Spinal Cord Implants for Nerve Regeneration

by
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ABSTRACT

It has only been in the last couple decades that the potential for regeneration in the spinal cord became accepted. However, there is still no proven method for enabling this regeneration. An implant model was developed to help aid in repair, recovery, and regeneration in the spinal cord following spinal cord injury (SCI). This is a polymer-based model with the ability to host neural stem cells.

This document briefly reviews the SCI model developed. It also discusses the intellectual property surrounding the implant model, as well as examines the possible pathways through the Food and Drug Administration (FDA) and to the market.

Thesis Supervisor: Robert S. Langer
Title: Germeshausen Professor of Chemical and Biomedical Engineering

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Contents

1.0 INTRODUCTION

The novel and early-stage technology being explored in this document is an implant for the cure of spinal cord injury (SCI). Not so many years ago, it was believed that there was no hope of regeneration in the spinal cord, but recent research has suggested otherwise [1]. This has created a unique situation in which there is a fully developed market with no product. There are many ways to alleviate some of the problems associated with SCI and cope with the many side effects, but to date there is no therapy available to promote repair. Full recovery occurs in fewer than 1% of the cases of SCI, and 45% of people injured do not recover feeling or function below the site of the injury [2].

1.1 Spinal Cord Injury Basics

Spinal cord injury (SCI) is defined as damage of the nerves either through trauma or disease. This damage does not necessarily imply a transection of the cord, but is actually achieved more frequently by contusions of the chord. After the initial trauma, the injury site actually expands over the course of weeks to months. The mechanisms following the initial trauma (secondary injury) are not well understood. Between the initial injury and the secondary degeneration, effects include loss of axonal connection, lost neurons and glia, epidural and glial scarring, and demyelination of axons. The perceivable effects of the injury can include impairments or loss of movement/muscle control, sensations, and organ system control. The seriousness of SCI tends to increase

with increasing injury sites: injuries suffered to the neck tend to have more serious consequences than injuries lower in the spine.

Currently, there are no complete or even semi-partial treatments for SCI. Any treatment will have to achieve a number of goals. It must (1) eliminate secondary injury, (2) mitigate the immune response, (3) promote neuronal survival, (4) foster axonal sprouting, and (5) provide guidance for axonal growth and synapse formation. Present day approaches and research avenues for treatment of SCI involve:

- •Methylprednisolone
  - –Improves recovery 20% if within 8 hours
- •Growth Factors
  - –Molecules that regulate protein synthesis for cell division and growth
  - –NGF (sensory), NT-3 (motor), BDNF, GDNF
- •Axonal Guidance
  - –Carbon fibers, collagen, matrigel
- •Myelin replacement via stem, Schwann, OEC's
- •Fetal Tissue
- •Stem Cells

Some of these areas have had limited success already, while others are believed to ultimately not be able to provide a complete cure as they do not address all of the goals mentioned above [3].

1.2 Spinal Cord Injury Incidence Statistics

The following tables and charts have been compiled by the National Spinal Cord Injury Statistical Center (NSCISC) and were published December 2003. They contain data from the 1970's to that date.

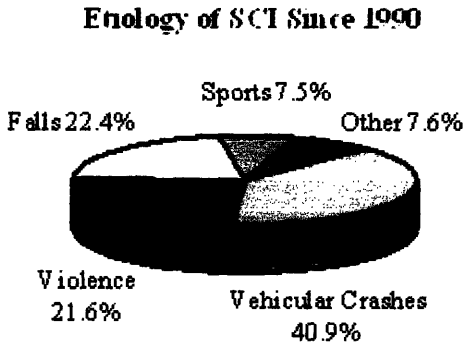

Figure 1. Origins of SCI [4]

Since 1973 the trends of SCI origin have indicated a decrease in proportion of injuries from motor vehicle crashes and sports and an increase in the proportion of injuries from falls and violence. Fifty-three percent of SCIs occur among young adults in the 16 to 30 year old range. Also, 81.2% of all injuries in the database have been for males. The following tables show life expectancy for individuals based on age at injury and initial survival rates.

Table 1. Life Expectancy for Persons who Survive the first 24 hours Post-Injury [4]

Age at Injury	No SCI	Motor Functional at any Level	Para	Low Tetra (C5-C8)	High Tetra (C1-C4)	Ventilator Dependent at any Level
20 yrs	57.8	52.9	45.3	40.5	36.0	16.3
40 yrs	38.9	34.4	27.7	23.7	20.1	7.0
60 yrs	21.6	17.8	12.7	10.0	7.7	1.3

Table 2. Life Expectancy for Persons who Survive at least 1 year Post-Injury [4]

Age at Injury	No SCI	Motor Functional at any Level	Para	Low Tetra (C5-C8)	High Tetra (C1-C4)	Ventilator Dependent at any Level
20 yrs	57.8	53.4	46.0	41.8	38.2	23.3
40 yrs	38.9	34.9	28.3	24.7	21.8	11.1
60 yrs	21.6	18.2	13.2	10.7	8.8	2.9

Until recently, the leading cause of death for those suffering from SCI was renal failure. However, recent new technologies and care have improved urologic management and have shifted the balance. The next most frequent causes of death as reported by the NSCISC are pneumonia, pulmonary emboli, and septicemia.

