Characterization of New and Defender Technologies

Working Paper #1

Prepared for

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RTI Project Number 6715-1 WP

January 1997

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1 Introduction

The National Institute of Standards and Technology's (NIST's) Advanced Technology Program (ATP) began in 1990 as a cost-sharing program to assist U.S. industry in pursuing high-risk, enabling technologies with significant commercial and economic potential. The ATP conducts economic analysis for the purpose of increasing and measuring the short- and long-run impacts of the technology development projects it funds and for the program overall.

This project furthers ATP's objectives for economic analysis by examining the economic impact of ATP-funded projects in tissue engineering. These seven projects, described in Table 1-1, constitute a "virtual program" in tissue engineering. If successful, these projects will serve as platforms for developing many new therapies to treat a variety of diseases and injuries. These therapies lead to significant social returns by improving patient outcomes, reducing the cost of medical care, or both. In addition, these technologies may bring significant private returns to ATP recipients. Research Triangle Institute (RTI), under contract to NIST, is conducting economic analyses of ATP's program in tissue engineering.

1.1 PROJECT OVERVIEW

Our approach to estimating the social and private returns to ATP-funded projects in tissue engineering is based on applied welfare economics principles. As advocated by Harberger (1971),

Table 1-1. Summary of ATP-Funded Programs in Tissue Engineering
The first three companies listed below are candidates for in-depth case studies.

Company Name: Aastrom Biosciences, Inc.	***Contact:*** Dr. R. Douglas Armstrong (313) 930-5555	***Phone:*** (313) 930-5555	***Fax:*** (313) 665-0485
Address: 24 Frank Lloyd Wright Drive Lobby L Ann Arbor, MI 48104		***Competition No./ Funding Years:*** 91-01 2 years	***Funding Level:*** $1,220 K
Project Title **"**Human Stem Cell and Hematopoietic Expansion Systems in Tissue Engineering" ***Project Description*** Develop prototype bioreactor to grow human stem cells, especially bone marrow cells			
Company Name: Integra LifeSciences Corp.	***Contact:*** George L. Brode (609) 936-2325	***Phone:*** (609) 683-0900	***Fax:***
Address: 150 Morgan Lane Plainsboro, NJ 08536		***Competition No./ Funding Years:*** 93-01 3 years	***Funding Level:*** $1,999 K
Project Title **"**Structurally New Biopolymers Derived from Alpha-L-Amino Acids" ***Project Description*** Develop synthetic polymers for orthopedic applications (repairing cartilage and tendons)			
Company Name: VivoRx, Inc.	***Contact:*** Derek Brown (310) 264-7768	***Phone:*** (310) 264-7768	***Fax:*** (310) 264-7775
Address: 3212 Nebraska Ave. Santa Monica, CA 90404		***Competition No./ Funding Years:*** 94-01 3 years	***Funding Level:*** $2,000 K
Project Title "Treatment of Diabetes by Proliferated Human Islets in Photocrosslinkable Alginate Capsules" ***Project Description*** Grow human islet cells and explore encapsulation techniques to help treat insulin-dependent diabetes			
Company Name: Tissue Engineering, Inc.	***Contact:*** Dr. Eugene Bell (617) 946-0520	***Phone:*** **(**617) 247-2922	***Fax:*** (617) 247-2922
Address: 305 Commonwealth Ave. Boston, MA 02115		***Competition No./ Funding Years:*** 92-01 3 years	***Funding Level:*** $1,999 K
Project Title **"**Fabrication of Clinical Prosthesis from Biomaterials" ***Project Description*** Develop animal-derived extracellular matrix materials technology for future prostheses			

(continued)

Table 1-1. Summary of ATP-Funded Programs in Tissue Engineering (continued)

Company Name: (a) BioHybrid Technologies, Inc. and (b) Synergy Research Corp.	***Contact:*** John L. Hayes (508) 842-4460	***Phone:*** (a) (508) 842-4460 (b) 603) 448-6322	***Fax:***
Address: (a) Park Nine West 910 Turnpike Rd. Shrewsbury, MA 01545 (b) 325 Mount Support Rd. Hanover, NH 03755-5056		***Competition No./ Funding Years:*** 93-01 3 years	***Funding Level:*** $4,263 K
Project Title ***"***Disease Treatment Using Living Implantable Microreactors" ***Project Description*** Develop living implantable microreactors that contain transplant cells			
Company Name: Alexion Pharmaceuticals	***Contact:*** David Keiser (203) 776-1790	***Phone:*** (203) 776-1790	***Fax:*** (203) 772-3655
Address: 25 Science Park, Suite 360 New Haven, CT 06511		***Competition No./ Funding Years:*** 95-01 3 years	***Funding Level:*** $1,999 K
Project Title "Universal Donor Organs for Transplantations" ***Project Description*** Develop techniques to produce animal organs that will not be rejected by patient			
Company Name: Progenitor, Inc.	***Contact:*** Douglass Given (614) 488-6688	***Phone:*** (614) 593-0496	***Fax:*** (614) 593-0641
Address: 1507 Chambers Road Columbus, OH 43212		***Competition No./ Funding Years:*** 94-01 3 years	***Funding Level:*** $1,996 K
Project Title ***"***Application of Gene Therapy to Treatment of Cardiovascular Diseases" ***Project Description*** Develop stem cells for cell-based therapies for vascular disorders and for anti-rejection (repair damaged tissue)			

