

(774)233-7300

(Registrant's telephone number, including area code)

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	The NASDAQ Capital Market
Preferred Stock Purchase Rights	

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

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. YES NO

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

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 during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files).
YES 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.

Edgar Filing: Biostage, Inc. - 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 the definitions of “large accelerated filer,” “accelerated filer” and “smaller reporting company” in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer Accelerated filer
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

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant, computed by reference to the price at which the common equity was last sold, or the average bid and asked price of such common equity, as of June 30, 2016 was approximately \$18,965,643. Shares of the registrant’s common stock held by each officer and director and each person known to the registrant to own 10% or more of the outstanding voting power of the registrant have been excluded in that such persons may be deemed affiliates. This determination of affiliate status is not a determination for other purposes.

At March 14, 2017, there were 37,116,570 shares of the registrant’s common stock issued and outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the Company’s definitive Proxy Statement in connection with the 2017 Annual Meeting of Stockholders (the “Proxy Statement”), to be filed within 120 days after the end of the Registrant’s fiscal year, are incorporated by reference into Part III of this Form 10-K. Except with respect to information specifically incorporated by reference in this Form 10-K, the Proxy Statement is not deemed to be filed as part hereof.

BIOSTAGE, INC.

TABLE OF CONTENTS

ANNUAL REPORT ON FORM 10-K

For the Year Ended December 31, 2016

INDEX

	Page
<u>PART I</u>	2
Item 1. <u>Business</u>	2
Item 1A. <u>Risk Factors</u>	18
Item 1B. <u>Unresolved Staff Comments</u>	32
Item 2. <u>Properties</u>	32
Item 3. <u>Legal Proceedings</u>	32
Item 4. <u>Mine Safety Disclosures</u>	32
<u>PART II</u>	33
Item 5. <u>Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities</u>	33
Item 6. <u>Selected Financial Data</u>	33
Item 7. <u>Management's Discussion and Analysis of Financial Condition and Results of Operations</u>	34
Item 7A. <u>Quantitative and Qualitative Disclosures About Market Risk</u>	38
Item 8. <u>Financial Statements and Supplementary Data</u>	38
Item 9. <u>Changes in and Disagreements with Accountants on Accounting and Financial Disclosure</u>	38
Item 9A. <u>Controls and Procedures</u>	38

Item 9B. <u>Other Information</u>	39
<u>PART III</u>	40
Item 10. <u>Directors, Executive Officers and Corporate Governance</u>	40
Item 11. <u>Executive Compensation</u>	40
Item 12. <u>Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters</u>	40
Item 13. <u>Certain Relationships and Related Transactions, and Director Independence</u>	40
Item 14. <u>Principal Accounting Fees and Services</u>	40
<u>PART IV</u>	
Item 15. <u>Exhibits, Financial Statement Schedules</u>	41
<u>Index to Consolidated Financial Statements</u>	F-1
<u>Signatures</u>	42

This Annual Report on Form 10-K contains statements that are not statements of historical fact and are forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934 (the "Exchange Act"), each as amended. The forward-looking statements are principally, but not exclusively, contained in "Item 1: Business" and "Item 7: Management's Discussion and Analysis of Financial Condition and Results of Operations." These statements involve known and unknown risks, uncertainties and other factors that 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 about management's confidence or expectations and our plans, objectives, expectations and intentions that are not historical facts. In some cases, you can identify forward-looking statements by terms such as "may," "will," "should," "could," "would," "seek," "expect," "plans," "aim," "anticipates," "believes," "estimates," "projects," "predicts," "intends," "think," "continue," "potential," "is likely," "permit," "objectives," "optimistic," "new," "goal," "target," "strategy" and similar expressions intended to identify forward-looking statements. These statements reflect our current views with respect to future events and are based on assumptions and subject to risks and uncertainties. Given these uncertainties, you should not place undue reliance on these forward-looking statements. We discuss many of these risks in detail under the heading "Item 1A. Risk Factors" beginning on page 18 of this Annual Report on Form 10-K. You should carefully review all of these factors, as well as other risks described in our public filings, and you should be aware that there may be other factors, including factors of which we are not currently aware, that could cause these differences. Also, these forward-looking statements represent our estimates and assumptions only as of the date of this report. We may not update these forward-looking statements, even though our situation may change in the future, unless we have obligations under the federal securities laws to update and disclose material developments related to previously disclosed information. Biostage, Inc. is referred to herein as "we," "our," "us," and "the Company."

PART I

Item 1. *Business.*

BUSINESS

We are a biotechnology company developing bioengineered organ implants based on our novel Cellframe™ technology. Our Cellframe technology is comprised of a biocompatible scaffold seeded with the patient's own stem cells. Our platform technology is being developed to treat life-threatening conditions of the esophagus, bronchus and trachea. By focusing on these underserved patients, we hope to dramatically improve the treatment paradigm for these patients. Our unique Cellframe technology combines the clinically proven principles of tissue engineering, cell biology and material science.

We believe that our Cellframe technology may provide surgeons a new paradigm to address life-threatening conditions of the esophagus, bronchus, and trachea due to cancer, infection, trauma or congenital abnormalities. Our novel technology harnesses the body's response and modulates it toward the healing process to restore the continuity and integrity of the organ. We are pursuing the Cellspan™ esophageal implant as our first product candidate to address esophageal atresia and esophageal cancer, and we are also developing our technology's applications to address conditions of the bronchus and trachea.

In collaboration with world-class institutions, such as Mayo Clinic and Connecticut Children's Medical Center, we are expecting to transition from a pre-clinical company to a clinical company in 2017. We plan to file an Investigational New Drug application, (IND) with the U.S. Food and Drug Administration (FDA) for our Cellspan esophageal implant in the third quarter of 2017 and expect to begin first in human clinical trials in the fourth quarter of 2017.