2.0 TECHNOLOGY

2.1 Implant Concept

A polymer-based implant model has been developed for aiming to cure SCI by Dr. Erin Lavik at the Massachusetts Institute of Technology in the research group of Professor Robert Langer in collaboration with Dr. Evan Snyder and Dr. Ted Terry. It has been designed to be a very flexible model so that as more is learned about the nature of SCI and the necessary conditions for nerve protection, regeneration, and repair, the model can be altered to incorporate the necessary features. The overall design of the implant

has been created to mimic the architecture of the natural spinal cord. As new tissue is created *in vivo*, the polymer will degrade. The figure below is a gives a rough idea of the implant structure. The length and diameter of the implant can be tailored for each individual injury. The gray section represents an inner porous sponge to mimic the gray matter, and the outer half-cylinders provide replacement for the white matter.

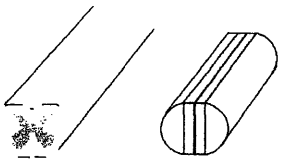

Figure 2 Implant Model

Some of the elements to control in this model are the surface chemistry, the role of pore size in the outer and inner scaffolds, the degradation rate of the scaffold, the inclusion of drugs and growth factors, the incorporation of microspheres for complex release profiles, and the incorporation of different cell types prior to implantation. It is hoped that by incorporating tissue engineering, drug delivery and polymer systems engineering, the model will be able to embody and keep pace with optimal SCI cures as they are discovered.

2.2 Implant Model

The scaffold selected for the preliminary study was made from a blend of 50:50 poly(lactic-co-glycolic acid) (PLGA) (75%, number average molecular weight, $M_n \cong$ 40,000) and a block copolymer of poly(lactic-co-glycolic acid)-polylysine (25%, PLGA block $M_n \cong 30{,}000$, polylysine block $M_n \cong 2000$). The degradation rate of the PLGA was about 30-60 days. The inner scaffold was created via salt leaching and had pores with a diameter range of 250-500 μm. The outer scaffold used a solid-liquid phase separation technique and dioxane sublimation to achieve axial porosity of around 10 μm [5,6].

The cells used were murine NSCs (clone C17.2) furnished by Dr. Evan Snyder of the Departments of Neurology, Pediatrics, and Neurosurgery of Harvard Medical School. The polymer was functionalized for future possible surface modifications although none were introduced in the following study. The functionalization was achieved by coupling PLGA with a carboxyl end group to poly(ε-carbobenzoxy-L-lysine) using dicyclohexyl carbodiimide (DCC) [7, 8].

2.2.1 Adult Rat Hemisection Model Study

An animal study of fifty adult female Sprague-Dawley rats was conducted using a series of different implant models. There were a total of four different treatments that could be performed across the group of fifty. All animals had a 4-mm-long hemisection of their spinal cord tissue removed between the 9^{th}-to-10^{th} thoracic spinal vertebrae. The

primary control animals (n = 12) received no implant ("lesion control"). A second group (n = 12) received murine NSCs (clone C17.2) suspended in medium ("cells alone") delivered to the lesion site. The third group (n = 11) received the polymer implant without any cells ("scaffold alone"), and the fourth group (n = 13) received the NSC-seeded scaffold ("scaffold plus cells"). Standard procedures were followed to minimize error, bias, and variability in the study.

Various behavioral studies were conducted, biotinylated dextran amine (BDA) tracing was performed, and general histology and immunocytochemistry on the recovered tissue was carried out. Extensive details of the animal study as well as the implant model can be found in Dr. Lavik's thesis [9] and published in the Proceedings of the National Academy of Sciences [10]. Most notably, one day after the surgery and then weekly, mobility analysis was conducted by independent observers using the Basso-Beattie-Bresnahan (BBB) scale. The study concluded after 10 weeks, at which time the spinal cords were removed, sectioned, and stained for analysis. The results of the study showed that the "scaffold plus cells" group exhibited the greatest ability for coordinated, weight-bearing hind limb stepping. At the conclusion of the study, 69% of the "scaffold plus cells" group, 54% of the "scaffold alone" group, 17% of the "cells alone" group, and 33% of the "lesion control" group had achieved a BBB score of 10 or greater. The score of 10 is considered to be the point of "significant walking behavior."

2.3 Future Research

Future research of course involves continued animal studies and eventually human trials. However, it is equally important to develop an *in vitro* model to test the

many different permutations of the model as well as test future additions and modifications. Results of the preliminary animal study suggest that the scaffold itself posed the greatest enabling aspect of the implant. Further studies should be done to assess the extent to which this is true. As research continues, larger animals will be used until clinical trials with humans are appropriate.

3.0 INTELLECTUAL PROPERTY (IP)

To assess the breadth available for intellectual property and patent claims, a search of the United States Patent and Trademark Office (USPTO) was conducted. The Internet site for the USPTO contains all patents from 1976 to the exact day the search is conducted. To ensure all potential patents were flagged, all queries were over the entire body of each patent. This allowed for a breadth that would ideally catch any extra patents that used similar but not the exact terms of this device.

The first step for a patent search would be to define search terms very narrowly to match the model as closely as possible. In this case, as was discussed earlier, there are no comparable patented systems. However, while polymeric implants for treating spinal cord injury are a novel area of research, the building blocks to get there are not. Consequently, any implant model must be comprised of non-patented components. It is also important to make sure that the methods to make the components are free from patent restrictions as well.

A final consideration that may not have crippling implications but is still important to study is the methods for the research and development of the implant system. If there are any diagnostic tools or cell stains, kits, or assays, these should be taken into account with respect to long-term production plans. Once the research moves from the university to a corporate setting, many of the tools afforded to researchers at low or no costs may acquire new or higher prices. Therefore, it would be important to try to avoid a dependence on auxiliary tools for quantitative analysis and product regulation that have the potential for hefty price tags. Unfortunately, there are certain standard protocols for cell-systems that may be unavoidable for creating a reputable product.

