with highly specific phages that will kill only those bacteria.

Phages have the potential to provide both an alternative to, and a synergistic approach with, antibiotic therapy. Since they use entirely different mechanisms of action, phages are unaffected by resistance to conventional antibiotics. Phage containing certain enzymes also have the ability to disrupt bacterial biofilms, thus potentiating the effect of chemical antibiotics when used in combination with them.

In fact, the ability to isolate and develop phages for any of a broad range of bacterial targets, combined with their ability to disrupt bacterial biofilms, suggests strong potential for this approach in the control of bacterial infections. Published literature indicates that phages have the potential to be used as topical agents for the control of bacterial infection, and that such use is compatible with the approaches that have been shown to be effective in the treatment of wound injuries.

Bacteriophage therapy for the treatment of bacterial infections has been in constant use since 1917. Most of the research on phage-based therapy was conducted in the former Soviet Union prior to and immediately after World War II. While the West primarily focused resources into the development of chemical antibiotics, physicians and researchers in the Soviet Union were mass-producing phages and demonstrating their efficacy against a wide range of bacterial infections affecting the GI tract (dysentery), wounds (surgical and combat), skin (boils) and bone (osteomyelitis). While these studies are compelling, most lacked appropriate control group design or lacked control groups completely. Furthermore, the standard of care has changed substantially during the ensuing decades since those studies were performed, making claims of improved cure rates open for debate.

Despite numerous encouraging case studies, bacteriophage treatment was never adopted by Western medicine due to a lack of robust scientific evidence generated through systematically planned, controlled and regulated clinical trials. Recently, however, an increasing number of papers, reviews and books appearing on bacteriophage therapy indicate an increasing appetite among the scientific community and healthcare industry for developing bacteriophage therapy as part of mainstream medicine. Current biomedical technology is vastly superior to that available during the early days of bacteriophage therapy and our understanding of phage biology and the mechanisms of phage-bacterial host interaction have improved, along with advances in knowledge concerning bacterial infection. Although our knowledge of the biology, genetics and bactericidal efficacy of bacteriophages *in vitro* is impressive, less is known about their pharmacokinetic behavior *in vivo*, in particular in human subjects. To date very few human clinical trials have been conducted to modern standards in either the United States or Europe. In 2009, a U.S. Phase 1 clinical trial carried out at the Southwestern Regional Wound Care Center in venous ulcers using a mixture or “cocktail” of phages which individually attack different species of bacteria (*S. aureus*, *P. aeruginosa* and *E. coli*) was reported. The results of this trial showed this multi-bacteriophage preparation to be safe in trial subjects.

These trials, alongside the body of less well-conducted studies, suggest that phage therapy shows promise for treating infectious diseases caused by antibiotic-resistant bacteria. One, conducted by the Polish Academy of Sciences, started in 2005 and is treating a broad range of infections and clinical conditions associated with antibiotic-refractory infections. This work derives from a phage therapy clinic that has operated at this location. A second is the European Union-sponsored “Phagoburn” Phase 1/2 clinical trial, which is being conducted at multiple centers in France, Belgium and Switzerland. The project has been under way since June 2013, using a large phage mix for treatment of burn wounds infected with *E. coli* and *P. aeruginosa*.

Our Strategy

Our strategy is to use techniques of modern biotechnology and current state-of-the-art practices for drug development in concert with existing regulatory guidance to develop a pipeline of bacteriophage products that will destroy bacterial pathogens such as MRSA, which are resistant to chemical antibiotics. Our business strategy will apply state-of-the-art techniques in molecular biology and in clinical trial design to build upon the long successful history of using phages therapeutically to treat and cure infections.

In collaboration with the U.S. Army, we plan to study the safety and tolerability of our phage product (AmpliPhage-002) developed for treating *S. aureus* (MRSA) infections in a Phase 1 study. We expect this study to commence in the first half of 2015. If the Phase 1 study is successful, we plan to conduct a Phase 2 study of wounds and skin infections. Additionally, subject to the availability of adequate financing, we expect to continue product selection and formulation work for AmpliPhage-001, and following final product selection, in conjunction with leading Centers of Excellence in the UK, we would expect to conduct a Phase 1/2 study using AmpliPhage-001 to treat CF patients with *P. aeruginosa* lung infections. Through our collaboration agreement with the University of Leicester, we are also continuing to develop AmpiPhage-004 to treat patients suffering from serious gastrointestinal infections caused by *C. difficile*.

Recent Acquisitions

In January 2011, we completed the acquisition of Biocontrol, with the goal of developing their phage therapy programs using funding from the sale of our legacy gene therapy assets. Under the terms of our acquisition of Biocontrol, we issued 22,817,198 shares of our common stock to the shareholders of Biocontrol with a total fair value of approximately $8.6 million as of January 6, 2011, resulting in Biocontrol's former shareholders owning approximately 50% of our outstanding equity securities at the time. As a condition to closing the acquisition, Biocontrol raised approximately £200,000 (US$310,000) in working capital for use by us.