Our Cellframe technology platform: how it works

Our Cellframe process begins with the collection of an adipose (fat) tissue biopsy from the patient followed by the use of standard tissue culture techniques to isolate and expand the patient's own (autologous) mesenchymal (multipotent) stem cells, or MSC. The cells are seeded onto a biocompatible, synthetic scaffold, produced to mimic the dimensions of the organ to be regenerated, and incubated in a proprietary organ bioreactor. The scaffold is electrospun from polyurethane (PU) to form a non-woven, hollow tube. The specific microstructures of the Cellspan implants are designed to allow the cultured cells to attach to and cover the scaffold fibers.

We have conducted large-animal studies to investigate the use of the Cellspan implants for the reconstitution of the continuity and integrity of tubular shape organs, such as the esophagus and the large airways, following a full circumferential resection of a clinically relevant segment, just as would occur in a clinical setting. We announced favorable preliminary preclinical results of large-animal studies for the esophagus, bronchus and trachea in November 2015. Based on the results of those studies, we chose the esophagus to be the initial focus for our organ regeneration technology.

*Illustration of intersection of Cellspan esophageal implant and native
esophagus at time of implant and proposed mechanism of action*

In May 2016, we reported an update of results from additional, confirmatory pre-clinical large-animal studies. We disclosed that the studies had demonstrated in a predictive large-animal model the ability of our Cellspan organ implant to successfully stimulate the regeneration of a section of esophagus that had been surgically removed. Cellspan esophageal implants, consisting of a proprietary biocompatible synthetic scaffold seeded with the recipient animal's own stem cells, were surgically implanted in place of the esophagus section that had been removed. After the surgical full circumferential resection of a portion of the thoracic esophagus, the Cellspan implant stimulated the reconstitution of full esophageal structural integrity and continuity.

*Illustration of esophageal reconstitution over Cellspan esophageal
implant following time of implant and proposed mechanism of action*

Study animals were returned to a solid diet three weeks after the implantation surgery. The scaffold portions of the Cellspan implants, which are intended to be in place only temporarily, were retrieved approximately three weeks post-surgery via the animal's mouth in a non-surgical endoscopic procedure. Within 2.5 to 3 months, a complete inner epithelium layer and other specialized esophagus tissue layers were regenerated. As of March 1, 2017, two animals in the study have not been sacrificed and are alive at eleven months and one year, respectively. These animals have demonstrated significant weight gain, appear healthy and free of any significant side effects and are receiving no specialized care.

Platform technology in life-threatening orphan indications

In November 2016, we were granted Orphan Drug Designation for our Cellspan esophageal implant by the FDA to restore the structure and function of the esophagus subsequent to esophageal damage due to cancer, injury or congenital abnormalities. Orphan drug designation provides a seven-year marketing exclusivity period against competition in the U.S. from the date of a product's approval for marketing. This exclusivity would be in addition to any exclusivity we may obtain from our patents. Additionally, orphan designation provides certain incentives, including tax credits and a waiver of the Biologics License Application fee. We also plan to apply for orphan drug designation for our Cellspan esophageal implant in Europe. Orphan drug designation in Europe provides market exclusivity in Europe for ten years from the date of the product's approval for marketing.

We are now advancing the development of our Cellframe technology, specifically a Cellspan esophageal implant, in large-animal studies with collaborators. As we believe that our recent studies provided sufficient confirmatory proof of concept data, we have initiated the Good Laboratory Practice (GLP) studies to demonstrate that our technology, personnel, systems and practices are sufficient for advancing into human clinical trials. In order to seek approval for the initiation of clinical trials for Biostage Cellspan esophageal implants in humans, GLP studies to support the safety of the Cellspan esophageal implant are required to submit an Investigational New Drug (IND) application with the FDA.

Our goal is to submit an IND filing in the third quarter of 2017.

Our product candidates are currently in development and have not yet received regulatory approval for sale anywhere in the world.

Changing the surgical treatment of Esophageal Cancer

Illustration of esophageal cancer site *Illustration of potential human application of Cellspan esophageal implant at site of esophageal cancer (depicting implant prior to esophageal tissue reconstitution over implant)*

According to the World Health Organization's International Agency for Research on Cancer, there are approximately 450,000 new cases of esophageal cancer worldwide each year. A portion of all patients diagnosed with esophageal cancer are treated via a surgical procedure known as an esophagectomy. The current standard of care for an esophagectomy requires a complex surgical procedure that involves moving the patient's stomach or a portion of their

colon into the chest to replace the portion of esophagus resected by the removal of the tumor. These current procedures have high rates of complications, and can lead to a severely diminished quality of life and require costly ongoing care. Our Cellspan esophageal implants aim to provide a simpler surgical procedure, with reduced complications, that may result in a better quality of life after the operation and reduce the overall cost of these patients to the healthcare system.

Congenital Abnormalities - Esophageal Atresia: a much needed focus on children

Each year, several thousand children worldwide are born with a congenital abnormality known as esophageal atresia, a condition where the baby is born with an esophagus that does not extend completely from the mouth to the stomach. When a long segment of the esophagus is lacking, the current standard of care is a series of surgical procedures where surgical sutures are applied to both ends of the esophagus in an attempt to stretch them and pull them together so they can be connected at a later date. This process can take weeks and the procedure is plagued by serious complications and may carry high rates of failure. Such approach also requires, in time, at least two separate surgical interventions. Other options include the use of the child's stomach or intestine that would be pulled up into the chest to allow a connection to the mouth. We are working to develop a Cellspan esophageal implant solution to address newborns' esophageal atresia, that could potentially be life-saving or organ-sparing, or both.