The first series of searches was conducted to confirm that there were indeed no spinal cord implant systems patented that could overlap with the discussed model. Again, the entire patent document was searched; this gives the possibility of a higher number of non-applicable returns, but reduces the possibility that a relevant patent slip through the search uncaught. A search on "spinal cord" returned 7,149 results and adding "scaffold" to the query reduced the number to 132. Further reducing the field to 10, "PLGA" was included, but none of those patents were at all applicable to this model and application. Along another track, the search on "nerve regeneration" returned 567 patents, adding "scaffold" narrowed the number to 72, and then "PLGA" cut it to 12. Again though, none of the returned patents were relevant.

The next series of searches was conducted with "Robert Langer" as an author. Professor Langer has over 800 articles, 420 abstracts, and over 500 issued or pending patents. This implant model was actually developed with the intent of piggybacking his patents so that any positive results could be investigated without worrying about

intellectual property infringement. Appendix A lists some of the patents currently relevant to the implant.

Even though the enormous number of patents under Professor Langer's name afford a lot of leeway for research avenues, it is still important to be diligent in considering the many components of the model. Because the model has many layers to it, the materials analysis of IP should include, but not be limited to, PLGA, PLA, PLGA-PLA block copolymer, and functionalized block copolymers. These materials should be combined with the methods of salt leaching and oriented pore creation via dioxane sublimation for the investigation of IP as it relates to processing. Finally, the broader ideas of polymers for tissue engineering, cells plus polymer systems, three-dimensional scaffolds, various drug delivery methods, and growth factor use should also be considered.

Currently the implant model has a very wide range of embodiments as many factors can be modified as well as switched. This versatility is wonderful in the laboratory setting as it facilitates much experiment mobility. However, getting a solid patent on such a device becomes challenging. It will be important to isolate certain features of the device quickly and protect them first, and then gradually expand the IP of the product as research and clinical studies support the other different facets of the model.

4.0 MARKET AND BUSINESS EVALUATIONS

The impact on the quality of life for an individual who suffers from SCI that a successful spinal cord implant would have is astronomical. And as will be discussed in the following sections, there are a great number of individuals who suffer from SCI and at a great personal cost. However, that alone is not enough to bring the system to market or even make it available to a select few. After the following market analysis, this section will then summarize the requisite interactions with the U.S. Food and Drug Administration (FDA), the organization the monitors and regulates all medical devices. Finally, a rough business plan will be outlined to specify short, medium, and long-term goals.

4.1 Market Potential for a Spinal Cord Implant System

Since 1973 there has been a national program for an SCI data center. From 1973-1981, it was the National Spinal Cord Injury Data Research Center, and from 1983 to the present, it has been the National Spinal Cord Injury Statistical Center (NSCISC). The following data comes from Spinal Cord Injury Facts and Figures at a Glance. Information Sheet, December 2003 [4]. It is estimated that over 10,000 people in the United States suffer some degree of SCI each year. The International Campaign for Cures of Spinal Cord Injury Paralysis provides the following table summarizing the published data on SCI.

Table 3. International Prevalence and Costs [11]

Country/ population (millions)	Injuries/ annum and ratio/ million	Population estimated living with SCI	Estimated annual cost (Local Currency)	Direct Govt. investment in SCI cure related research
USA (260)	10000 (40)	250,000	$7.736 billion (USD)	70 million (USD)
CANADA (30)	843 (27)	30,000	$1.5 billion (CDN)	6 million (CDN)
UK (59)	700 (12)	35,000	>500 Mill (GBP)	NYK*
AUSTRALIA (17)	241 (13.2)	10000	$1.0 Billion (AUS)	2 million (AUS)
JAPAN (125)	2665 (21.3)			
TURKEY (61)	1000 (16.9)			
TAIWAN	1353 (16.6)			
GERMANY (81)	1500 (18.5)			
NETHERLANDS (16)	439	11,864		
ITALY (58)	700 (12)			
JORDAN (4)	70 (18)			
FIJI (.75)	16 (18.7)			
RHONE ALPS FRANCE regional	(12.7)			
DENMARK regional	(9.2)			
CHINA (1200)	10,000 (8.4)	420,000		
PORTUGAL CENTRAL REGION	(57.8)			
sub total (1582)	29,527 (14.23)	~760,000 (6 nations)		

REST OF WORLD (4418)	62868 (14.23)			
TOTAL	92,395 NEW CASES / YR	2 million conservatively	$10 billion in 4 of 200 nations	perhaps $150 million

Furthermore, the organization estimates that by the close of 2005, 2.5 million people will be living with SCI-induced paralysis. With an estimated cost of $10 billion in four nations alone and somewhere on the order of $150 million spent on research for finding a cure to SCI, there is great market potential for the right device. In the U.S, the NSCISC estimates that an injury sustained at age 25 that results in any minimal loss of motor function at any level will cost that individual over $500,000 in his lifetime. The following two tables delineate the average yearly expenses and the lifetime costs, respectively, for individuals with varying levels of SCI.

