Harvard Apparatus Regenerative Technology, Inc.
Form 10-K
March 27, 2015

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

x **Annual report pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934**
For the fiscal year ended December 31, 2014

or

¨ **Transition report pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934**
For the transition period from to

Commission File Number 001-33957

HARVARD APPARATUS REGENERATIVE TECHNOLOGY, INC.

(Exact Name of Registrant as Specified in Its Charter)

Delaware	**45-5210462**
(State or other jurisdiction of Incorporation or organization)	(I.R.S. Employer Identification No.)

84 October Hill Road, Suite 11, Holliston, Massachusetts 01746

(Address of Principal Executive Offices, including zip code)

(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 x

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 x

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

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T 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 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 x

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

The aggregate market value of the voting 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, 2014 was approximately $73,323,261. 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 20, 2015, there were 10,069,676 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 2015 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.

HARVARD APPARATUS REGENERATIVE TECHNOLOGY, INC.

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ANNUAL REPORT ON FORM 10-K

For the Year Ended December 31, 2014

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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," "expects," "plans," "aim," "anticipates," "believes," "estimates," "projects," "predicts," "intends," "think," "strategy," "potential," "objectives," "optimistic," "new," "goal," "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 21 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. Harvard Apparatus Regenerative Technology, Inc. is referred to herein as "we," "our," "us," and "the Company."

PART I

Item 1. ***Business.***

BUSINESS

We are a clinical stage biotechnology company making regenerated organs for transplant.

Our first product, the HART-Trachea, is intended to be used to restore the structure and/or function of a severely damaged trachea (windpipe). The HART-Trachea is comprised of the patient's own bone marrow cells seeded on our proprietary InBreath porous plastic scaffold in our proprietary InBreath organ bioreactor.

We believe our HART-Trachea could enable surgeons to cure nearly all life-threatening constrictions of the airway. Our HART-Trachea addresses both of the critical challenges to trachea transplant: the shortage of suitable donor tracheas and the risk and expense of lifelong anti-rejection drug therapy. Because the scaffolds are synthetic, they can be made in large quantities and therefore will eliminate the need to wait for suitable donor tracheas. Because the cells are from the patient, the patient's body does not reject the HART-Trachea and therefore the patients do not need to take anti-rejection drugs. Because these substantial costs and risks can be reduced or even eliminated with our technology, we believe our products can both help save lives and reduce overall healthcare costs.

To date, the HART-Trachea has been implanted in five adult human patients. Average survival among the three of these patients who have died to date has been 22 months. This is a significant improvement over the prognosis at the time of implant which was typically just a few months. Of the three patients who have died, none of them have died because of a failure of our scaffold. Two of the patients are still alive. Of those two patients, one is at approximately 9 months and the other is at approximately two and one half years from being first implanted.

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

The Office of Combination Products of the U.S. Food and Drug Administration, or FDA, has confirmed for us that the FDA intends to regulate the HART-Trachea as a combination product under the Biologics License Application, or BLA pathway under the primary jurisdiction of the Center for Biologics Evaluation and Research, or CBER. In the EU, the European Medicines Agency, or EMA, has designated the HART-Trachea as an Advanced Therapy Medicinal

Product, or ATMP. The ATMP regulatory pathway in Europe is approximately similar to the BLA pathway in the U.S. The initial indication for which we intend to seek FDA and EMA approvals will be to restore the structure and function of the trachea subsequent to tracheal damage or stenosis due to cancer, injury or infection.

We have received orphan drug designation from the FDA for the HART-Trachea in the U.S. market. Orphan drug designation provides market exclusivity in the U.S. for seven years from the date of the product's approval for marketing. This exclusivity is in addition to any exclusivity we may obtain due to our patents. Additionally, orphan designation provides a waiver of the BLA application fee of $672,000.

We have also filed an application for orphan designation in the EU for our HART-Trachea product. We expect to receive a response from the EMA with respect to our orphan designation application in the second quarter of 2015. In the EU orphan status would provide market exclusivity for ten years.

We are currently engaged in pre-clinical development of our HART-Trachea. Assuming we are able to complete the necessary pre-clinical work to the satisfaction of the U.S. and EU regulatory agencies we would expect to submit our request for IND approval for the HART-Trachea in the first half of 2016. Assuming we are then able to complete the clinical trials with approximately 30 patients and with a 3 month follow-up period we would expect to submit our BLA application for marketing in late 2017. If we are granted Fast Track, Accelerated Review and Breakthrough status in the U.S. we would expect our BLA to be reviewed quickly in which case it is possible we would receive FDA approval to market the HART-Trachea in the U.S. in the first half of 2018. Because the EU ATMP pathway allows for a "hospital exemption" it is possible that we could begin collecting clinical data in the EU before we do so in the U.S. This may allow us a somewhat faster path to approval in the EU than in the U.S. These estimates depend on many assumptions that are inherently uncertain and on scientific and clinical trials whose outcomes are unknowable at this time. The process of obtaining regulatory marketing clearance or approval is lengthy, expensive, and uncertain, and we cannot be sure that our products will be approved in this timeframe, or at all.