Our Mission and Our Strategy

Our mission is to be the leading developer and supplier of bioengineered organ implants for restoring organ function for patients with life-threatening conditions of the esophagus, the bronchus and the trachea. Our business strategy to accomplish this mission includes:

Targeting life-threatening medical conditions. We are focused on creating products to help physicians treat life-threatening conditions like esophageal cancer, central lung cancer and damage to the trachea caused by cancer, trauma or infection. We are also developing products for the treatment of congenital abnormalities of the esophagus and the airways. We are not targeting less severe conditions that have reasonable existing treatment options. Solutions for life-threatening medical conditions present a favorable therapeutic index, or risk/benefit relationship, by providing the opportunity of a significant medical benefit for patients who have poor or no treatment alternatives. We believe that product candidates targeting life-threatening medical conditions may be eligible for review and approval by regulatory authorities under established expedited review programs, which may result in savings of time in the regulatory approval process. Also, we believe that products targeting life-threatening medical conditions may be more likely to receive favorable reimbursement compared with treatments for less critical medical conditions.

Developing products that have a relatively short time to market. Since the number of patients diagnosed with esophageal cancer in the U.S. each year is relatively small, we expect the number of patients that we would likely need to enroll in a clinical trial will also be relatively small. A small number of patients implies a relatively fast enrollment time and a less expensive clinical development program. Therefore, we expect to be able to conduct a clinical trial in a relatively short period of time compared to clinical trials in indications with larger patient populations. We intend to work closely with regulatory agencies and clinical experts to design and size the clinical studies appropriately based on the specific conditions our products are intended to treat.

Using our Cellframe technology as a platform to address multiple organs. We believe that pre-clinical data we have produced to date may suggest that our Cellframe technology is a novel and innovative approach to restoring organ function that may provide an ability to develop products that would address life-threatening conditions impacting organs like the esophagus, bronchus and trachea, and perhaps lower portions of the gastrointestinal (GI) tract. We believe that our Cellframe technology may allow physicians to treat certain life-threatening conditions in ways not currently possible, and in some combination, to save patients' lives, avoid or reduce complications experienced in the current standard of care, and improve the patients' quality of life, while at the same time reducing the overall cost of patient care to the healthcare system.

Supplying the finished organ implant to the surgeon. Our technology includes our proprietary organ bioreactor, as well as our proprietary biocompatible scaffold that is seeded with the patient's own cells. We believe there is considerable value in supplying the final cell-seeded scaffold implant to the surgeon so that the hospital and surgeon may focus solely on performing the implantation.

Collaborating with leading medical and research institutions. We have and will continue to collaborate with leading medical and research institutions. We have a co-development initiative with Mayo Clinic for regenerative medicine organ implant products for the esophagus and airways, and we are currently conducting large-animal studies with Mayo Clinic to develop our Cellframe technology. We are also collaborating with Connecticut Children's Medical Center on a co-development project to research regenerative medicine-based solutions to esophageal atresia. We believe the use of our product candidates by leading surgeons and institutions will increase the likelihood that other surgeons and institutions will use our products.

Our Technology

Our Cellframe technology is comprised of our proprietary bioengineered organ scaffold seeded with the patient's own stem cells in our proprietary organ bioreactor prior to implantation. We believe that our Cellframe technology combines a highly-engineered, biocompatible scaffold and a robust population of cells that, by tapping into the stem cell niche of the surrounding native tissue after implantation, may potentially enable a tubular organ to remodel or regenerate tissue to close the gap created by a surgical resection of a portion of that organ. This unique combination of technologies, developed through our extensive testing performed during the last two years, may potentially provide solutions to life-threatening conditions for patients with unmet medical needs.

We believe that our new technology is unique, in that its mode of action appears to be different from other tissue engineering organ scaffold products developed previously, of which we are aware. Prior to our development of the Cellframe technology, our approach attempted to implant an organ scaffold that would be incorporated into the patient's body by the surrounding native tissue growing into the scaffold. To our knowledge, all previous research and development efforts by other investigators were based on that same concept. Our Cellframe technology appears to work very differently. We believe that the unique combination of our highly-engineered organ scaffold with a population of the patient's own mesenchymal stem cells enables an organ to develop new native tissue around our scaffold, but not into it, so the scaffold acts as a type of frame or staging for the new tissue. As a result, our scaffold is not incorporated into the body. Instead, it is retrieved from the body via an endoscopic or bronchoscopic procedure, not surgically, after sufficient tissue remodeling and regeneration has occurred to restore the organ's integrity and function.

A Cellframe technology-based organ implant includes two key components: a biocompatible synthetic scaffold and the patient's own stem cells.

Biocompatible Scaffold Component

Our proprietary biocompatible scaffold component of the Cellspan esophageal implant is constructed primarily of polyurethane (PU; a plastic polymer). This material was chosen based on extensive testing of various materials. The scaffold is made using a manufacturing process known as electrospinning. The combination of the electrospinning process, which provides control over the desired microstructure of the scaffold fabric, with the PU results in a scaffold that we believe has favorable biocompatibility characteristics.

The Patient's Cells

Based on current pre-clinical development efforts, the cells we seed onto the scaffold are obtained from the patient's adipose tissue (abdominal fat). This fat tissue is obtained from a standard biopsy before the implant surgery. Mesenchymal stem cells are extracted and isolated from the adipose tissue biopsy. The isolated cells are then expanded, or grown, for a short period prior to surgery in order to derive a sufficient cell population to be seeded on the scaffold. The cells are then seeded on the scaffold in our proprietary organ bioreactor and incubated there before the implant surgery.

We believe the Cellspan esophageal implant has the potential to provide a major advance over the current therapeutic options for treating esophageal cancer, damage from infection or trauma and congenital abnormalities. We believe our Cellframe technology has the potential to overcome the major challenges in restoring organ function for a damaged esophagus. With our Cellspan esophageal implant we are developing a surgical procedure that has the objective of reconstituting the continuity of the patient's esophagus without having to relocate another organ in its place. In addition, by reducing or eliminating complications that occur in the current standard of care, we expect to reduce the costs of addressing and treating those additional complications. Because these substantial costs can be reduced or even eliminated with our technology, we believe our products, if successfully developed, can help save lives, improve the quality of life for patients and reduce overall healthcare costs.