Table 4. Annual Costs for an Individual [4]

Average Yearly Expenses
(in 2000 dollars)

Severity of Injury	First Year	Each Subsequent Year
High Tetraplegia (C1-C4)	$626,588	$112,237
Low Tetraplegia (C5-C8)	$404,653	$45,975
Paraplegia	$228,955	$23,297
Incomplete Motor Functional at any Level	$184,662	$12,941

Table 5. Lifetime Costs for an Individual [4]

Estimated lifetime costs by Age at Injury
(discounted at 2%)

Severity of Injury	25 years old	50 years old
High Tetraplegia (C1-C4)	$2,393,507	$1,409,070
Low Tetraplegia (C5-C8)	$1,353,360	$857,050
Paraplegia	$799,721	$545,460
Incomplete Motor Functional at any Level	$533,474	$386,619

This data further supports the idea that there is a great deal of money circulating due to SCI. The motivations for an implant to come to the market may not exist for the healthcare industry or for individual doctors, but certainly, the market does exist in terms of the desire of injured individuals and their families. Later in this section the path to market will be discussed in greater depth.

Besides the Langer Lab at MIT, there are many other centers for research on nerve regeneration in the spinal cord. Because the research is so expensive and fundamental, currently there is very little industry involvement in the field. Some of the extensive United States research programs in academia have been established at MIT, Harvard, University of Miami, University of Louisville, the University of Alabama at Birmingham. Research is not only being conducted domestically, but there are also programs in Europe and Australia working to find a cure for SCI. Additionally, the U.S. government funds a 16 Model SCI Systems which exist to "demonstrate improved care, maintain a national database, participate in independent and collaborative research and provide continuing education relating to spinal cord injury." These centers are spread throughout the U.S. and can be regarded as the premier sites of cutting-edge SCI

research. The funding they receive for their roles as Model Systems comes from the National Institute on Disability and Rehabilitation Research (NIDRR), Office of Special Education and Rehabilitative Services, US Department of Education. All of the above groups should be regarded as competitors for the SCI market even though there is a great deal of collaboration that takes place. However, there is an enormous range of tactics for curing SCI being investigated, and thus the groups are not competing for the same technology, rather the same ends. As such, it will most likely be that the product or approach that best achieves these ends will have control of the market.

4.2 Animal and Clinical Trials for the Center for Devices and Radiological Health, United States Food and Drug Administration

Any medical devices that are going to be tested in animals or humans are subject to regulations by the Center for Devices and Radiological Health (CDRH), a division of the U.S. Food and Drug Administration. Even though this poses major cost and research burdens and can be regarded as an unnecessarily lengthy process, the act of getting FDA approval can also serve to convince peer researchers of the merits of the implant model. All medical devices are categorized as Class I, Class II, or Class III, with Class III being the most highly regulated and monitored division. This implant model falls into the Class III range of devices, defined as "those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury." In fact, the FDA regards all spinal systems as "significant risk devices." As such, an Investigational Device Exemption

(IDE) is necessary before any sort of clinical data can be obtained. The IDE must include (1) the nature and design of the device, (2) risk analysis, (3) patient safety, (4) manufacturing and monitoring, (5) clinical protocol and consent forms, and (6) the institutions and investigators, etc. for the study.

Obtaining an IDE and completing some of the clinical trials then prepare the way for obtaining the Premarket Notification 510(k) or Premarket Approval (PMA). In the case of this Class III medical device, a PMA is required. The CDRH's overview of the PMA is given below. This introduction highlights the extensive knowledge and proof of such knowledge that one must supply for any approved device.

> PMA is the most stringent type of device marketing application required by FDA. The applicant must receive FDA approval of its PMA application prior to marketing the device. PMA approval is based on a determination by FDA that the PMA contains sufficient valid scientific evidence to assure that the device is safe and effective for its intended use(s). An approved PMA is, in effect, a private license granting the applicant (or owner) permission to market the device. The PMA owner, however, can authorize use of its data by another.
>
> The PMA applicant is usually the person who owns the rights, or otherwise has authorized access, to the data and other information to be submitted in support of FDA approval. This person may be an individual, partnership, corporation, association, scientific or academic establishment, government agency or organizational unit, or other legal entity. The applicant is often the inventor/developer and ultimately the manufacturer.
>
> FDA regulations provide 180 days to review the PMA and make a determination. In reality, the review time is normally longer. Before approving or denying a PMA, the appropriate FDA advisory committee may review the PMA at a public meeting and provide FDA with the committee's recommendation on whether FDA should approve the submission. After FDA notifies the applicant that the PMA has been approved or denied, a notice is published on the Internet (1) announcing the data on which the decision is based, and (2) providing interested

persons an opportunity to petition FDA within 30 days for reconsideration of the decision.

The regulation governing premarket approval is located in Title 21 Code of Federal Regulations (CFR) Part 814, Premarket Approval. A class III device that fails to meet PMA requirements is considered to be adulterated under section 501(f) of the FD&C Act and cannot be marketed. [12]

Below is the listing of scientific elements that the researchers (assumed to be the PMA applicants in this case) must provide. As with IP and patent claims as well, the language of the regulations is very often used to make claims or defend decisions. As such, the requirements were not summarized but rather are given as reported by the CDRH.

Data Requirements

A Premarket Approval (PMA) application is a scientific, regulatory documentation to FDA to demonstrate the safety and effectiveness of the class III device. There are administrative elements of a PMA application, but good science and scientific writing is a key to the approval of PMA application. If a PMA application lacks elements listed in the administrative checklist, FDA will refuse to file a PMA application and will not proceed with the in-depth review of scientific and clinical data. If a PMA application lacks valid clinical information and scientific analysis on sound scientific reasoning, it will delay FDA's review and approval. PMA applications that are incomplete, inaccurate, inconsistent, omit critical information, and poorly organized have resulted in delays in approval or denial of PMA applications. Manufacturers should perform a quality control audit of a PMA application before sending it to FDA to assure that it is scientifically sound and presented in a well organized format.