In addition to the trachea, we believe that our bioreactor and scaffold technologies are applicable to the regeneration of other organs. In January 2015 we announced the signing of a joint development agreement with Mayo Clinic to bring the HART-Trachea to clinical trials, and to develop a tissue engineered solution for the esophagus using regenerative medicine principles.

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 has been designing and manufacturing devices for life science researchers for over 100 years. Harvard Bioscience first explored the regenerative medicine market in 2007 and began focusing on providing devices to scientists involved in regenerative medicine research in 2008. Since early 2009, Harvard Bioscience's regenerative medicine business initiative operated as a division of Harvard Bioscience.

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 2013. Prior to the distribution of shares of our common stock to the Harvard Bioscience stockholders (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. The Distribution was effected on November 1, 2013, and since that time we have been a separately traded public company. Also, since that time Harvard Bioscience has not been a stockholder of our common stock and has no longer controlled our operations. We had no material assets or activities as a separate corporate entity until the contribution to us by Harvard Bioscience of the regenerative medicine assets and business.

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.

Market Opportunity

There are two major sources of life-threatening constrictions of the trachea: trachea stenosis (narrowing of the trachea caused by physical damage) and trachea cancer. We engaged third parties to analyze databases of clinical records of patients diagnosed with life-threatening trachea stenosis or trachea cancer, and based on that analysis we estimate that there are approximately 7,700 patients per year in the U.S. and EU combined. For more details please see the section "Industry Overview — Overview of the Trachea Transplant Opportunity" below.

While we cannot predict what the total potential market will be when and if we obtain regulatory approval to market our HART-Trachea, based solely on there being at least 7,700 patients per year at the time of such approval, we estimate the total potential revenue opportunity for the HART-Trachea could exceed $770 million per year if we were able to charge at least $100,000 per HART-Trachea. Although we have not yet established pricing for the HART-Trachea, we estimate that pricing between $100,000 and $200,000 may be justifiable based on the costs of treating these patients today, and the potentially life-saving nature of our product.

Additionally, we believe that our current technology may also in the future be used to address replacement or partial replacement of the esophagus and other hollow, tubular organs in the body. We believe that these markets collectively contain considerably more potential patients with life-threatening and expensive conditions than exist for the trachea alone.

Industry Overview

The first human organ transplant was a kidney transplant performed in 1954. The donor of the kidney was the identical twin of the recipient and therefore there was no immune rejection of the organ. The recipient lived for eight years following the transplant and the surgeon who performed the transplant, Dr. Joseph Murray, went on to win the Nobel Prize for this work. The recipient of the first heart transplant, performed in 1967 by Dr. Christiaan Barnard, lived only 18 days. The patient did not die because the new heart failed, but because of pneumonia that the patient acquired due to the patient's immune system being compromised by the anti-rejection drugs that the patient had to take. These two cases illustrate both the promise and the challenges of organ transplantation: donor organs can greatly extend life, but there is a critical shortage of donors and, unless the donor is the identical twin of the recipient, the recipient's body will always reject the donor organ. In order to combat this rejection, the patient must take lifelong anti-rejection drugs which compromise the immune system and greatly increase the risk of the patient dying from infections.

In the 1960s, anti-rejection drugs were very poor and hence very few organ transplants took place. In the 1970s, better anti-rejection drugs, particularly cyclosporine, were developed and by the late 1970s many heart transplant patients were living up to five years with their donor hearts. In 1983, the FDA approved cyclosporine for use in organ transplantation, and the first lung transplant patient survived more than six years.

Although the improved anti-rejection drugs increased the life expectancy for patients receiving organ transplants, they came with harmful side effects that shortened the recipient's natural life span. In addition to the side effects, the anti-rejection drugs are also very expensive and can cost $20,000 to $30,000 per year and must be taken for as long as the patient lives. Despite the side effects and costs, organ transplants have become common enough that the shortage of donors is now a key constraint to organ transplants. To increase the number of organ transplants the U.S. government made a considerable effort to increase organ donation. This included Congress passing seven separate pieces of legislation, Medicare paying for donor transplants, several Surgeons General making personal appeals for more organ donors and the U.S. Department of Health and Human Services making the Emmy award-winning documentary *No Greater Love* on the benefits of organ donation. Despite all these efforts, waiting lists for organ transplants continued to grow and by 2011 there were over 100,000 Americans waiting for a donor organ.