prices and quantities of commodities traded in competitive markets can be used to produce Marshallian measures of welfare. However, because the market for medical treatment is distorted by institutional factors, we cannot use prices and quantities to infer the change in welfare due to advances in treatment. Instead, we must estimate the benefits of the technology by directly measuring the benefits of the new technology to patients. We must measure the costs to society by considering not only the costs of R&D, commercialization, marketing, and production, but also resources

that must be used to apply the new technology to its intended medical applications.

We plan to give NIST a spreadsheet model that will provide the capability to analyze the returns to these projects under alternative assumptions. We will build a single model that will be generally applicable to each of the seven tissue engineering projects that NIST has specified. We will collect data to inform the model for each of the seven projects. However, for the three projects that NIST has identified as case studies, we will conduct a more intensive data collection effort. Because the benefits and costs of these technologies will be uncertain for a number of years, we will incorporate the capability for computing confidence intervals and for updating the data as it becomes available.

Figure 1-1 provides an overview of our workplan, which includes five tasks. A more detailed description of our plans for completing this project is contained in our project workplan.

1.2 WORKING PAPER OBJECTIVES

This working paper reports our findings from Task 1. The objective of Task 1 was to provide background and input to Tasks 2, 3, and 4. Specifically, we aimed to

- describe each of the new technologies;
- identify and describe each technology's applications (e.g., the disease or condition they address);
- identify and describe alternative (defender) technologies or treatment methods;
- compare patient outcomes for new and defender technologies;
- describe resource use under new and defender technologies; and
- develop the assumptions for each analysis.

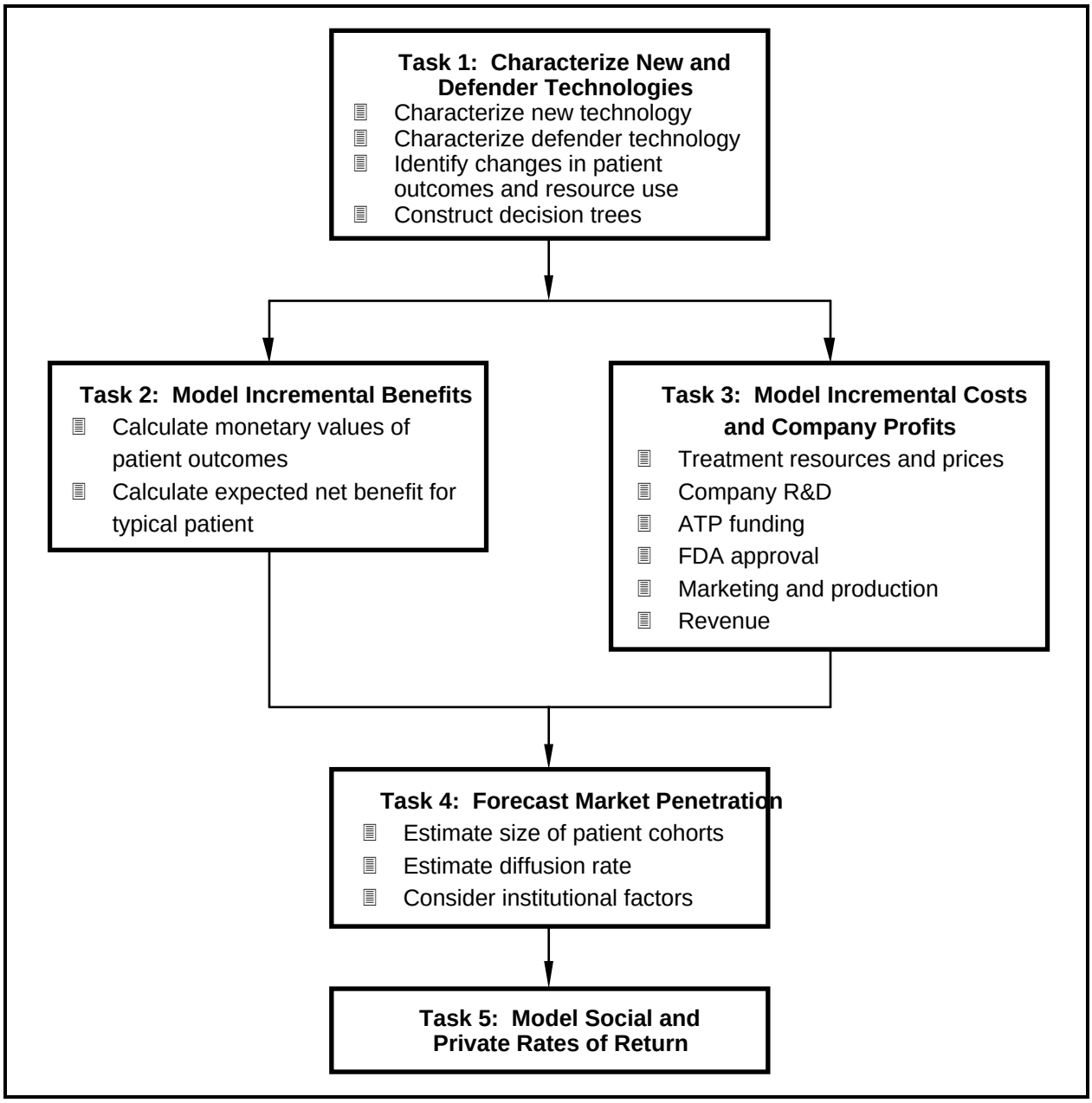
In making our decisions about model structure and assumptions, we must consider