Technical Sections: The technical sections containing data and information should allow FDA to determine whether to approve or

disapprove the application. These sections are usually divided into non-clinical laboratory studies and clinical investigations.

Non-clinical Laboratory Studies' Section: Non-clinical laboratory studies' section includes information on microbiology, toxicology, immunology, biocompatibility, stress, wear, shelf life, and other laboratory or animal tests. Non-clinical studies for safety evaluation must be conducted in compliance with 21CFR Part 58 (Good Laboratory Practice for Nonclinical Laboratory Studies).

Clinical Investigations' Section: Clinical investigations' section includes study protocols, safety and effectiveness data, adverse reactions and complications, device failures and replacements, patient information, patient complaints, tabulations of data from all individual subjects, results of statistical analyses, and any other information from the clinical investigations. Any investigation conducted under an Investigational Device Exemption (IDE) must be identified as such.

Like other scientific reports, FDA has observed problems with study designs, study conduct, data analyses, presentations, and conclusions. Investigators should always consult all applicable FDA guidance documents, industry standards, and recommended practices. Numerous device-specific FDA guidance documents that describe data requirements are available. The guidance document database on the Internet can be found at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfGGP/Search.cfm. Study protocols should include all applicable elements described in the device-specific guidance documents. [12]

5.0 BUSINESS PLAN FOR SPINAL CORD IMPLANT MODEL

As has been detailed above, the market for a cure for SCI is enormous not only in the U.S. but in the world. It is also a longstanding market that will not disappear with time. There is also an enormous advantage to being the first company to begin to capture the market, as there are over 250,000 people alive today in the U.S. suffering from SCI.

The U.S. injury rate of 11,000/year could be taken as some measure of the future national market size.

In this section, two pathways to market will be discussed. The first one approach represents a more typical plan of attack than the second approach, which details the actual chosen direction for the future of the SCI implant research.

5.1 Approach One

A feasible product timeline is given below. Because of the nature of tissue engineering research, exact dates were not hypothesized as each step has such a variable duration.

Table 6. Anticipated Steps to Market

Step 1	Step 2	Step 3	Step 4	Step 5
-Refine Model -Repeat Studies -Streamline Production	-Move from MIT setting -IDE -Primary patents	-FDA clinical trials	-Product used at select hospitals -Doctor Education	-Market Dominance

The first steps involve more fundamental research into the implant and system. It would be greatly advantageous to have a thorough *in vitro* model developed to test the different implant parameters to supplement and direct the animal studies. Also, it would be helpful at this time to start developing a method to regulate implant production to ensure consistency. This is somewhat implicit in conducting proper animal trials, but it is

important to stress this step as automating the production of implants will be out of the question until much later in the development process.

During this research period, all work can be kept at MIT. This keeps the door open for a breadth of funding and collaboration not available in the corporate setting. In the financial year of 2000 alone, the International Campaign for Cures of Spinal Cord Injury Paralysis (ICCP) funded over $25 million in research projects. However, it also keeps all IP as joint property of MIT, so this must be factored in when computing the cost balances. Collaborations can also be established at this time with potential surgeons to perform the first series of surgeries. As this is a high-risk for low-yield research area, it is important to identify surgeons who have a scientific curiosity and desire for medical progress who won't be swayed by skepticism from peers or financial motives.

In the second stage, the move from MIT and the beginning of FDA interaction, an off-campus laboratory site will need to be acquired. At this point, it will be necessary to look elsewhere for supplemental funding. Some research money will still be available, but it is important to expect much of it to be linked to university settings. Venture capital firms are one consideration. In the past 10 years, $40+ billion has been invested in the U.S. by such firms in the medical device/biotech field [11]. However, the "easy" money may not be enough to offset the consequences- loss of decision-making control, loss of complete ownership, etc.- that are well-known requirements for interaction. Another funding supplement could come from "angel" investors; the area of SCI actually is a very likely place for these people or organizations to exist. Finally, supplements for small businesses should be explored and the resources of the United States Small Business Administration organization tapped.

The FDA clinical trials for obtaining the PMA (roughly the third stage) will also be quite expensive. At this point, in conducting a cost analysis for business strategy one should make the decision between keeping all research "in house" or employing a Contract Research Organization (CRO) to help with the many aspects of research needed to create a comprehensive case to submit to the CDRH. CRO's can offer services for clinical trials such as:

> Bibliography analysis
> Clinical investigation plan and final report preparation
> Investigator brochure and interface with physicians and hospitals
> Design of Case Report Form (CRF)
> Interaction with ethical committee
> Selection of investigators, investigation sites, study monitoring and inspection
> Data management, result evaluation and statistical analysis
> Clinical risk analysis
> Assistance in regulatory submissions
> Materiovigilance [13].

However, the infrastructure may already be present in the company for conducting these processes as a result of the previously completed research and such outsourcing may not be cost-effective.

Finally, the implant will be ready and approved for human surgeries. At this stage, the surgeons brought on board during the first steps of the project will become indispensable. They will be responsible for successful surgeries and, just as importantly, for educating the medical community. Initially, surgery for the implantation of the model will only be available through these surgeons. Giving these doctors this luxury of initial exclusivity will provide the necessary incentive for their participation in the research and company. The recognition for scientific advancement will hopefully prove successful in motivating the surgeons to help bring the model to the forefront of the medical community, as there is monetary incentive for the larger hospital organizations to keep

the current SCI treatments in place. Finally, the structure of the national SCI Model Systems could be exploited to provide enough centers throughout the U.S. for patients to receive the surgery.