In the late 1980s, the field of regenerative medicine emerged as scientists began to apply principles of engineering and cell biology to develop techniques that could restore, maintain or improve body function. Regenerative medicine now includes products that use cells to repair damaged organs and to grow organs outside the body for transplant into the patient. Early successes in regenerative medicine included the skin grafting products Apligraf and Dermagraft, which were approved by the FDA in 1998 and 2001, respectively. Apligraf has since been used to treat over 200,000 patients. However, the regeneration of more complex three-dimensional structures like the trachea proved much harder than two-dimensional structures like the skin. Additional progress came with using regenerated tissue grafts to increase urinary bladder capacity and with regenerating blood vessels for grafting between veins and arteries.

In 2008, a milestone was reached when the two fields of organ transplant and regenerative medicine were combined with the world's first transplant of a regenerated airway. Even though the airway scaffold came from a donor, because the patient's own bone marrow cells were used to seed the scaffold after the cells from the donor had been removed, the patient did not require anti-rejection drugs. Other than the transplant of organs between genetically identical twins, such as the first kidney transplant described above, we believe this regenerated airway transplant was the world's first organ transplant that has not required anti-rejection drugs. In 2011, another milestone was reached with the world's first transplant of a regenerated airway using a synthetic scaffold. In 2013, additional milestones were reached with the first regenerated trachea transplant in the U.S. and the first regenerated trachea transplant using a synthetic scaffold in a child. To date, the patients receiving these transplants also have not needed to take anti-rejection drugs, and because the scaffolds were made in a laboratory, the patients did not have to wait for a suitable donor organ to become available. These breakthroughs open the possibility that the waiting lists for organ transplants can be reduced or even eliminated.

Overview of the Trachea Transplant Opportunity

There are two major sources of life-threatening constrictions of the trachea: trachea stenosis (narrowing of the trachea caused by physical damage) and trachea cancer. We commissioned an independent third-party (Exponent) to analyze a database (The National Inpatient Sample, or NIS) of U.S. hospital stays to identify the number of patients with life-threatening damage to the trachea. This database is provided by the Agency for Healthcare Research and Quality which is a Federal/State/Industry consortium. It contains patient diagnosis, treatment and discharge data on over 1000 hospitals in the U.S. stratified in such a way as be able to predict data for the entire U.S. Data is broken down by the diagnosis received by the patient at the hospital and uses the ICD9 (International Statistical Classification of Diseases) categories. The ICD9 codes for trachea trauma are:

- 519.02, mechanical complications of tracheostomy, including tracheal stenosis
- 519.09, other tracheostomy complications, and
- 519.19, tracheal stenosis

The data was analyzed for the average number of patients diagnosed annually from 2003 to 2011, which is the latest year for which the data is available. On average there were 39,375 patients diagnosed in these three categories each year in the U.S. Each patient with this diagnosis is also assigned a risk of death. The categories of risk of death are: minor likelihood of dying, moderate likelihood of dying, major likelihood of dying and extreme likelihood of dying. Taking only those patients in the above diagnostic codes with an extreme likelihood of dying there were, on average, 7,247 patients per year in the U.S. On average approximately 22% of these patients diagnosed with an extreme likelihood of death actually do die within that single hospital visit which averages approximately 22 days. We cannot tell from the NIS database how many of these patients die after discharge therefore the 22% actual death rate is a minimum death rate. The average cost of the hospital stay to treat these patients with an extreme likelihood of dying was $248,511. The total cost of treating these patients with an extreme likelihood of dying is approximately $1.8 billion per year in the U.S. We are working with our collaborators to further refine this data to identify the subset of these patients who are at an extreme likelihood of dying that would be candidates for the HART-Trachea. For the purposes of estimating the market size for treating tracheal stenosis patients we have assumed that 50% of these patients, or approximately 3,600 patients per year in the U.S. would be treatable with the HART-Trachea.

For trachea cancer we similarly commissioned Exponent to analyze a different database, the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) database. We used the SEER database for trachea cancer rather than the NIS database as some trachea cancer patients are not admitted as in-patients to the hospital and so do not appear in the NIS database whereas almost all patients with life-threatening trachea trauma are admitted to a hospital on an in-patient basis. This analysis showed there were approximately 250 patients per year diagnosed with trachea cancer in the U.S. We have excluded the much larger population of patients suffering from cancer of the main bronchi

as initially we are pursuing trachea transplant only and not transplant of the main bronchi. Cancer of the main bronchi is approximately 35 times more common than cancer of the trachea alone with an incidence in the U.S. of approximately 9,000 per year.

Current treatments for trachea cancer, such as radiation therapy, chemotherapy and surgery have poor outcomes, resulting in a five-year survival rate of only 27%.