- the need for flexibility,
- the limitations of the available data, and
- the limitations of the project's scope.

This task is very important to the remainder of the project. We must make important decisions about assumptions and model structure that will affect the reminder of the project and its results. In making these decisions, we must consider the following:

1. The need for flexibility. Our objective is to develop an analysis model that NIST will be able to apply to many projects. Tissue engineering is only one area in which NIST funds projects that affect medical costs and outcomes. To maximize the flexibility of the model, our approach must not be structured with restructive assumptions about the impacts of the projects on medical outcomes and costs.

Figure 1-1. Overview of Project Workplan
Our workplan consists of five tasks.



2. The limitations of the available data. In making our assumptions, we must recognize that much of the data required to construct an estimate of the social and private rates of return to ATP projects in tissue engineering are, at best, uncertain. We must construct a model with the flexibility to incorporate new data as it becomes available and to conduct sensitivity analysis so that we are aware of the implications of the uncertainty of our data for the empirical results.
3. The limitations of the scope of the project. There is an inevitable tension between our desire to perfect the model and analysis and NIST's need for a usable product in time to provide insight to the economic impact of its projects. We must make choices regarding the best way to allocate the time and resources available for model building and analysis.

1.3 REPORT ORGANIZATION AND NEXT STEPS

Section 2 describes our assumptions regarding the characterization of new and defender technologies developed through ATP projects in tissue engineering. Appendix A contains summaries of each of the interviews we have conducted as part of this task.[1]

Our next working paper will describe the model we will use to calculate the health benefits of these new technologies. In Working Paper #3, we will describe how the costs and revenues to companies will be modeled. In Working Paper #4, we will describe our methodology and results of our market penetration forecast for each of these technologies. Finally, we will combine all of this information to derive measures of social and private rates of return. We will report the results of this analysis in the final report.

[1] At this time, we have completed five of the seven interviews for tissue engineering projects. Of these, three companies have approved the release of our interview summaries. We will send NIST the remainder of these interview summaries as soon as each company has approved its release.

2 Tissue Engineering Technologies

This section discusses and summarizes our assumptions regarding the characterization of the new technologies developed in tissue engineering and their defender technologies.

First, we identify a single application for each of the ATP projects. Second, we describe the patient population relevant to each technology. Third, we describe how we identified the defender technology for each project—that is, the technology against which we will evaluate the new technology. Fourth, we describe differences in health outcomes for new and defender technologies. Finally, we describe differences between the new and defender technologies with respect to their use of medical resources.

Throughout this section, we summarize our assumptions in brief tables. Further details of each project can be found in Appendix A.

2.1 IDENTIFY APPLICATIONS

Although ATP projects in tissue engineering will probably have many applications, we will model only the application that is most likely to develop in the short term.

We began our analysis by identifying a single application for each of the ATP-funded projects in tissue engineering. Although these enabling technologies will have many applications, if successful, each of these projects also has an immediate application that is most likely to develop in the short term. We decided to model only these most immediate applications because the data regarding their impacts on health outcomes, resource use, and the timing of their diffusion will be much more reliable than for the more distant and uncertain applications.

This assumption probably leads to an underestimate of the benefits of these enabling technologies. The knowledge created from developing

the first application of these technologies will likely spillover to other applications. We will try to mitigate this problem by measuring costs commensurate with our measurement of benefits (e.g., measure only the costs associated with developing and commercializing this particular application).

We developed an initial assumption about the most immediate application of each technology from reading project proposals, abstracts, and other publicly available information. We confirmed this information in our interviews with representatives of the recipient companies.[1] For each technology, Table 2-1 lists the application, the patient population, and the defender technology.

For most of these projects, the most immediate and likely application was readily apparent. However, this was not the case for the project—"Application of Gene Therapy to Treatment of Cardiovascular Disease." The recipient company intended its original application to be vascular diseases (in particular, angioplasty), but they have since made a discovery that has taken their commercialization plans in a new direction. They are now focusing on two applications: imaging of solid tumors and treatment of solid tumors. Of these, the imaging application is much closer to commercialization, so our model will address the benefits of this application.

2.2 IDENTIFY THE PATIENT POPULATION

We asked each company to identify the relevant patient population. We will supplement this information with data from the health literature.