5.2 Approach Two

As can be seen from the above approach, the process of getting an implant to market has many levels and variables and requires a good amount of expertise in a variety of areas. The actual approach selected to continue pursuing this technology was to enter into collaboration with GMP Companies, Inc. [14] The company uses an intense technology evaluation process to select various pharmaceutical, diagnostic, and medical device technologies to "drive innovations through every step of research, development, and commercialization." GMP requires that the technology meet the following criteria:

- High impact on society by serving an unmet need
- Obviousness - an idea that is easy to explain and to understand
- Accomplished innovators with proven track records
- Ahead of its time - ground breaking clinically and scientifically
- Strong intellectual property protection - patentability and freedom to operate
- Long product life cycles in large markets
- Significant potential profit margins [15]

It is evident from this list that the SCI technology being discussed is a natural fit for the ideal GMP technology.

Once the technology has been selected by GMP, the appropriate patents are licensed from the host so that GMP can work freely with the product. The incentive for collaboration with GMP is that they will help provide a streamlined, efficient process for

getting the technology into production. They do so by "strategic relationships" with companies such as 3M, Motorola, P&G, Medtronic, Hillenbrand Industries, and Quest Diagnostics. They also have a network of scientific advisors who are considered to be the top researchers in their respective fields. Included in this group are Professor Langer, Dr. M. Judah Folkman, Dr. Brem, and Dr. Joseph P. Vacanti, who would all be able to give important insight for the SCI technology development. Specifically, in exchange for licensing the technology to GMP, they offer to:

- Provide the R&D, medical, business, financial and legal resources necessary to move promising product candidates forward
- Develop protocols for pre-clinical research and clinical trials that facilitate movement through the regulatory process
- Develop a broad spectrum of programs including business development, product design, marketing and sales
- Provide a comprehensive team of legal and regulatory specialists with expertise in the areas of patent and intellectual property and FDA regulations
- Listen closely, respect confidentiality and work collaboratively to develop and commercialize promising technologies in a timely manner [15]

Fourteen MIT patents have been licensed to MIT, on thirteen of which Professor Langer is listed as an Inventor. Listed in Appendix A, these patents protect the wide range of research avenues for the SCI implant. It is also important to note that seven of these patents have corresponding European and Japanese patents so that the technology is protected internationally as well. GMP has a special division for Tissue Engineering / Neurocare headed by Professor Langer, Dr. Vacanti, and Dr. Snyder. They have just entered into a three-year Sponsored Research Agreement with The Burnham Institute in La Jolla, California to further research in this division. While research will still continue at the original institutions as well, the partnership with GMP provides the overall

pathway and complete set of resources to bring some form of the implant model to market.

6.0 CONCLUSIONS

The potential for exploiting the huge untapped market of SCI exists but there are a few barriers. The first is obviously the development of the proper technology. The proposed model provides enough flexibility to keep pace with the evolving scientific understanding of the mechanisms behind SCI and its cure. Next, the FDA regulations and requirements must be met. Finally, the business model must include a way to increase acceptance of the implant and find a way to avoid getting blocked by those who benefit the most from the huge current market of SCI treatment and care. If the clinical results hold and the FDA can be convinced, a great deal of profit is available especially if the product is the first to the market. Additionally, the path through the FDA and to the market is not cleared once one group passes through. Thus there is a certain amount of buffer available between future product development and their presence (and thus competition) in the market. Finally, it must be stressed that while this is a technology that must be treated as all others, if it indeed can become a reality, the global non-financial impact will be orders of magnitude greater than monetary profits.

REFERENCES

1. McDonald, J.W. & Sadowsky, C. Spinal-cord Injury. *Lancet* 2002; 359:417-25.

2. Center, N.S.C.I.S. (University of Alabama, Birmingham, Alabama, 2000).

3. Schmidt, C.E. & Leach, J.B. Neural Tissue Engineering: Strategies for Repair and Regeneration. *Annual Review Biomedical Engineering* 2003; 5:293-347.

4. Center, N.S.C.I.S. Facts and Figures at a Glance. (University of Alabama, Birmingham, Alabama, December 2003).

5. Bellamkonda, R., Ranieri, J.P., Bouche, N. & Aebischer, P. Hydrogel-Based Three Dimensional Matrix for Neural Cells. *Journal of Biomedical Materials Research* **29**, 663-671 (1995).

6. Chang, A.S. & Yannas, I.V. in *Neuroscience Year, Supplement to the Encyclopedia of Neuroscience* (eds. Smith, B. & Adelman, G.) 125-126 (1992).

7. Hermanson, G.T. *Bioconjugate Techniques* (Academic Press, San Diego, 1996).

8. Rich, D.H. & Singh, J. in *The Peptides: Analysis, Synthesis, Biology* (eds. Gross, E. & Meienhofer, J.) 241-261 (Academic Press, New York, 1979).

9. Lavik, Erin. *Functional Recovery following Traumatic Spinal Cord Injury Mediated by a Novel Polymer Scaffold Seeded with Neural Stem Cells*, Sc.D. Thesis, Department of Materials Science and Engineering, MIT (2001).