Further, human embryonic stem cells are not part of any of our implant product candidates. This eliminates both the medical risks and ethical controversy associated with regenerative medicine approaches that use human embryonic stem cells.

Unmet Patient Needs and Cellspan Implant Solutions

Esophageal Cancer

There are approximately 456,000 new diagnoses of esophageal cancer globally each year, according to the World Health Organization's International Agency for Research on Cancer. According to the American Cancer Society, there are approximately 17,000 new diagnoses of esophageal cancer in the U.S. each year, and there are more than 15,000 deaths from esophageal cancer each year. Esophageal cancer is very deadly - the five-year survival rate for people with esophageal cancer is 18% in the U.S. Approximately 5,000 esophagectomy surgeries occur in the U.S. annually to treat esophageal cancer, and approximately 10,000 esophagectomies occur in Europe annually. We believe that our Cellspan esophageal implant, if approved, has the potential to provide a major advance over the current esophagectomy procedures for addressing esophageal cancer, which have high complication and morbidity rates.

The current standard of care for the esophagectomy requires either (A) a gastric pull-up, where the stomach is cut and sutured into a tubular shape, then pulled up through the diaphragm to replace a portion of the esophagus resected by the removal of the cancerous tumor; or (B) a colon interposition, where a portion of the colon is resected and used to replace the portion of the esophagus resected by the removal of the cancerous tumor. Esophagectomies have 90-day mortality rates of up to 19%. Serious complications, such as leakage at the anastomoses, which can lead to infections and sepsis, and pulmonary complications, such as impaired pulmonary function or pneumonia, occur in up to 30% of esophagectomy cases. Other complications from esophagectomies, such as a narrowing of the esophagus post-surgery, gastroesophageal reflux and dumping syndrome (repetitive nausea, dizziness and vomiting) can also pose significant quality of life issues for patients.

We believe that the Cellspan esophageal implant has the potential to provide physicians a new, simpler procedure to restore organ function while significantly reducing complication and morbidity rates compared with the current standard of care, and without creating significant quality of life issues for patients.

Esophageal Atresia

Esophageal Atresia (EA) is a rare congenital abnormality in which a baby is born without part of the esophagus. About 1 in 4,000 babies in the U.S. is born with EA. In some cases, the two sections can be connected surgically. However, in cases where the gap is too great for a simple surgical reconnection, the current standard of care is a gastric pull-up, a colon interposition, or a procedure known as the Foker process. In the Foker process, traction devices are surgically attached to the two ends of the esophagus. Traction is then applied, usually for several weeks during which time the baby remains in an Intensive Care Unit, to stimulate the ends of the esophagus to grow and

narrow the gap. If the Foker process is successful in narrowing the gap sufficiently, a second surgery is necessary to connect the two ends of the esophagus. In addition to the Foker process being complex, it is also a very expensive procedure, because the baby will normally be several months in hospital for the process.

We believe that a pediatric Cellspan esophageal implant may provide pediatric surgeons with a better procedure to treat EA that would result in a connected esophagus with higher success rates, lower complications and lower overall costs to the healthcare system.

Central Lung Cancer

Lung cancer is the most common form of cancer and the most common cause of death from cancer worldwide. There are more than 450,000 new lung cancer diagnoses annually in the U.S. and Europe. In approximately 25% of all lung cancer cases, the cancerous tumor resides only in a bronchus and not in the lobes of the lungs, and is known as central lung cancer. Approximately 33,000 central lung cancer cases diagnosed in the U.S. and Europe are Stage I and II and are considered eligible for surgical resection, often with adjuvant chemotherapy and radiation. Approximately 5,000 of those patients are treated via pneumonectomy, a surgical procedure involving the resection of the cancer tumor, the whole bronchus below the tumor and the entire lung to which it is connected. It is a complex surgery and, due to the removal of a lung, results in a 50% reduction in the patient's respiratory capacity. The procedure has reported rates of post-surgical (in hospital) mortality of 8% to 15%. Complication rates associated with pneumonectomy are reported as high as 50%, and include post-operative pneumonia, supraventricular arrhythmias and anastomotic leakage, placing patients at significant mortality risk post-discharge.

We believe that a Cellspan bronchial implant, once developed and approved for marketing, has the potential to provide physicians a treatment alternative superior to the sleeve pneumonectomy to address central lung cancer, a simpler procedure to restore organ function of the bronchus without sacrificing one of the patient's lungs, resulting in fewer post-surgery complications, improved mortality rates and improved quality of life for the patient.

Life-threatening conditions of the Trachea

There are approximately 8,000 patients per year in the U.S. and Europe who suffer from a condition of the trachea that put the patient at high risk of death. These conditions can be due to tracheal trauma, tracheal stenosis or trachea cancer. There are approximately 40,000 tracheal trauma patients diagnosed each year in the U.S. Of those, approximately 1,000 are severe enough to need surgical resection procedures. Tracheal stenosis is a rare complication from tracheostomies, but may have a devastating impact on respiratory function for patients. Approximately 2,000 patients are diagnosed with stenosis from tracheostomy in the U.S. each year. Trachea cancer is a very rare but extremely deadly cancer. Trachea cancer patients in the U.S. have a median survival of 10 months from diagnosis and a 5-year survival of only 27%. There were approximately 200 cases of primary trachea cancer diagnosed in the U.S. in 2013. Based on these facts, we estimate that there are approximately 8,000 patients in the U.S. and Europe with conditions of the trachea that put them at high risk of death, but for whom there is currently no clinically effective

tracheal implant or replacement method currently available.