The second important characteristic of each technology is the patient population that will benefit from the technology. We must determine not only the type of patient (e.g., specific medical condition) for the application, but also the number of patients that fall into these patient categories.

During our project interviews, we asked the company representatives to identify the patients that would benefit from each of the applications identified. In some cases, the companies were able to provide an estimate of the size of this population; in other

[1]We have not yet interviewed two of the seven companies. We will verify our initial assessment during our upcoming interviews with these companies.

Table 2-1. Applications, Patient Populations, and Defender Technologies for ATP Projects in Tissue Engineering
Our model of the costs and benefits of ATP projects in tissue engineering will incorporate these assumptions about the relevant applications, patient populations, and defender technologies.

ATP Project	Application	Patient Population	Defender Technology
Human Stem Cell and Hematopoietic Expansion Systems	Stem cell harvest	Patients receiving stem cell therapy for dose-sensitive cancers (autologous transplants) or their donors (allogenic transplants)	Peripheral blood progenitor cell collection (PBPC)
Structurally New Biopolymers Derived from Alpha-L Amino Acids	Fracture fixation	Patients with the following injuries: ‰ nonweight-bearing fractures (e.g., mulleolus, condyles, small bones in hand or foot) ‰ dental and maxillofacial fractures ‰ weight-bearing, long bone fractures	Metal fixation devices
Treatment of Diabetes by Proliferated Human Islets in Photocrosslinkable Alginate Capsules	Insulin-dependent diabetes	All Type I diabetics, Insulin-dependent Type II diabetics	Daily insulin injections
Disease Treatment Using Living Implantable Microreactors	Insulin-dependent diabetes	All Type I diabetics, Insulin-dependent Type II diabetics	Daily insulin injections
Universal Donor Organs for Transplantations[a]	Organ transplants	Major organ (heart, lung, liver, pancreas, kidney) transplant candidates	Wait for human donor and receive standard treatment
Application of Gene Therapy to Treatment of Cardiovascular Diseases[a]	Tumor imaging	Patients with solid tumor cancers	Standard tumor imaging technologies
Fabrication Using Clinical Prosthesis from Biomaterials[a]	Vascular prosthesis	Varies	Varies

[a]Preliminary assessment to be verified through project interviews.

cases, we will collect this information from the relevant health literature.

Table 2-1 provides the assumptions we will make about the relevant patient population for each technology.

2.3 IDENTIFY DEFENDER TECHNOLOGY

The defender technology is the most widely used current treatment regimen for the specific application of interest.

Our model requires that we measure the benefits of the new technology compared to some alternative. Ideally, that alternative would be the treatment regimen that the new technology would replace. In some cases, competitors of ATP recipients are currently developing technologies for the same applications as the ATP projects. We had to decide whether to consider these emerging technologies as candidates for defender technologies. We decided that, given the uncertainty of the technical and market success of these emerging technologies, we would define the defender technology as the most widely used current treatment regimen for the specific application of interest.

As with the technology applications, we identified the defender technologies from reading project proposals and other publicly available information and verified these technologies during project interviews.

Table 2-1 lists the defender technologies for each application. In most cases, these defender technologies were easy to identify. However, the defender technology was more difficult to identify for some projects, particularly those with broad applications.

Identifying a single defender technology for each application may lead to understatement or overstatement of the benefits of the new technology. For certain classes of patients, a different defender technology would be more appropriate because of their age or medical condition. The less uniform the current treatment for each application, the more serious the implications of this assumption. A future project might improve the accuracy of the empirical results of the model by dividing the patient population for some projects into different groups according to their most appropriate defender technology.

2.4 DESCRIBE DIFFERENCES IN HEALTH OUTCOMES

New technologies can affect patient welfare and treatment costs in two ways:

- They can change the probability of certain outcomes (e.g., death, immobility, pain). For example, the ability to achieve tight glycemic control through transplantation of human islet cells may reduce the probability that diabetes leads to limb amputation or blindness.
- They can change the cost of a health intervention by affecting the methods used to obtain given health outcomes. For example, while a human stem cell and hematopoietic expansion system may not affect the ultimate health outcomes of bone marrow transplants, it can reduce the pain, suffering, hospitalization, risk of complications, and cost associated with the procedure.

New technologies can affect patient welfare and treatment costs by

- changing the probability of health outcomes and
- changing the methods used to achieve a health outcome.

During our interviews with company representatives, we asked them to identify the differences between their technology and the new technology that will have an impact on the patient's health outcomes or treatment costs. In most cases, they were able to describe these impacts qualitatively; in some cases, they were able to provide estimates of changes in probabilities of health outcomes.

Table 2-2 summarizes the information they provided. We will supplement this primarily qualitative data with data we will gather from the available health literature. Table 2-2 also provides sources of data for some of these health outcomes. We will explain our health benefits model and the data we will use to populate it more completely in Working Paper #2.