10. Teng, Y.D., Lavik, E.B., Qu, X.L., Park, K.I., Ourednik, J., Zurakowski, D., Langer, R., Snyder, E.Y. (2002) *Functional Recovery following traumatic spinal cord injury mediated by a unique polymer scaffold seeded with neural stem cells.* Proc Natl Acad Sci USA 99:3024-3029.

11. *Global Summary of Spinal Cord Injury, Incidence, and Economic Impact.* International Campaign for Cures of Spinal Cord Injury Paralysis (ICCP), October 2001.

12. Center for Devices and Radiological Health, U.S. Food and Drug Administration (http://www.fda.gov/cdrh/)

13. North American Science Associates (NAMSA) (http://www.namsa.com/index.asp)

14. **GMP Companies, Inc.** (http://www.gmpcompanies.com)

15. **GMP Companies, Inc.**
(http://www.gmpcompanies.com/htmlsite/researchanddev/subpages/tech.eval.html)

Appendix A: MIT Patents Licensed to GMP Companies, Inc.

1. M.I.T. Case No. 3946, "Novel Non-Peptide Bioerodible Polymers Based On Naturally Occurring X-Amino Acids," by Joachim B. Kohn and Robert S. Langer

   United States of America Patent No. 4638045, Issued January 20, 1987
   "Non-Peptide Polyamino Acid Bioerodible Polymers", by Joachim B. Kohn and Robert S. Langer

2. M.I.T. Case No. 4051, "The Use Of Biodegradable Poly (Iminocarbonates) As Biomaterials For Medical Applications," by Joachim B. Kohn and Robert S. Langer

   United States of America Patent No. 4806621, Issued February 21, 1989
   "Biocompatible Bioerodible Hydrophobic Implantable Polyamino Carbonate Article", by Joachim B. Kohn and Robert S. Langer

3. M.I.T. Case No. 4279, "Controlled Cellular Implantation Using Artificial Matrices," by Robert S. Langer and Joseph P. Vacanti

   Japan Patent No. 2067741, Issued July 10, 1996
   "Chemical Neomorphogenesis Of Organs By Controlled Cellular Implantation Using Artificial Matrices."
   Canada Patent No. 1340581, Issued June 8, 1999
   United States of America Patent No. 5759830, Issued June 2, 1998
   United States of America Patent No. 5770193, Issued June 23, 1998
   United States of America Patent No. 5770417, Issued June 23, 1998
   "Chimeric Neomorphogenesis Of Organs By Controlled Cellular Implantation Using Artificial Matrices"
   Austria Patent No. E139432, Issued June 19, 1996
   Belgium Patent No. 0299010, Issued June 19, 1996
   European Patent Convention Patent No. 0299010, Issued June 19, 1996
   France Patent No. 0299010, Issued June 19, 1996
   Germany Patent No. P3751843.7, Issued June 19, 1996
   Italy Patent No. 0299010, Issued June 19, 1996
   Luxembourg Patent No. 0299010, Issued June 19, 1996
   Netherlands Patent No. 0299010, Issued June 19, 1996
   Sweden Patent No. 0299010, Issued June 19, 1996
   Switzerland Patent No. 0299010, Issued June 19, 1996
   United Kingdom Patent No. 0299010, Issued June 19, 1996
   "Chimeric Neomorphogenisis Of Organs By Controlled Cellular Implantation Using Artificial Matrices"
   by Robert S. Langer and Joseph P. Vacanti

4. M.I.T. Case No. 4332, "Biodegradable Materials For The Regeneration Of Tissues," by Ariel G. Ferdman, Elaine Lee and Ioannis V. Yannas

United States of America Patent No. 4947840, Issued August 14, 1990
"Biodegradable Templates For The Regeneration Of Tissues"
by Ariel G. Ferdman, Elaine Lee and Ioannis V. Yann

5. M.I.T. Case No. 4371, "Hydroxamic Acid Polymers From Primary Amide Polymers," by Ernest G. Cravalho, Abraham J. Domb, Gershon Golumb, Robert S. Langer, Cato T. Laurencin and Edith Mathiowitz

United States of America Patent No. 5,128,420, Issued July 7, 1992
"Method of Making Hydroxamic Acid Polymers From Primary Amide Polymers, by Ernest G. Cravalho, Abraham J. Domb, Gershon Golumb, Robert S. Langer, Cato T. Laurencin and Edith Mathiowitz

6. M.I.T. Case No. 4973, "Method Of Implanting Large Cell Volume On A Polymeric Matrix," by Lynt Johnson, Robert S. Langer and Joseph P. Vacanti

Australia Patent No. 636346, Issued August 23, 1993
Austria Patent No. E119787, Issued October 25, 1995
Belgium Patent No. 0422209, Issued October 5, 1995
Canada Patent No. 2031532, Issued February 25, 2003
France Patent No. 0422209, Issued October 5, 1995
Germany Patent No. 69017820, Issued October 5, 1995
Italy Patent No. 0422209, Issued October 5, 1995
Japan Patent No. 3073766, Issued June 2, 2000
Netherlands Patent No. 0422209, Issued October 5, 1995
Spain Patent No. 0422209, Issued October 5, 1995
Sweden Patent No. 0422209, Issued March 15, 1995
Switzerland Patent No. 0422209, Issued October 5, 1995
United Kingdom Patent No. 0422209, Issued October 5, 1995
United States of America Patent No. 5804178, Issued September 8, 1998
"Method For Implanting Large Volumes Of Cells On Polymeric Matrices"
by Lynt Johnson, Robert S. Langer and Joseph P. Vacanti