We believe that a Cellspan tracheal implant may potentially provide physicians a treatment to re-establish the structural integrity and function of a damaged or diseased trachea to address life-threatening conditions due tracheal trauma, stenosis or cancer.

Our History

We were incorporated under the laws of the State of Delaware on May 3, 2012 by Harvard Bioscience, Inc. (“Harvard Bioscience”) to provide a means for separating its regenerative medicine business from its other businesses. Harvard Bioscience decided to separate its regenerative medicine business into our company, a separate corporate entity (the “Separation”), and it spun off its interest in our business to its stockholders in November 2013. Since the Separation we have been a separately-traded public company and Harvard Bioscience has not been a stockholder of our common stock or controlled our operations. Following the Separation, we continued to innovate our bioreactors based on our physiology expertise, we developed our materials science capabilities and we investigated and developed a synthetic tracheal scaffold. In April 2014, Saverio LaFrancesca, M.D., joined our company as Chief Medical Officer. By that time we had built and staffed cell biology laboratories at our Holliston facility, to give ourselves the ability to perform and control our scientific investigation and developments internally. At that point, we began the second phase of our company’s development.

In mid-2014, under Dr. LaFrancesca’s leadership, we increased the pace of our scientifically-based internal analysis and development of our first-generation tracheal implant product, the HART-Trachea. From large-animal studies conducted thereafter we found that the product elicited an unfavorable inflammatory response after implantation, which required additional development and testing. These requirements extended our expectations regarding our regulatory milestones and we announced the additional testing and extended milestone expectations in January 2015. During 2015 we isolated and tested all major variables of the organ scaffold and the cell source and protocols, examining the effects of alternatives against the then-existing product approach. Through extensive *in vitro* preclinical studies, and small-animal and large-animal studies, we made dramatic improvements, and discovered that the mechanism of action of this new approach was very different from our hypothesis regarding that of the first-generation product. We call this new implant approach our Cellframe technology. Our Cellframe technology uses a different scaffold material and microstructure, a different source and concentration of the patient’s cells and several other changes from our earlier trachea initiative. We believe that our Cellframe technology, although built on learnings from our earlier-generation product initiative, represents a new technology platform resulting from our rigorous science and development. We see the development of our Cellframe technology platform as the beginning of a new, third phase in our company’s progression.

We discontinued development of our earlier initiative in 2014; that first-generation product approach was significantly different from our new Cellframe technology and Cellspan product candidates currently in development. We have focused our development efforts on our Cellframe technology and Cellspan product candidates, which we have and will continue to develop internally, and with our collaborators, via a rigorous scientific development process. As a result, we believe that prior statements by others regarding the patients whose surgeries utilized our HART bioreactor or HART-Trachea scaffold, or such products, are not pertinent to our Cellframe technology or Cellspan products, or their respective future development.

Clinical Trials

In order to market our product candidates, we will need to successfully complete clinical trials. The initial indication for which we intend to seek FDA approval will be to restore the function of the esophagus subsequent to esophageal damage or stenosis due to cancer, injury or infection.

Because esophageal cancer affects only approximately 17,000 patients per year in the U.S. we anticipate that our clinical trials will involve relatively few patients. Therefore, once commenced, we expect to be able to conduct a clinical trial in a relatively short period of time compared to clinical trials in indications with larger patient populations. We intend to work closely with regulatory agencies and clinical experts to design and size the clinical studies appropriately based on the specific conditions our products are intended to treat. We also intend to request expedited review from the FDA for the Cellspan esophageal implant product. Receipt of expedited review would reduce the overall time through the regulatory approval process.

We intend to pursue regulatory approval for the Cellspan esophageal implant in the U.S., Canada and Europe initially. Following clinical trials in other foreign markets, we expect to pursue regulatory approval for the Cellspan esophageal implant in those foreign markets, as well.

Research and Development

Our primary research and development activities are focused in three areas: materials science, cell biology and engineering. In materials science, we focus on designing and testing biocompatible organ scaffolds, testing the structural integrity and the cellularization capacities of the scaffolds. In cell biology, we focus on developing and testing isolation and expansion protocols, cell characterization and fate studies, investigating the effects of various cell types and concentrations, evaluating the biocompatibility of scaffolds, experimenting with different cell seeding methodologies, and developing protocols for implantation experiments. Our engineering group supports the materials science and cell biology groups across an array of their activities, i.e. designing, engineering and making our proprietary organ bioreactors. All three of our R&D groups combine to plan and execute the in vitro studies. A fundamental part of our R&D effort in developing the Cellframe technology has been dedicated to the discovery and development of small and large animal model studies. The large-animal model employs the use of Yucatan mini-pigs. Our Cellspan scaffolds were implanted in the cervical portion as well as the thoracic portion of the esophagus and the airways in studies to date. As of December 31, 2016, we employed 14 full-time scientists and engineers and we also hire other consultants and part-time employees from time to time.

In addition to our in-house engineering and scientific development team, we collaborate with leaders in the field of regenerative medicine who are performing the fundamental research and surgeries in this field to develop and test new products that will advance and improve the procedures being performed. As these procedures become more common, we will work with our collaborators to further enhance our products to make them more efficient and easier to use by surgeons. In the U.S., our principal collaborations have been with Mayo Clinic and Connecticut Children's Medical Center. Collaboration typically involves us developing new technologies specifically to address issues these researchers and clinicians face. In certain instances, we have entered into agreements that govern the ownership of the

technologies developed in connection with these collaborations.

We incurred approximately \$4.8 million and \$7.6 million of research and development expenses in 2015 and 2016, respectively. As we have not yet applied for or received regulatory approval to market any clinical products and sales of our research bioreactor products have not been significant in relation to our operating costs, no significant amount of these research and development costs have been passed on to our customers.