2.5 DESCRIBE DIFFERENCE IN RESOURCE USE

Another important characteristic of the new technologies compared to the defender technologies is the differences in the cost of treating patients. New technologies can change the use of resources for treating a patient by reducing the risk of associated health outcomes (e.g., reducing the risk of retinopothy in diabetes patients reduces the overall cost of treating diabetics for retinopathy). These technologies can also reduce costs by improving the efficiency with which diseases and injuries are treated.

Table 2-2. Impact of New Technologies on Patient Outcomes: Characterization and Data Sources
We will consult the available data on health outcomes to quantify these qualitative assessments.

ATP Project	Patient Outcomes Affected by New Technology	Source of Outcome Data
Human Stem Cell and Hematopoietic Expansion Systems	Minimal impact. May reduce the probability of metastasis	Boogaerts and Demuynch (1994) Champlin (1996) Faucher et al. (1994) Hillner, Smith, and Desch (1993)
Structurally New Biopolymers Derived from Alpha-L Amino Acids	Reduces stress shielding Reduces risk of secondary fractures due to screw holes Eliminates removal surgery Reduces potential for tissue abrasion or device loosening and migration	Sinisaari et al. (1996) Rokkanen et al. (1996)
Treatment of Diabetes by Proliferated Human Islets in Photocrosslinkable Alginate Capsules	Reduces complications of diabetes as noted by the Diabetes Complications and Control Trial (DCCT) study	Eastman et al. (1993) DCCTRG (1996) DCCTRG (1995)
Disease Treatment Using Living Implantable Microreactors	Reduces risk of complication ranges from the findings of the DCCT to a low of zero complication rate	Eastman et al. (1993) DCCTRG (1996) DCCTRG (1995)
Universal Donor Organs for Transplantations[a]	Makes more organs available, eliminating complications of standard treatment (eventual organ failure)	Evans (1993) Eggers and Kucken (1994) Schaeffer and Alexander (1992)
Application of Gene Therapy to Treatment of Cardiovascular Diseases[a]	Imaging improves diagnosis	Wolf (1994) Griffith and Williams (1992) Meyenberger et al. (1995)
Fabrication Using Clinical Prosthesis from Biomaterials[a]	To be determined	Vieth and Marin (1996) Perler (1995) Paaske and Laustsen (1995)

[a]Preliminary assessment to be verified through project interviews.

During our interviews with company representatives, we asked them to identify how the new technology would change the expenditure of health care resources. Table 2-3 provides their answers. In many cases, savings result from improvement in health outcomes and from the increased efficiency of providing a specific health benefit. In other cases, however, the treatment uses more resources than the defender treatment but reduces resource expenditures by improving health effects. In other cases, there are virtually no health effects and the total amount of savings is due to the increased efficiency of the treatment. A good example of this last case is the human stem cell expansion project: the long-term health outcomes do not change, only the method of achieving them. This technology saves resources compared to the defender technology because it requires fewer outpatient visits and fewer drugs.

We will supplement the data provided by the company representatives with data we will gather from secondary sources. Tables 2-2 and 2-3 provide sources of data for these resources. We will develop these data and the assumptions involved in applying them to each technology in Working Paper #3.

Table 2-3. Impact of New Technologies on Resource Use
We will quantify the qualitative impacts identified by company representatives with cost data from the health economics literature.

ATP Project	Impact on Resource Use	Source of Cost Data
Human Stem Cell and Hematopoietic Expansion Systems	Decreases the number of visits; decreases procedure time; eliminates need for cell migration drugs	Boogaerts and Demuynch (1994) Champlin (1996) Faucher et al. (1994) Hillner, Smith, and Desch (1993)
Structurally New Biopolymers Derived from Alpha-L Amino Acids	Eliminates need for removal surgery May decrease length of stay May decrease operating room time Reduces costs associated with secondary fractures due to stress shielding and screw holes	Bostman (1994) Levin and Condit (1996) Shaw and Lawton (1995) Tiel-van Buul et al. (1995)
Treatment of Diabetes by Proliferated Human Islets in Photocrosslinkable Alginate Capsules	Reduces cost of complications Increases cost of treatment	Eastman et al. (1993) Ray et al. (1996) DCCTRG (1996) DCCTRG (1995)
Disease Treatment Using Living Implantable Microreactors	Reduces cost of complications Increases cost of treatment	Eastman et al. (1993) Ray et al. (1996) DCCTRG (1996) DCCTRG (1995)
Universal Donor Organs for Transplantations[a]	Eliminates the following costs associated with transplants: ‰ maintaining human donors on life support ‰ transporting organ ‰ hospitalizing recipients for extended periods while awaiting organs	Evans (1993) Eggers and Kucken (1994) Schaeffer and Alexander (1992)
Application of Gene Therapy to Treatment of Cardiovascular Diseases[a]	Reduces unnecessary treatment due to incorrect diagnosis	Stommel, Given, and Given (1993) Schuette et al. (1995) Griffith and Williams (1992)
Fabrication Using Clinical Prosthesis from Biomaterials[a]	Unknown	Vieth and Marin (1996) Perler (1995) Paaske and Laustsen (1995)

[a]Preliminary assessment to be verified through project interviews.