Combining patients with trachea stenosis and trachea cancer we estimate the patient population potentially treatable with the HART-Trachea to be approximately 3,850 per year in the U.S. Assuming the EU market is approximately the same size as the U.S. market we estimate the combined U.S. and EU patient population potentially treatable with the HART-Trachea to be approximately 7,700 patients per year.

Previous attempts to implant a tracheal prosthetic have been unsuccessful in improving long-term survival as they have been unable to allow the body to create a functional lining of the trachea which is essential to the clearance of mucus or have caused other severe complications like narrowing of the trachea, migration of the implanted material into other organs or infections. Without the clearance of mucus, patients have poor prognosis and typically die from pneumonia or respiratory failure shortly after transplant.

Our Solution

We believe the HART-Trachea is a major advance over the current therapeutic options for treating trachea cancer and trachea trauma. We believe our products are the first to enable the application of regenerative medicine techniques to the production and transplant of complex, three-dimensional organs like the trachea. With continued development, we believe that our technologies will be applicable to the repair or transplant of other important human organs such as the esophagus, lungs, heart valves, and heart. Our bioreactor technology was used in both the world's first transplant of a regenerated airway in 2008 and in the world's first transplant of a synthetic regenerated airway in 2011. The complete HART-Trachea combining our scaffolds with our bioreactors and the patient's cells was used for the first time in April 2013.

We believe our products will overcome the major challenges in trachea and other organ transplantation. Unlike traditional organ transplants, our products will eliminate the need for a donor because the scaffold will be manufactured in a factory. In addition, for hollow organs, such as the trachea, our technology enables the production of an implant that precisely matches the patient's anatomy. Because we use the patient's own bone marrow cells to seed the scaffold, our technology also eliminates the risk and expense of lifelong anti-rejection drug therapy. In addition, patients with trachea cancer treated using our technology have not required either chemotherapy or radiation therapy after the transplant, thus eliminating the significant side effects and expense of such therapies. Because these substantial costs can be reduced or even eliminated with our technology, we believe our products can both help save lives and reduce overall healthcare costs.

Further, human embryonic stem cells have not been used in any of the procedures involving our trachea transplant products. This eliminates both the medical risks and ethical controversy associated with regenerative medicine approaches using human embryonic stem cells and other controversial sources of cells.

We believe the use of our products together with the patient's own bone marrow cells solves both the major challenges facing organ transplant: a synthetic scaffold avoids the need to wait for a donor and the use of the patient's own cells avoids the risk and costs of anti-rejection drug therapy. The first application of our products is in trachea repair or replacement but we believe the technology can be developed to apply to other important human organ transplants as well.

Our Strategy

Our objective is to be the leading supplier of regenerated organs for transplant. Our business strategy to accomplish this objective includes:

Target life-threatening medical conditions. We are focused on creating products to help surgeons treat life-threatening conditions like trachea cancer, trachea stenosis, and diseases requiring esophagus, heart or lung transplant. We are not targeting less severe conditions that have reasonable alternative treatment options like damage to the skin, bones, muscles, ears or nose. By targeting life-threatening conditions, we believe it is easier to get patient informed consent for treatment, hospital ethics committee or Institutional Review Board approval and government regulatory authority approval as the patients often have poor or no treatment alternatives. We believe it will also be easier for our customers to get reimbursement for treatments for life-threatening conditions that have poor and/or more expensive alternative treatments.

Develop products that have a relatively short time to market. Since the number of patients with trachea damage is relatively small, we expect the number of patients that we would likely need to enroll in a clinical trial would be relatively small. A small number of patients implies a relatively fast and inexpensive clinical trial. In addition, since lung function is likely to be a key endpoint in any trachea transplant trial and lung function can recover and be measured fairly quickly after transplant (for instance the first patient treated with a regenerated trachea was evaluated for FEV1 (forced expiratory volume in one second) at 3 months after the surgery) we expect we would be able to conduct a clinical trial in a relatively short period of time compared to clinical trials in indications with larger patient populations and longer required follow-up periods. 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.

Use trachea transplant as a platform to address other organs. We believe our experience in developing proprietary scaffolds, bioreactors and cell seeding protocols for tissue engineered trachea implants gives us substantial expertise and intellectual property for developing products addressing diseases impacting other organs like the esophagus, lungs, heart valves, and heart. We intend to use such expertise and intellectual property to develop regenerated organs to help treat other serious medical conditions requiring organ repair or replacement.

Supply the finished organ implant to the surgeon. Our technology includes the bioreactor and scaffold which are used by us together with the cells from the patient to create the tissue engineered organ implant together with all the required quality control data. We believe there is considerable value in supplying the final organ to the surgeon so that the hospital and surgeon may focus solely on performing the transplant.