In November 2012, we acquired SPH, pursuant to our offer to acquire all outstanding shares of SPH from its shareholders under the terms of a Shareholder Sale Agreement and a Managers Warranty Deed, collectively referred to as the SPH Agreements, in exchange for up to 40,000,000 shares of our common stock. 20,000,000 of those shares were issued directly to the selling stockholders of SPH upon the closing of the acquisition, and the remaining 20,000,000 shares were issued and held in escrow. Of the escrow shares, 8,000,000 shares, referred to as Claims Shares, were subject to claims by us for breaches of representations by the selling stockholders of certain individual representations and certain additional representations made with respect to SPH itself and its operations by Dr. Anthony Smithyman and Mrs. Margaret Smithyman, the two largest shareholders of SPH, referred to as the Managers. The Claims Shares were released from escrow in November 2013, 12 months following the closing of the acquisition. The remaining 12,000,000 shares held in escrow, referred to as Contingent Shares, are to be released to the Managers upon the meeting (within 24 months of the closing) of three clinical and developmental milestones relating to SPH's phage therapy projects. At the satisfaction of each of those milestones, one third of the Contingent Shares will be released to the Managers. If, within 24 months of the closing, any of those milestones has not been met, as a result of our failure to use best endeavors to cause such milestones to occur or as a result of a natural and unavoidable catastrophe that prevents the milestone from occurring, the unsatisfied milestone will be deemed satisfied and we will be required to release the applicable number of Contingent Shares to the Managers. Contingent Shares relating to milestones that have not been released to the Managers as of the 24 th month following the acquisition, and that are not subject to claim by the Managers that such milestone was met or is otherwise due, will be returned to us. The Contingent Shares are also subject to claims for breaches of the representations being made by the Managers to the extent that the Claims Shares are insufficient to satisfy our claims under the terms of the SPH Agreements. Further, the Managers are not eligible to retain any dividends or other distributions by us that are allocable to unreleased Contingent Shares and have designated our President and Chairman of the Board, and each of them, as proxies to vote unreleased Contingent Shares.

In connection with our acquisition of SPH, we entered into certain other arrangements, including the repayment under a Loan Repayment Deed (as amended) of a $770,000 loan originally made by Cellabs Pty Ltd, or Cellabs, an Australian company affiliated with Dr. Smithyman, to SPH, a consulting agreement with Dr. Smithyman and the payment of $3,017 per month to Cellabs for our laboratory space in Australia. Under the terms of the Loan Repayment Deed, the loan from Cellabs to SPH was to be repaid and fully satisfied partly in cash and partly by issuing 2,000,000 shares of our common stock to Cellabs. As of December 31, 2013, $350,000 has been paid by us to Cellabs and all 2,000,000 shares have been issued. The SPH acquisition also included several phage therapy projects which had reached the pre-clinical or animal study stage, including the Brompton Hospital CF study, the Adelaide University MRSA chronic rhinosinusitis study and the University of Leicester *C. difficile* project. We believe that acquisition of SPH brings substantial phage scientific expertise and know-how to the Company sufficient to develop, manufacture and commercialize phage-based therapeutics. Under the terms of the consulting agreement with Dr. Smithyman, we were obligated to pay a fee of $10,000 per month to Dr. Smithyman, who provided management consulting services as an independent contractor for an initial term of 12 months ending October 2013. Between the acquisitions of Biocontrol and SPH, we believe that we are the leading therapeutically focused phage company in the world.

Strategic Alliances and Research Agreements

As discussed below, we have established collaborations with Intrexon, the U.S. Army and the University of Leicester, which provide us with access to the considerable scientific, developmental, and regulatory capabilities of our collaborators. We believe that our collaborations contribute to our ability to rapidly advance our product candidates, build our product platform and concurrently progress a wide range of discovery and development programs.

Exclusive Channel Collaboration with Intrexon

On March 29, 2013, we entered into the ECC with Intrexon that governs a collaboration arrangement in which AmpliPhi uses Intrexon's technologies directed towards the research, development and commercialization of new bacteriophage-based therapies to target specific antibiotic-resistant infections. We believe that combining the broadest and most advanced synthetic biology platform with our world-leading phage capabilities will lead to the development of innovative second-generation phage products. The ECC establishes committees comprised of representatives of the Company and Intrexon that govern activities related to the bacteriophage programs in the areas of project establishment and prioritization, as well as budgets and their approval, chemistry, manufacturing and controls, clinical and regulatory matters, commercialization efforts and intellectual property.

Intrexon is a publicly held biotechnology company focused on the industrial engineering of synthetic biology. According to Intrexon, their advanced bioindustrial engineering platform enables Better DNA™ technology by combining DNA control systems with corresponding advancements in modular transgene design, assembly and optimization to enable unprecedented control over the function and output of living cells.