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Appendix A

Draft Results of Company Interviews

This appendix contains an overview of our discussions with people involved in NIST's ATP projects in tissue engineering. These interviews provide a basis for the modeling decisions we made in this working paper.

A.1 AASTROM BIOSCIENCES, INC.

We conducted a telephone interview with R. Douglas Armstrong, President of Aastrom Biosciences, Inc., on December 13, 1996, at 10:00 a.m. RTI Project Team members Sheila A. Martin, Dan Winfield, and John Farris participated in the interview. This section incorporates information derived from this interview, as well as information we learned from reading project abstracts, project proposals, and other publicly available company information. Dr. Armstrong has read and approved the release of this information.

Table A-1 provides a summary of the assumptions we will use in modeling the economic impact of this project.

A.1.1 Overview

Aastrom's 2-year ATP project was funded in 1991. The total project budget was $2.734 million; the ATP provided $1.22 million.

Aastrom's ATP project, entitled "Human Stem Cell and Hematopoietic Expansion Systems," was fairly short and well defined. The 2-year project was funded in 1991 for $1.22 million; total project funds were estimated in the ATP project proposal at $2.734 million.

Aastrom sought to develop a bioreactor-based cell expansion system that would support many direct therapeutic applications, including

- autologous (ABMT) and allogenic bone marrow transplants,
- autologous peripheral stem cell transplant (APST),
- human gene therapy, and
- adjutant therapy for T-cell-related disorders like AIDS.

This project also aimed to advance the state of the art by characterizing novel human growth factors and cell growth reagents.

At the time Aastrom applied for ATP funds, they employed only four people. The company has grown very quickly, and, as of September 30, 1996, employed 61 individuals full time. At the time that Aastrom applied for the ATP grant, the University of Michigan

Table A-1. Summary: Model Assumptions for "Human Stem Cell and Hematopoietic Expansion Systems"[a]

Application	Stem cell harvest and transplant, especially as used in high-dose chemotherapy and radiation	
Defender technology	PBPC collection	
Applicable patient population	Patients receiving stem cell therapy for dose-sensitive cancers (autologous transplants) or donors (allogenic transplants)	
Differences in health outcomes	1. Reduction of the probability of reintroducing tumor cells in some patients	
	2. Donor time and discomfort, as noted below	
Differences in resource use	PBPC	Aastrom CPS
Number of outpatient visits	5-7	1
Procedure time (hours)	23-27	1-2
Needle sticks	20-30	4-10
(Additional resources such as anesthesia and drugs to be added)		
R&D costs to company		
ATP grant	$1,220,000	
Initial match	$1,514,000	
Total investment to date	$27.5 million[b]	
Expected total investment to year 2000		
Costs of production and marketing	Unknown	
Expected revenues		
Expected revenue per patient	$12,000 per treatment	
Expected market share	To be estimated via physician interview and diffusion modeling	
Expected date to market	1997 in Europe; 2000 in the U.S.	
Impact of ATP		
Acceleration	1 to 2 years	
Scope effects	None	
Availability of capital	Nonquantifiable effects on the availability of equity capital and partnerships	

[a]There is considerable uncertainty associated with many of the parameters in this table. We will use uncertainty analysis to provide a range of results based on a range of values for some of the most uncertain parameters.

[b]This is total R&D cost to the company. We must try to determine what portion of this is attributable to developing the CPS for this application.

had identified a process for growing stem cells and could accomplish this in small volumes. However, they had not developed a culture system, although they had a couple of prototype devices. The ATP project proposed to develop the Cell Production System (CPS) so that the technology could be used on a clinical scale.

A.1.1.1 Objectives

The objectives of the grant project were to

- identify the parameters of a culture chamber that could implement the conditions for growing bone marrow by controlling the biological and physiological components of the process,
- develop a clinical-scale culture chamber, and
- develop the instrumentation required to run the culture chamber.

A.1.1.2 Applications

The most immediate application of the Aastrom CPS is stem cell replacement for cancer patients undergoing high-intensity chemotherapy and radiation therapy.

This technology will be applied to a number of therapeutic applications that require transplanting stem cells. The most immediate application is for cancer patients who receive high-intensity chemotherapy and radiation therapy that destroy their blood and immune system. These patients typically undergo ABMT (or, more recently, peripheral blood progenitor cell [PBPC] collection and replacement) to replace the body's immune system after this intense chemotherapy and radiation treatment. The technology decreases the pain, inconvenience, and expense of harvesting stem cells. We focus on this application for the purpose of estimating the benefits of this technology.

This technology has a number of other applications in the long term, including the following:

- It can replace stem cells in patients that receive myelotoxic therapy.
- It can provide stem cell therapies for diseases other than cancer, such as autoimmune disorders, including rheumatoid arthritis, lupus, and multiple sclerosis. The technology would be part of a therapy that would destroy the patient's faulty immune system and replace it with a new immune system from generated stem cells. This application is less promising commercially because there are problems with third-party reimbursement.
- This technology can be used to decrease the chance of rejection of a transplanted organ by transplanting stem cells along with an organ. The immune system will recognize the organ.