Manufacturing

For our scaffolds we use a process called electrospinning to create the fabric part of the scaffold. Electrospinning is a well-known fabrication process. It is useful for cell culture applications as it can create extremely thin fibers (much thinner than a human hair) that can make a fabric with pores approximately the same size as a cell. The electrospinning process parameters can be tuned to create a structure that is very similar to the natural structure of the collagen fibers in human extracellular matrix. Our Cellspan scaffolds are made from polyurethane, an inert polymer that is not bioresorbable. However, we also perform studies on the use of scaffolds made from bioresorbable materials. While we do not manufacture the cells, as they will come from the patient's adipose tissue, for regulatory purposes we are responsible for the quality control of the cells and the seeding of the cells onto the scaffold in the bioreactor. For this we have, in collaboration with our partners, developed standard operating procedures for the seeding of cells on the scaffold. For U.S. clinical trials we anticipate that the seeding will be performed in an automated version of our bioreactor at a pre-qualified third-party contract manufacturer using current Good Manufacturing Procedures (cGMP) using our proprietary protocol and under the supervision of our staff.

For our scaffolds, our primary materials are medical-grade plastic resins and solvents used to liquefy the resins in our manufacturing process. These materials are readily available from a variety of suppliers and do not currently represent a large proportion of our total costs. For our bioreactors, we perform final assembly and testing of components that we buy from third parties like machine shops, parts distributors, molding facilities and printed circuit board manufacturers. These operations are performed primarily at our Holliston, MA headquarters.

Sales and Marketing

We expect that most surgeries using the Cellspan esophageal implant product will be performed at a relatively small number of major hospitals in the U.S., Canada and European countries that will establish themselves as specialized centers of excellence. We believe that a relatively small number of centers of excellence in each country would be able to treat a very large percentage of that country's patients annually, given the expected number of patients to be treated each year. So, we expect our markets to be served by a concentrated number of treatment centers. Further, our three Cellspan product candidates are for the esophagus, the bronchi and the trachea, three organs all treated by thoracic surgeons. Therefore, all three products, once approved, would be marketed primarily to physicians practicing in a single surgical specialty, so we expect that the total number of physicians using our products will be a much smaller population than if our products were to be used by physicians in multiple areas of surgical specialties. Due to

our expectation of a population of physicians in one surgical specialty being the primary users of our products in a concentrated number of centers of excellence in each national market, we expect to be able to support our markets with a fairly small field sales force.

We expect to price the product commensurate with the medical value created for the patient and the costs avoided with the use of our product. We further expect to be paid by the hospital that buys the product from us. Finally, we expect that the hospital would seek reimbursement from payers for the entire transplant procedure, including the use of our products.

Harvard Bioscience is the exclusive distributor for the research versions of our organ bioreactors. Harvard Bioscience can only sell those products to the research markets in accordance with the terms of our distribution agreement. We retain all rights to manufacture and sell all our products for clinical use.

Intellectual Property and Related Agreements

We actively seek to protect our products and proprietary information by means of U.S. and foreign patents, trademarks and contractual arrangements. Our success will depend in part on our ability to obtain and enforce patents on our products, processes and technologies to preserve our trade secrets and other proprietary information and to avoid infringing on the patents or proprietary rights of others.

We have rights in the patent and the patent applications listed below. The patent or patents that may issue based on the patent applications are scheduled to expire as provided below:

Patent/Technology	Jurisdiction	Expiration
Patent application covering aspects of synthetic scaffolds and organ and tissue transplantation	U.S.	2032
Patent application relating to methods and compositions for producing elastic scaffolds for use in tissue engineering	U.S.	2033
Patent application relating to support configurations for tubular tissue scaffolds, and airway scaffold configurations	U.S., Europe	2033
Patent application relating to methods and compositions for promoting the structural integrity of scaffolds for tissue engineering	U.S.	2033
Issued Patent covering methods for analyzing engineered tissues	U.S.	2033
Patent application covering aspects of clinical scale bioreactors and tissue engineering	U.S., Europe	2030
Issued Patent covering aspects of liquid distribution in a rotating bioreactor	Germany	2031
Issued Patent covering aspects of liquid distribution in a rotating bioreactor	Germany	2021
Patent application covering aspects of liquid distribution in a rotating bioreactor	U.S.	2032
Patent application relating to bioreactors with supports to facilitate culturing organs	U.S.	2034
Patent application relating to bioreactor adaptors for tubular tissue scaffolds	U.S.	2034
Patent applications relating to engineered hybrid organs	U.S.	2034
Patent applications relating to infrared-based methods for evaluating tissue health including methods for evaluating burns	U.S.	2033
Patent applications relating to methods and compositions for esophageal repair	U.S.	2036

We also rely on unpatented proprietary technologies in the development and commercialization of our products. We also depend upon the skills, knowledge and experience of our scientific and technical personnel, as well as those of our advisors, consultants and other contractors. To help protect our proprietary know-how that may not be patentable, and our inventions for which patents may be difficult to enforce, we rely on trade secret protection and confidentiality agreements to protect our interests. To this end, we require employees, consultants and advisors to enter into agreements that prohibit the disclosure of confidential information and, where applicable, require disclosure and assignment to us of the ideas, developments, discoveries and inventions that arise from their activities for us. Additionally, these confidentiality agreements require that our employees, consultants and advisors do not bring to us,

or use without proper authorization, any third party's proprietary technology.

Exclusive License Agreement and Sponsored Research Agreement - InBreath Bioreactor

We had an exclusive license agreement with Sara Mantero and Maria Adelaide Asnaghi to intellectual property rights relating to our earlier generation InBreath Bioreactor. Under this agreement, we had worldwide rights to intellectual property (including patents, data, and know-how) relating to the hollow organ bioreactor, related techniques, and improvements thereof. We had exclusive worldwide rights to make, use and sell the hollow organ bioreactor, and the right to grant sublicenses and distribution rights. Under this agreement, we were obligated to pay the licensor royalties at various percentage rates in the low to mid-single digits pertaining to any applicable bioreactors we sell. This agreement terminated on August 6, 2016.