Collaborate with leading surgeons and institutions. We have and will continue to collaborate with leading surgeons and institutions. For example, we have collaborated with Professor Macchiarini of the Karolinska Institutet to improve our bioreactors and to create earlier versions of our scaffolds for use in trachea transplant, and we have collaborated with Dr. Harald Ott of Massachusetts General Hospital to develop our lung bioreactor system. We have collaborated with researchers at Mayo Clinic to develop our heart valve bioreactor and we recently expanded our collaboration with Mayo Clinic to include efforts to assist with the advancement of our HART-Trachea product to clinical trials and the development of a regenerated esophagus. We believe the use of our products by leading surgeons and institutions will increase the likelihood that other surgeons and institutions will use our products.

Our Products

HART-Trachea

The initial indication for which we intend to seek FDA and EMA approval for the HART-Trachea will be to restore the structure and function of the trachea subsequent to tracheal damage or stenosis due to cancer, injury or infection. The HART-Trachea consists of three key components: a scaffold, the patient’s cells and a bioreactor.

InBreath Scaffold Component

The InBreath Scaffold has a physical shape and strength similar to the natural trachea. This allows it to resist the forces of compression caused by the muscles, skin, bones and other organs of the neck that surround the trachea and also to resist collapse due to the partial vacuum caused by breathing air into the lungs through the trachea. In addition, the scaffold is porous which allows cells to penetrate the scaffold during the seeding process prior to implant and also allows blood vessels from the body to grow into the scaffold once it is in the body. The scaffold used for the first regenerated trachea transplant in 2008 was a donated human trachea with its cells removed before being seeded with bone marrow cells taken from the patient. All subsequent trachea transplants using our products have utilized synthetic scaffolds. Because the synthetic scaffolds are manufactured, they can be made to the exact dimensions of the patient and in large quantities. The synthetic scaffolds used in surgeries prior to 2013 were made by third parties including Nanofiber Solutions, Inc., or NFS, as well as Dr. Alex Seifalian and other scientists at University College London. The scaffold used in the first surgery using a synthetic scaffold was made in collaboration with University

College London and Dr. Macchiarini. The NFS scaffolds were made in collaboration with our company and Dr. Macchiarini. In order to improve upon and replace those scaffolds, we collaborated with Professor Macchiarini and others to develop our initial scaffold product and our manufactured synthetic trachea scaffold was first used in a surgery in April 2013. Our scaffolds can be made from a variety of plastic polymers but are typically made from polyethelyne terephthalate, or PET, which is the same polymer used in the well-known brand of implantable materials known by the trade name Dacron. PET has a long history of safe use in long-term human implants. We intend to continue providing our proprietary scaffolds to surgeons for use in future transplants. We believe that our scaffolds are superior in quality compared to those used in surgeries prior to 2013. Our scaffolds have several novel features including the sandwiching of stiff rings between layers of porous fabric to simulate the rigidity and flexibility of the natural trachea.

The Patient's Bone Marrow Cells

The cells we seed onto the scaffold are obtained from the patient's bone marrow. The bone marrow is obtained in a standard bone marrow biopsy approximately 2 days before the transplant surgery. The cells are purified using a standard sterile, automated centrifugation process to obtain the mononuclear cells. The mononuclear cells are all the cells left after the red blood cells have been removed by the centrifuge. These mononuclear cells are then seeded onto the scaffold in the bioreactor. The cell-seeded trachea construct is then kept in the bioreactor in a sterile incubator at body temperature for approximately 2 days before the transplant surgery.

InBreath Bioreactors

Our InBreath bioreactor is a device that we use to seed cells onto a scaffold as part of the manufacturing process of the HART-Trachea. The InBreath bioreactor enables us to:

- seed the patient's cells on the scaffold under sterile conditions;
- automatically rotate the scaffold to allow good cell distribution into the pores of the scaffold; and
- monitor the scaffold remotely during the course of the two to three days incubation period before the transplant.

We believe our InBreath hollow organ bioreactor is the world's first bioreactor that has been used to perform a human transplant of a regenerated organ.

Other Development Efforts

Esophagus

We believe that our current technology will also prove helpful in developing tissue engineered solutions for the regeneration of tubular organs other than the trachea. We recently manufactured our first human-sized synthetic scaffold prototypes for esophageal transplant. These scaffolds are intended to be used to replace a segment of the esophagus that has been removed due to infection, injury or disease. The first indication we are likely to pursue is esophageal cancer. Esophageal cancer is life-threatening and far more common than trachea cancer. We are beginning pre-clinical work now and expect further development, including animal studies, to occur on the esophagus in 2015. In January 2015 we announced our signing of a collaboration agreement with Mayo Clinic. That collaboration will focus on co-developing regenerative medicine solutions for the esophagus, as well as the trachea, and turning laboratory discoveries into proven treatments and making them available to patients.