Under the terms of the ECC, the Company will receive an exclusive, worldwide license to utilize Intrexon's proprietary technology and expertise for the standardized design and production of genetically modified bacteriophages, which we refer to collectively as the Bacteriophage Program. The ECC seeks to develop bacteriophage-containing human therapeutics for use in the treatment of bacterial infections associated with acute and chronic wounds, the treatment of acute and chronic *P. aeruginosa* lung infections and the treatment of infections of *C. difficile*, which we collectively refer to as AmpliPhi Products. The ECC grants the Company a worldwide license to use patents and other intellectual property of Intrexon in connection with the research, development, use, importing, manufacture, sale and offer for sale of AmpliPhi Products. Such license is exclusive with respect to any clinical development, selling, offering for sale or other commercialization of AmpliPhi Products, and otherwise is non-exclusive. Subject to limited exceptions, we may not sublicense the rights to Intrexon's technology without Intrexon's written consent.

Under the ECC, and subject to certain exceptions, we are responsible for, among other things, the performance of the Bacteriophage Program, including development, commercialization and certain aspects of manufacturing AmpliPhi Products. Intrexon is responsible for the costs of establishing manufacturing capabilities and facilities, subject to certain exceptions, for the bulk manufacture of products developed under the Bacteriophage Program, certain other aspects of manufacturing and costs of basic-stage research with respect to Intrexon Channel Technology and Intrexon materials, i.e., platform improvements and costs of filing, prosecution and maintenance of Intrexon's patents.

Subject to certain expense allocations and other offsets provided in the ECC, AmpliPhi has agreed to pay Intrexon on a quarterly basis tiered royalties on net sales derived in that quarter from the sale of AmpliPhi Products, which are based on or incorporate Intrexon's technology, calculated on a product-by-product basis. If AmpliPhi sublicenses a product developed under the collaboration with Intrexon, AmpliPhi has likewise agreed to pay Intrexon on a quarterly basis a certain percentage of revenues received from the sublicensee. Pursuant to the ECC, Intrexon received 24,000,000 shares of our common stock as an upfront technology access fee. We may also pay Intrexon up to $7.5 million in aggregate milestone payments for each product, payable either in cash or equity upon the achievement of certain events. Intrexon is also entitled to tiered royalties as a percentage in the upper-single digits of the net product sales of a product developed under the ECC.

The ECC is effective until terminated by either Intrexon or AmpliPhi. Intrexon may terminate the ECC if AmpliPhi fails to use diligent efforts to develop and commercialize AmpliPhi Products or if AmpliPhi elects not to pursue the development of an AmpliPhi Program identified by Intrexon that is a "Superior Therapy" as defined in the ECC. AmpliPhi has the right to terminate the ECC upon 90 days' written notice to Intrexon at any time.

Upon termination of the ECC, AmpliPhi may continue to develop and commercialize any AmpliPhi Product that, at the time of termination:

- is being commercialized by the Company;
- has received regulatory approval;
- is a subject of an application for regulatory approval that is pending before the applicable regulatory authority; or
- is the subject of an ongoing Phase 2 or completed Phase 3 clinical trial in the field.

AmpliPhi's obligation to pay royalties described above with respect to these "retained" products will survive termination of the ECC.

Global R&D Agreement with U.S. Army

In June 2013, we entered a CRADA with the USAMRMC and the WRAIR. The CRADA will focus on developing bacteriophage therapeutics to treat at least three types of infections: *S. aureus*, *E. coli* and *P. aeruginosa*. The increasing prevalence of antibiotic-resistant bacteria poses a serious threat to public health and military personnel and is a major problem in hospitals and clinics around the world. The initial indication will be wounds and skin infections from *S. aureus*, which is the leading pathogen in healthcare-associated infections in the United States as a whole, accounting for 30.4% of surgical site infections.

In connection with our CRADA with the U.S. Army, we submitted a Pre-IND briefing package to the FDA to obtain their feedback on our Chemistry, Manufacturing and Controls (CMC) program and plans for our first human study with our lead product, AmpliPhage-002 (*S. aureus*). The FDA endorsed our plan for progressing bacteriophage therapy to the clinic, specifically agreeing to our platform's manufacturing process, product specifications and the absence of any need of non-clinical toxicology to initiate our first Phase 1 study.

We plan to conduct our Phase 1 study at the WRAIR and to conduct further clinical trials at various sites throughout the world. We plan to initiate a Phase 1 feasibility and safety study in phage treatment of *S. aureus* infections in the first half of 2015. Upon successful completion of this study we plan to conduct a Phase 2 study of AmpliPhage-002 in patients with *S. aureus* infections.

We will retain global regulatory ownership and commercial rights to all products developed by us under the agreement. USAMRMC will gain access rights to any products developed. We also have the rights to exclusively license any intellectual property developed by USAMRMC under the collaboration on terms to be agreed upon.

The CRADA expires in June 2018 and can be terminated by either USAMRMC or AmpliPhi upon 60 days' written notice to the other party at any time.

University of Leicester Development Agreements

On April 24, 2013, we entered into the April Collaboration Agreement and on September 5, 2013, we entered into the "Leicester License Agreement" with the University of Leicester to develop a phage therapy that targets and kills all toxin types of *C. difficile*. We also entered into the August Collaboration Agreement with the University of Leicester and the University of Glasgow, whereby the University of Glasgow will carry out certain animal model development work.

Under these agreements, which we refer to collectively as the Leicester Development Agreements, we are funding the University of Leicester to carry out *in vi*