We have entered into a sponsored research agreement with Sara Mantero, Maria Adelaide Asnaghi, and the Department of Bioengineering of the Politecnico Di Milano, or PDM. Under the terms of this agreement, PDM is required to use its facilities and best efforts to conduct a research program relating to the development of bioreactors, clinical applications, and automated seeding processes. We are required to provide engineering support to PDM with respect to bioreactor designs. Intellectual property developed by PDM or its employees, including Dr. Mantero or Ms. Asnaghi, under this sponsored research agreement will be owned by Dr. Mantero or Ms. Asnaghi and covered by our exclusive license agreement described above. In addition, we have an option to an exclusive license for intellectual property relating to new technology that may not be covered by the exclusive license agreement. We will own any inventions and discoveries that we solely develop in connection with the research program and any inventions and discoveries that are jointly developed in connection with the research program will be owned jointly by the parties. On February 28, 2017, we provided 90 days' prior written notice to terminate the sponsored research agreement.

Sublicense Agreement with Harvard Bioscience

We have entered into a sublicense agreement with Harvard Bioscience pursuant to which Harvard Bioscience has granted us a perpetual, worldwide, royalty-free, exclusive, except as to Harvard Bioscience and its subsidiaries, license to use the mark "Harvard Apparatus" in the name Harvard Apparatus Regenerative Technology. The mark "Harvard Apparatus" is used under a license agreement between Harvard Bioscience and Harvard University, and we have agreed to be bound by such license agreement in accordance with our sublicense agreement. We currently have no affiliation with Harvard University.

Separation Agreements with Harvard Bioscience

On November 1, 2013, to effect the Separation, Harvard Bioscience distributed all of the shares of our common stock to the Harvard Bioscience stockholders (the "Distribution"). Prior to the Distribution Harvard Bioscience contributed the

assets of its regenerative medicine business, and approximately \$15 million in cash, to our company to fund our operations following the Distribution.

In connection with the Separation and immediately prior to the Distribution, we entered into a Separation and Distribution Agreement, Intellectual Property Matters Agreement, Product Distribution Agreement, Tax Sharing Agreement, Transition Services Agreement, and Sublicense Agreement with Harvard Bioscience to effect the Separation and Distribution and provide a framework for our relationship with Harvard Bioscience after the Separation. These agreements govern the current relationships among us and Harvard Bioscience and provided for the allocation among us and Harvard Bioscience of Harvard Bioscience's assets, liabilities and obligations (including employee benefits and tax-related assets and liabilities) attributable to periods prior to the Separation.

Government Regulation

Any product that we may develop based on our Cellframe technology, and any other clinical products that we may develop, will be subject to considerable regulation by governments. We were in the past informed by the FDA that our previous-generation tracheal product candidate would be regulated under the Biologics License Application, or BLA, pathway in the U.S. and we were informed by the European Medicines Agency (EMA) that the previous generation tracheal product would be regulated under the Advanced Therapy Medicinal Products(ATMP), pathway in the EU. On October 18, 2016, we also received written confirmation from FDA's Center for Biologics Evaluation and Research(CBER), that FDA intends to regulate our Cellspan esophageal implant as a combination product under the primary jurisdiction of CBER. We further understand that CBER may choose to consult or collaborate with the FDA's Center for Devices and Radiological Health (CDRH), with respect to the characteristics of the synthetic scaffold component of our product based on CBER's determination of need for such assistance. Although our Cellframe technology differs in design and performance from the first generation product candidate, we expect that Cellframe-based products will be regulated by the FDA and EMA under the same pathways as the first generation tracheal product candidate. This expectation is based on the fact that the Cellframe technology is centered on the delivery of the patient's own cells seeded on an implanted synthetic scaffold in order to restore organ function and our belief that the cells provide the primary mode of action. Of course, it is possible that some of our current and future products may use alternative regulatory pathways.

Combination Product/Biologic

Government Regulation Combination Products/Biologics

We believe that products derived from our Cellframe technology may be defined as combination products consisting of two or more regulated components, a biologic and a medical device. In the U.S., a combination product usually is assigned by the FDA to one of the agency's centers, such as CBER, or CDRH, with the chosen center to take the lead in pre-marketing review and approval of the combination product. Other FDA centers also may review the product in regard to matters that are within their expertise. The FDA selects the lead center based on an assessment of the combination product's "primary mode of action." Some products also may require approval or clearance from more than one FDA center.

To determine which FDA center or centers will review a combination product submission, companies may submit a Request for Designation to the FDA. Those requests may be handled formally or informally. In some cases, jurisdiction may be determined informally based on FDA experience with similar products. However, informal jurisdictional determinations are not binding on the FDA. Companies also may submit a formal Request for Designation to the FDA Office of Combination Products. The Office of Combination Products will review the request and make its jurisdictional determination within 60 days of receiving a Request for Designation. We believe that regenerative medicine products containing cells will be reviewed by CBER, possibly with CBER's consultation with CDRH.

Domestic Regulation of Our Products and Business

The testing, manufacturing, and potential labeling, advertising, promotion, distribution, import and marketing of our products are subject to extensive regulation by governmental authorities in the U.S. and in other countries. In the U.S., the FDA, under the Public Health Service Act, the Federal Food, Drug and Cosmetic Act, and its implementing regulations, regulates biologics and medical device products.