Automated Solid Organ Bioreactor

A solid organ bioreactor shares many of the features of the InBreath bioreactor such as the ability to seed cells on an organ scaffold and keep them sterile and healthy during the growth phase prior to transplant. However, for solid organs like the heart and lungs, the bioreactor must also supply pulsatile blood flow and ventilation to mimic the natural action of the heart and lungs. In addition, the physiology of the heart and lung is considerably more complex than that of the trachea and so the measuring, monitoring and control equipment needed is considerably more advanced. During the first half of 2010, one of our physician collaborators, Dr. Harald Ott at Massachusetts General Hospital, succeeded in regenerating a lung that was subsequently transplanted into the body of a rat showing near normal lung function. In collaboration with Dr. Ott and Massachusetts General Hospital, we designed and developed a novel bioreactor that was used to grow the rat lung used in this procedure. The work was published in *Nature Medicine* in July 2010.

We have collaborated with Dr. Ott since 2008 and continue to develop organ bioreactor technologies for his use. The current generation bioreactor is considerably more advanced as it is capable of controlled decellularization and recellularization of an organ, including an organ as large as a human lung. We intend to continue developing bioreactors and scaffolds in collaboration with leading researchers with the goal of eventually using our products to perform a first-in-human transplant of a regenerated organ other than the trachea.

In addition to our human lung bioreactor we also make a similar system for the human heart. This system was developed in collaboration with Dr. Ott, Dr. Macchiarini, Dr. Doris Taylor (at the Texas Heart Institute) and others. We are also collaborating with leading clinical researchers to develop bioreactors for the esophagus and for the heart valve. The heart valve bioreactor is being developed at the Mayo Clinic. None of these solid organ technologies has yet to be extensively tested in animals.

Clinical Experience

Summary of Patient Experience

To date, the HART-Trachea has been implanted in five adult human patients. Average survival among the three of these patients who have died to date has been 22 months. This is a significant improvement over the prognosis at the time of implant which was typically just a few months. Of the three patients who have died, none of them have died because of a failure of our scaffold. Two of the patients are still alive. Of those two patients, one is at approximately 9 months and the other is at approximately two and one half years from being first implanted. In addition, the HART-Trachea has been implanted in one pediatric patient.

A description of individual patient trachea transplant information follows. In procedures prior to April 2013, the InBreath organ bioreactor was used, but not the HART-Trachea product which includes use of the InBreath organ bioreactor and HART's proprietary scaffold. In the procedures described below that occurred since April 2013 the HART-Trachea product was used. The patient's own bone marrow cells were used in each of the transplant procedures described below.

World's First Human Transplant of a Regenerated Airway

In 2008, our InBreath airway bioreactor technology was used to perform the world's first human transplant of a regenerated airway. The patient had suffered a collapse of her airway following a severe tuberculosis infection. To create the regenerated airway, a donor human trachea was obtained and stripped of its cells, and then the patient's own bone marrow cells were used to seed the donor trachea and prepare it for implantation. Following such regeneration, the regenerated airway was then implanted into the patient. In addition to improving her breathing, because the cells used in the transplant were her own cells taken from her own bone marrow, she has not had to take anti-rejection drugs after the surgery. This surgery was published in *The Lancet* in November 2008. In October 2013 the five-year follow up on this patient was published in *The Lancet* showing an excellent clinical outcome. In summary the authors stated, "...the tissue-engineered trachea itself remained open over its entire length, well vascularised, completely re-cellularised with respiratory epithelium, and had normal ciliary function and mucus clearance. Lung function and cough reflex were normal. No stem-cell-related teratoma formed and no anti-donor antibodies developed. Aside from intermittent bronchoscopic interventions, the patient had a normal social and working life." In terms of specific lung function, the patient's FEV1 (forced expiratory volume in one second, a clinically standard measure of lung function) improved by 85% from before the surgery to 3 months after the surgery. According to the American Thoracic Society the change in FEV1 should be greater than 20% to be clinically significant in evaluations in this time frame.

World's First Successful Transplantation of a Synthetic Tissue Engineered Trachea

In June 2011, our InBreath bioreactor was used for the world's first successful transplantation of a synthetic tissue engineered trachea. For the first time in history, a patient was given a new trachea made from a synthetic scaffold seeded with his own cells and grown in our bioreactor. The operation was performed at the Karolinska University Hospital in Stockholm, Sweden by Dr. Macchiarini and his team of surgeons. The patient had been suffering from late-stage trachea cancer, which before the surgery would have been inoperable. He was given only a few weeks to live and as such the transplant surgery using our product was a last-resort measure to save the patient's life. The patient required a tracheo-bronchial scaffold transplant, whereby the scaffold mimics the branched shape of the airway. To create the new synthetic trachea, Dr. Alex Seifalian and other scientists at University College London developed a plastic scaffold shaped like the patient's natural airway and Dr. Macchiarini seeded it with the patient's own bone marrow cells. This seeding process prepared the synthetic trachea for implantation and thereafter the regenerated synthetic trachea was implanted into the patient. Because the cells used to regenerate the trachea were the patient's own, there has been no rejection of the transplant, and, like the first patient described above, this patient is not taking anti-rejection drugs. This surgery was published in *The Lancet* on November 24, 2011.