- In the long run, the research conducted in this project will enable gene therapy.

A.1.1.3 Factors Affecting Technical Success

The main factors affecting technical success are whether and how quickly the cells will engraft.

The main factors affecting technical success are whether and how quickly the cells will engraft. Through preliminary trials, Aastrom has demonstrated that the cells it has grown in its prototype cell culture chamber are safe and do engraft, and Aastrom is very encouraged by these preliminary results. However, it remains to be seen whether Aastrom can demonstrate long-term sustained engraftment of cells comparable to cells obtained from current stem cell therapy procedures.

The other primary technical issue is whether the CPS is sufficiently automated to be operated with minimal operator activity by a medical or laboratory technician at patient care sites with reliable results. Note that no special training will be required for people to use the CPS.

Aastrom expects to begin a multicenter trial of the CPS in late 1997. The results of these trials will support their FDA PMA submission.

Aastrom is currently conducting a pre-clinical trial to show that CPS works and the cells function correctly. Provided these trials are successful, Aastrom will initiate a multicenter trial for using CPS in stem cell therapy. This trial will be used to support the Premarket Approval (PMA) submission to the U.S. Food and Drug Administration (FDA). Aastrom expects to begin these trials, which will take approximately 14 months, by the end of 1997. If these trials are successful, Aastrom will apply for FDA Office of Premarket Approval (OPA) approval. Writing the application will take a few months, and the OPA approval process may take about a year.[1]

Aastrom is currently preparing to initiate clinical trials in France with the hope of obtaining a CE Mark registration that will allow them to market the CPS in Europe. They expect to receive the CE Mark by the end of 1997.

Aastrom has filed for an Initial Public Offering (IPO) of common stock. Because of the restrictions imposed by the Securities and Exchange Commission under the IPO, Dr. Armstrong was not able to provide us his estimates of the probability of technical success.

[1]This implies FDA approval by May 2000. According to *JNCI News* (1996), the CPS will go into pivotal clinical trials in 1996 and could be on the market in 2 or 3 years.

A.1.1.4 Factors Affecting Market Success

The market for this technology in this application includes 35,000 cancer patients who receive high-intensity chemotherapy and radiotherapy that destroy their blood and immune system. These patients include both allogenic bone marrow transplants (10,000) and autologous transplants (25,000). The number of patients that might benefit from this stem cell harvest technique is growing rapidly as stem cell therapy becomes a more popular therapy for breast and ovarian cancer.[2]

The market success of the CPS will depend on two factors:

- whether it will be reimbursed by third-party payers, and
- its cost relative to the current state of the art for stem cell harvest, PBPC collection.

The market for the Aastrom CPS is growing rapidly as stem call therapy becomes more popular for the treatment of breast and ovarian cancer.

In the U.S., third parties are already reimbursing ABMT as a therapy for some cancers, and its acceptance is growing. Once Aastrom has demonstrated the technical success of the CPS and it is no longer regarded as experimental, third-party reimbursement should not be a constraint on Aastrom's market success, particularly if Aastrom demonstrates that the CPS provides similar results to alternative stem cell harvest techniques at a lower cost to the health care provider.

Although the stem cell collection method enabled by Aastrom's CPS requires fewer resources than PBPC as currently practiced (as shown below), the costs associated with these PBPC procedures have begun to decline.

Aastrom has a number of competitors in the field of stem cell therapy. Because of the IPO, Dr. Armstrong was reluctant to comment on the company's expected market share and competitors.

A.1.2 Impact on Medical Treatment and Patient Outcomes

A.1.2.1 Description of Application

This research will reduce the pain, inconvenience, and cost of harvesting stem cells compared to the current state-of-the-art method. The technology will be embodied in the CPS, a fully automated system for growing stem cells. The CPS consists of a single-use disposable cassette, reagents, and microprocessor-controlled instruments. A small amount of the donor's bone marrow is injected into a cassette, which contains the required media to grow the stem cells. The cassette is then inserted into

[2]We will obtain the most current number from the IBMT registry for use in the model.

the CPS, which activates the process. Over a period of 12 days, the cell population that is injected into the cassette expands five to ten times while the stem and progenitor cells expand at a greater rate.

Stem cell harvest and transplant is part of a therapy for treating some kinds of dose-sensitive solid tumors, such as breast and ovarian cancers. These therapies, including high-dose and multicycle chemotherapy and radiation treatments, provide a greater chance for eradicating dose-sensitive cancer but are toxic to the hematopoietic system. Thus, they cannot be used unless the toxic effects can be reversed. By harvesting stem cells prior to treatment and returning them afterwards, the patient's hematopoietic system is restored. Thus, stem cell therapy enables these patients to be treated more effectively.

A.1.2.2 Description of Status Quo Defender Technology

Currently, PBPC collection is the status quo state-of-the-art technology, which has replaced traditional bone marrow harvest because it is less costly and painful and does not require general anesthesia. Dr. Armstrong indicated that the CPS should be compared to PBPC for the purpose of calculating benefits.