7. M.I.T. Case No. 5573, "Preparation Of Highly-Porous Biodegradable Polymer Membranes By A Particulate-Leaching Technique," by Linda G. Griffith, Robert S. Langer, Antonios G. Mikos, Georgios Sarakinos and Joseph P. Vacanti

United States of America Patent No. 5514378, Issued May 7, 1996
"Biocompatible Polymer Membranes And Methods Of Preparation Of Three Dimensional Membrane Structures"
by Linda G. Griffith, Robert S. Langer, Antonios G. Mikos, Georgios Sarakinos and Joseph P. Vacanti

8. M.I.T. Case No. 5729, "Prevascularized Polymeric Implants For Organ Transplantation," by James C. Gilbert, Donald E. Ingber, Robert S. Langer, James E. Stein and Joseph P. Vacanti

Austria Patent No. 0610423, Issued May 7, 1997
Belgium Patent No. 0610423, Issued May 7, 1997
Canada Serial No. 2121040, Filed October 28, 1992
European Patent Convention Patent No. 0610423, Issued May 7, 1997
France Patent No. 0610423, Issued May 7, 1997
Germany Patent No. 69219613, Issued May 7, 1997
Italy Patent No. 0610423, Issued May 7, 1997
Japan Patent No. 3524919, Issued February 20, 2004
Japan Serial No. 2001-397626, Filed October 28, 1992
Luxembourg Patent No. 0610423, Issued May 7, 1997
Netherlands Patent No. 0610423, Issued May 7, 1997
Sweden Patent No. 0610423, Issued May 7, 1997
United Kingdom Patent No. 0610423, Issued May 7, 1997
United States of America Patent No. 6309635, Issued October 30, 2001
United States of America Serial No. 09/942535, Filed August 29, 2001
"Prevascularized Polymeric Implants For Organ Transplantation"
by James C. Gilbert, Donald E. Ingber, Robert S. Langer, James E. Stein and Joseph P. Vacanti

9. M.I.T. Case No. 6560, "Porous Biodegradable Polymeric Materials For Cell Transplantation," by Linda G. Griffith, Donald E. Ingber, Robert S. Langer, Antonios G. Mikos, Georgios Sarakinos and Joseph P. Vacanti

United States of America Patent No. 6689608, Issued February 10, 2004
United States of America Serial No. 10/775768, Filed February 10, 2004
"Porous Biodegradable Polymeric Materials For Cell Transplantation"
by Linda G. Griffith, Donald E. Ingber, Robert S. Langer, Antonios G. Mikos, Georgios Sarakinos and Joseph P. Vacanti

10. M.I.T. Case No. 6798, "Localized Delivery Of Growth Factors To Transplanted Cells," by Robert S. Langer, David J. Mooney and Joseph P. Vacanti

Austria Patent No. 0794790, Issued April 17, 2002
Belgium Patent No. 0794790, Issued April 17, 2002
Canada Patent No. 2207286, Issued October 7, 2003
Denmark Patent No. 0794790, Issued April 17, 2002
European Patent Convention Patent No. 0794790, Issued April 17, 2002
France Patent No. 0794790, Issued April 17, 2002
Germany Patent No. 0794790, Issued April 17, 2002
Greece Patent No. 0794790, Issued April 17, 2002
Ireland Patent No. 0794790, Issued April 17, 2002

Italy Patent No. 0794790, Issued April 17, 2002
Japan Serial No. 8-519275, Filed December 14, 1995
Liechtenstein Patent No. 0794790, Issued April 17, 2002
Luxembourg Patent No. 0794790, Issued April 17, 2002
Monaco Patent No. 0794790, Issued April 17, 2002
Netherlands Patent No. 0794790, Issued April 17, 2002
Portugal Patent No. 0794790, Issued April 17, 2002
Spain Patent No. 0794790, Issued April 17, 2002
Sweden Patent No. 0794790, Issued April 17, 2002
Switzerland Patent No. 0794790, Issued April 17, 2002
United Kingdom Patent No. 0794790, Issued April 17, 2002
United States of America Patent No. 6281015, Issued August 28, 2001
"Localized Delivery Of Factors Enhancing Survival Of Transplanted Cells", by Robert S. Langer, David J. Mooney and Joseph P. Vacanti

11. M.I.T. Case No. 6984, "Functional, Degradable Poly(Lactic Acid-Co-Amino Acid) Graft Copolymers," by Jeffrey S. Hrkach, Robert S. Langer and Noah Lotan

United States of America Patent No. 5654381, Issued August 5, 1997
"Functionalized Polyester Graft Copolymers"
by Jeffrey S. Hrkach, Robert S. Langer and Noah Lotan

12. M.I.T. Case No. 7138, "Neuronal Stimulation Using An Electrically Conductive Polymer-Polypyrrole," by Robert S. Langer, Christine E. Schmidt, Venkatram P. Shastri and Joseph P. Vacanti

Australia Patent No. 720275, Issued September 11, 2000
Canada Serial No. 2236749, Filed October 31, 1996
European Patent Convention Serial No. 96937894.2, Filed October 31, 1996
Japan Serial No. 9-517608, Filed October 31, 1996
Korea (south) Serial No. 98-703320, Filed October 31, 1996
New Zealand Patent No. 321886, Issued June 8, 2000
United States of America Patent No. 6095148, Issued August 1, 2000
"Neuronal Stimulation Using Electrically Conducting Polymers"
by Robert S. Langer, Christine E. Schmidt, Venkatram P. Shastri and Joseph P. Vacanti