World's Second Successful Transplantation of a Synthetic Tissue Engineered Trachea

In November 2011, our InBreath bioreactor was again used by Dr. Macchiarini to seed the cells on a synthetic scaffold to treat a patient who was suffering from late-stage trachea cancer and required a tracheo-bronchial transplant. The operation was performed at the Karolinska University Hospital by Dr. Macchiarini and his team of surgeons. The procedure was similar to the world's first successful transplantation of a synthetic tissue engineered trachea performed in June 2011, with the exception that the plastic scaffolding material was changed to a fiber construction rather than a porous solid construction. The fibrous scaffold seeded in our bioreactor for this November 2011 procedure was manufactured by NFS and was made in a different laboratory than the one made for the June 2011 patient. The patient recovered well from the transplant surgery and was discharged home from the hospital. Approximately four months after the surgery, the patient passed away from pneumonia secondary to a tracheal tumor. There is no indication that our bioreactor or the third-party scaffold played any role in his death. This patient, like the June 2011 patient, had undergone extensive radiation and chemotherapy treatment prior to the transplant, and his tumor was not responsive to these forms of treatment.

June 2012 Russian Transplants

In June 2012, our InBreath bioreactors were used for the world's first two successful laryngo-trachea transplants, using synthetic laryngo-trachea scaffolds seeded with cells taken from the patients' bone marrow. The surgeries took place at the Krasnodar Regional Hospital in Krasnodar, Russia and were performed by Professors Porhanov and Macchiarini and their team. These two surgeries differed from the June and November 2011 procedures described above in that the patients in those prior surgeries both had late stage trachea cancer and both required a tracheo-bronchial scaffold. These Russian patients each had trachea trauma caused by automobile accidents. Both of the Russian patients required laryngo-trachea transplants, whereby the scaffold mimics the shape of the windpipe from the larynx to the point where the trachea branches into the two bronchi which lead to the lungs. Both patients had difficulties breathing and talking and had suffered repeated infections prior to the surgeries. The scaffolds in these two cases were fibrous scaffolds manufactured by NFS and similar to the one used in the November 2011 surgery, but were made with a different fiber formulation.

August 2012 and 2013 Transplants — Outside the U.S.

In August 2012 a sixth patient received a trachea transplant created using our InBreath bioreactor. The surgery took place at the Karolinska Hospital and was performed by Dr. Macchiarini and his team of surgeons. The patient was in critical condition and the trachea transplant was performed in an emergency procedure in an attempt to save the patient's life. In July 2013, this patient had the original scaffold, which was not manufactured by us, removed and a new scaffold manufactured by us implanted to replace the explanted one. This was done due to the partial collapse of the previous scaffold. In the third calendar quarter of 2013 another two surgeries were performed using the

HART-Trachea in Krasnodar, Russia.

First Successful U.S. Transplant and First Use of Our Scaffold

On April 9, 2013, our HART-Trachea was used in the first successful transplant of a regenerated trachea in the United States. The recipient of the implant, a two-year-old girl, initially recovered well but approximately two months after the trachea transplant surgery the patient underwent a second surgery to correct a defect in her esophagus. On July 6, approximately one month after the second surgery and three months after the initial surgery the patient died from complications of the second surgery. Dr. Macchiarini, who led the team performing the trachea surgery, noted that the implanted trachea was not the cause of the patient’s death, pointing out that the girl's native tissue was very fragile.

The surgery was also the world’s first successful pediatric regenerated trachea transplant using a synthetic scaffold. The patient was born on August 22, 2010 in Seoul, South Korea with tracheal agenesis (lack of a trachea), and was only able to breathe through a tube inserted in her esophagus that connected to her lungs. Tracheal agenesis is 100 percent fatal, and children born with the condition typically die shortly after birth. The patient had lived in the intensive care unit for two and a half years at Seoul National Hospital before being transported to Illinois for the surgery. This was the first regenerated trachea transplant surgery using a scaffold manufactured by us. Other than the use of a scaffold manufactured by us the procedure was similar to the other surgeries described above. The procedure was performed by a team led by Dr. Macchiarini and Drs. Mark J. Holterman and Richard Pearl both of Children’s Hospital of Illinois. The surgery was approved by the FDA under an Investigational New Drug application made by Dr. Holterman.