The labeling, advertising, promotion, marketing and distribution of biopharmaceuticals, or biologics and medical devices also must be in compliance with the FDA and U.S. Federal Trade Commission (FTC), requirements which include, among others, standards and regulations for off-label promotion, industry sponsored scientific and educational activities, promotional activities involving the internet, and direct-to-consumer advertising. The FDA and FTC have very broad enforcement authority, and failure to abide by these regulations can result in penalties, including the issuance of a warning letter directing us to correct deviations from regulatory standards and enforcement actions that can include seizures, injunctions and criminal prosecution. Recently, promotional activities for FDA-regulated

products of other companies have been the subject of enforcement action brought under healthcare reimbursement laws and consumer protection statutes. In addition, under the federal Lanham Act and similar state laws, competitors and others can initiate litigation relating to advertising claims. Further, we are required to meet regulatory requirements in countries outside the U.S., which can change rapidly with relatively short notice.

The FDA has broad post-market and regulatory enforcement powers. Manufacturers of biologics and medical devices are subject to unannounced inspections by the FDA to determine compliance with applicable regulations, and these inspections may include the manufacturing facilities of some of our subcontractors. Failure by manufacturers or their suppliers to comply with applicable regulatory requirements can result in enforcement action by the FDA or other regulatory authorities. Potential FDA enforcement actions include:

- untitled letters, warning letters, fines, injunctions, consent decrees and civil penalties;

- unanticipated expenditures to address or defend such actions;

- customer notifications for repair, replacement, refunds;

- recall, detention or seizure of our products;

- operating restrictions or partial suspension or total shutdown of production;

- operating restrictions;

- refusal to grant export approval for our products; or

- criminal prosecution.

In addition, other government authorities influence the success of our business, including the availability of adequate reimbursement from third party payers, including government programs such as Medicare and Medicaid. Medicare and Medicaid reimbursement policies can also influence corresponding policies of private insurers and managed care providers, which can further affect our business.

Biologics Regulation

Biological products must satisfy the requirements of the Public Health Services Act and the Food, Drug and Cosmetics Act and their implementing regulations. In order for a biologic product to be legally marketed in the U.S., the product must have a BLA approved by the FDA.

The BLA Approval Process

The steps for obtaining FDA approval of a BLA to market a biopharmaceutical, or biologic product in the U.S. include:

• completion of pre-clinical laboratory tests, animal studies and formulation studies under the FDA's GLP regulations;

• submission to the FDA of an IND application, for human clinical testing, which must become effective before human clinical trials may begin and which must include Institutional Review Board (IRB), approval at each clinical site before the trials may be initiated;

- performance of adequate and well-controlled clinical trials in accordance with Good Clinical Practices (GCP), to establish the safety and efficacy of the product for each indication;

• submission to the FDA of a BLA, which contains detailed information about the chemistry, manufacturing and controls for the product, extensive pre-clinical information, reports of the outcomes of the clinical trials, and proposed labeling and packaging for the product;

• the FDA's acceptance of the BLA for filing;

• satisfactory review of the contents of the BLA by the FDA, including the satisfactory resolution of any questions raised during the review or by the advisory committee, if applicable;

• satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the product is produced to assess compliance with cGMP regulations, to assure that the facilities, methods and controls are adequate to ensure the product's identity, strength, quality and purity; and

FDA approval of the BLA.

Pre-clinical studies include laboratory evaluations of product toxicity, as well as animal studies.

An IND will automatically become effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions about issues such as the conduct of the trials as outlined in the IND. In that case, the IND sponsor and the FDA must resolve any outstanding FDA concerns or questions before clinical trials can proceed.

Clinical trials are subject to extensive monitoring, recordkeeping and reporting requirements. Clinical trials must be conducted under the oversight of an IRB for the relevant clinical trial sites and must comply with FDA regulations, including but not limited to those relating to GCP. Adverse events must be reported and investigated in a timely manner. To conduct a clinical trial, a company is also required to obtain the patients' informed consent in form and substance that complies with both FDA requirements and state and federal privacy and human subject protection regulations. The sponsor, the FDA or the IRB could suspend a clinical trial at any time for various reasons, including a belief that the risks to trial subjects outweigh the anticipated benefits. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. In addition, an IRB at each site at which the trial is conducted must approve the protocol and any amendments. If foreign clinical trials are intended to be considered by the FDA for approval of a product in the U.S. then those foreign clinical trials performed under an IND must meet the same requirements that apply to U.S. studies. The FDA will accept a foreign clinical trial not conducted under an IND only if the trial is well-designed, well-conducted, performed by qualified investigators in accordance with international principles for GCP, or with the laws and regulations of the country in which the research was conducted, whichever provides greater protection of the human subjects. The FDA, however, has substantial discretion in deciding whether to accept data from foreign non-IND clinical trials.

Clinical trials involving biopharmaceutical products are typically conducted in three sequential phases. The phases may overlap or be combined. A fourth, or post-approval, phase may include additional clinical trials. These phases are described generally below. We note, however, that the exact number of study subjects required for each specific intended use, and our intent to combine or "telescope" various study phases together, are both areas where we will actively seek FDA feedback to streamline the clinical evaluation process. Briefly, the phases of clinical development generally include the following:

Phase I. Phase I clinical trials involve the initial introduction of the product into human subjects to determine the adverse effects associated with increasing doses. Such Phase I studies frequently are highly abbreviated or combined with Phase II studies (as outlined below), when the product involves the patient's own cells.

Phase II. Phase II clinical trials usually involve studies in a limited patient population to evaluate the efficacy of the product for specific, targeted indications, to determine dosage tolerance and optimal dosage, and to identify possible adverse effects and safety risks. Products that contain the patient's own cells frequently are studied for initial safety and effectiveness determinations in combined or "telescoped" Phase I/II clinical studies.

Phase III. If the product is found to be potentially effective and to have an acceptable safety profile in Phase II (or sometimes Phase I) trials, the clinical trial program will be expanded to further demonstrate clinical efficacy, optimal dosa