In December 2013 and in June 2014 additional patients received the HART-Trachea in surgeries conducted in Krasnodar, Russia. One of those patients was a re-transplant, where a scaffold that was first transplanted into the patient in June 2012, as described above, was removed and replaced by a HART-Trachea. The other patient had a trachea transplant for the first time.

All these patients have been treated under compassionate-use protocols meaning their prognosis was very poor. Typically, their bodies are very weak as a result of disease, trauma and extensive treatments that often include radiation, chemotherapy and prior surgeries. We believe that patients that undergo such extensive treatments are inherently susceptible to serious medical complications following the transplants. These transplant surgeries are typically the last-resort measure to save the patient's life. We expect that some transplant patients are likely to suffer serious complications or death following the transplants due to issues that are not directly related to the use of our products.

Clinical Trials

In order to market the HART-Trachea widely, we will need to successfully complete clinical trials. The initial indication for which we intend to seek FDA and EMA approval will be to restore the structure and function of the trachea subsequent to tracheal damage or stenosis due to cancer, injury or infection.

Because trachea cancer and severe trachea stenosis combined affect only approximately 7,700 patients per year in the U.S. and EU we anticipate that our clinical trials will involve relatively few patients. Because lung function can be measured fairly shortly after transplant (for example at 3 months post-transplant) we expect a fairly short evaluation period for establishing the efficacy of the HART-Trachea.

We intend to pursue regulatory approval for the HART-Trachea in the U.S. and the EU. Hence, we expect clinical trials to take place in those markets. During the second half of 2014 we elected not to perform future transplant procedures at Krasnodar, Russia a site of previous compassionate-use cases as part of their ongoing airway transplant studies. This shift in focus allows us to concentrate our resources on completing preclinical work necessary to initiate clinical trials for our HART-Trachea product in the EU and U.S. as those are the markets within which we believe we have the fastest paths to treating the most patients and the best reimbursement rates.

Research and Development

Our primary research and development activities are in designing and testing synthetic organ scaffolds, testing the cellularization of the scaffolds and engineering and making our organ bioreactors. As of December 31, 2014, we employed 17 full-time engineers and scientists 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 collaboration is with Mayo Clinic. 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. These agreements are discussed below in “Intellectual Property and Related Agreements.” Sometimes we are paid for our products directly, sometimes we are partners on grants and sometimes we give away or loan our technologies to the researchers or clinicians in return for feedback to improve the designs and/or license rights to intellectual property.

We have incurred approximately $9.7 million of research and development expenses in the last two fiscal years. As we have not yet sold any of our HART-Trachea products, 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. The rings that mimic the natural rings of the trachea are fabricated separately and the fabric and rings are combined. 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 a decellularized human trachea. Our scaffolds are made from a polymer that does not dissolve in the human body, in other words our scaffolds are intended to be permanent. We believe permanent scaffolds are a better approach for trachea regeneration than using solely resorbable materials as it is hard to control the strength of the scaffold as the polymer resorbs.

While we do not manufacture the cells, they come from the patient's bone marrow, 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 all the surgeries performed so far the seeding has been performed in the hospital by the medical team involved in the surgery in collaboration with our staff. For a U.S. clinical trial we anticipate that the seeding will be performed in an automated version of the InBreath bioreactor and under the supervision of our staff.

For our scaffolds, our primary materials are 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 test components 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 transplants with the HART-Trachea will be performed at a relatively small number of major hospitals in the U.S., EU and other developed countries. As a result we expect to need only a fairly small field sales force. We expect to price the product commensurate with the medical value created for the patient and the high costs avoided with the use of our product. We expect to be paid by the hospital that buys the product from us. We expect that the hospital would seek reimbursement from payors 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.	2033
Patent application relating to support configurations for tubular tissue scaffolds, and airway scaffold configurations	E.P.	2033
Patent application relating to methods and compositions for promoting the structural integrity of scaffolds for tissue engineering	U.S.	2033
Patent application covering aspects of clinical scale bioreactors and tissue engineering	Australia, Canada, Europe, Japan, Russia, U.S.	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	Australia, Canada, Europe, Japan, Russia, Singapore, U.S.	2032
Patent application relating to bioreactors with supports to facilitate culturing organs	PCT – international stage	2034
Patent application relating to bioreactor adaptors for tubular tissue scaffolds	PCT – international stage	2034
Patent applications relating to engineered hybrid organs	PCT – international stage	2034
Patent applications relating to infrared-based methods for evaluating tissue health including methods for evaluating burns	U.S.	2033
Patent application covering aspects of syringe devices and methods for delivering cells to tissues	Canada, Europe, U.S.	2030
Patent application relating to meshes and patches for tissue repair	PCT – international stage	2034
Provisional application relating to systems and methods for delivering cells to fluid passages, such as respiratory passages	U.S.	N/A

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.

Patent Rights Assignment — Dr. Macchiarini