We will compare the costs and benefits of using the Aastrom CPS to those of PBPC collection.

Under PBPC, the patient is given injections to encourage the migration of stem cells into the peripheral blood over a week or more. The mobilized cells are then collected by connecting the patient to an apheresis device via an intravenous line or a surgically placed catheter. The patient's or donor's blood cells are collected, and the therapeutic volume of stem and progenitor cells is separated from it. Then the blood is returned to the patient. The donor must undergo this procedure for 2 to 3 days, for 4 to 6 hours per day.[3] Researchers are trying to reduce the amount of time required for this procedure to a single session. Specialized laboratory testing is conducted to determine whether a sufficient quantity of the desired cells has been collected.

PBPC is costly and imposes significant inconveniences on the donor. There is also a slight risk that the patient or donor will react to the growth factors or cytotoxic drugs that are used to mobilize the stem and progenitor cells.

Note that an emerging source of stem cells may make a live human donor obsolete in the future: umbilical cord blood (UCB). UCB has a much

[3] *JNCI News* indicates that the procedure requires two to four sessions of 3 to 5 hours each.

higher concentration of stem cells than traditional bone marrow and PBPC blood and is tumor-free. Furthermore, because these cells are less differentiated than adult cells, they can match a greater number of patients. While adult sources of stem cells match at the rate of 1 in 200,000, people can be a stem cell match for a given individual, the experience of a recently developed UCB shows that, with only 6,500 samples, they were able to match half of all the requests they received.

The limited supply of UCB limits its current applications. Aastrom believes that providing the transplant site with the capability to carry out the UCB cell expansion via the Aastrom CPS will be a major factor in the increased use of UCB for stem cell therapy and a significant business opportunity.

A.1.2.3 Differences in Treatment Between Defender and New Technology

Compared to the PBPC collection method, Aastrom's CPS will be considerably simpler for the donor.

Using the CPS will be considerably simpler for the donor than PBPC. In an outpatient procedure, the donor will receive a local anesthetic, and a small aspirate of bone marrow will be taken from the hip. No drugs or procedures are required to prepare the patient for this procedure.

Using the CPS will decrease the risk of tumor contamination of the stem cells compared to PBPC because

- beginning with a smaller sample of cells reduces the risk of contamination of the initial sample, and
- Aastrom has shown that some primary human tumor cells die or do not grow during hematopoietic cell culture.

These factors will be very important to clinicians choosing between the CPS and PBPC. For example, for a lymphoma patient, a tumor-free product is very important. However, for some other types of cancers, this is not a factor.

The method of harvest will have essentially no effect on the patient's long-term outcomes, provided that Aastrom meets the technical challenge of engraftment in a sufficient period of time so that the patient's hematopoietic system recovers.

Table A-2 provides a comparison of the resources used during three alternative stem cell harvest techniques: traditional bone marrow transplant, PBPC, and the Aastrom CPS. Using the CPS will cost approximately $12,000 per harvest.

Table A-2. Comparison of Resources for Three Stem Cell Harvest Techniques

Cell Source	Number of Visits[a]	Procedure Time (Hours)	Needle Sticks[b]
Bone marrow harvest[c]	6	22	100+
PBPC[d]	5-7	23-27	20-30
Aastrom CPS[e]	1	1-2	4-10

[a]Includes all outpatient, inpatient, and home care episodes.

[b]Includes bone marrow aspirates, blood samples, catheter placements, and subcutaneous injections.

[c]Includes operating room procedure and all preparatory screening and testing.

[d]Based on two to three 4-hour rounds of PBPC mobilization and collection after sequential G-CSF blood mobilization injections.

[e]Based on data gathered during Aastrom's clinical trials.

Source: Form S-1 for Aastrom Biosciences, Inc., filed November 1, 1996, with the Securities and Exchange Commission

A.1.3 Costs to the Company

Aastrom incorporated in 1991—the year in which the NIST ATP grant was awarded. Research into the stem cell technology that is the basis of the Aastrom CPS was begun at the University of Michigan in 1988.

A.1.3.1 R&D Costs

As of September 30, 1996, Aastrom had spent approximately $27.5 million on R&D (according to the IPO prospectus). In their ATP project proposal, Aastrom projected the total cost of the project to be $2.734 million, consisting of the $1.22 million ATP award and a match by Aastrom of $1.514 million. Dr. Armstrong did not feel comfortable projecting future R&D costs.

According to the company's prospectus, Aastrom has spent approximately $7 million in general and administrative costs as of September 30, 1996.

A.1.3.2 Production and Marketing Costs

Aastrom does not intend to manufacture any products. Instead, it has entered into partnerships with SeaMED Corporation and Ethox Corporation for developing and manufacturing Aastrom CPS components. Aastrom's partner, COBE BCT, will provide marketing, distribution, and customer support for the CPS. Production costs are difficult to estimate because they are still in the prototype phase.

A.1.4 Revenues to the Company

The CPS may be marketed in France in 1997. It may reach the U.S. market in 2000.

Aastrom's plans to obtain revenue from the sale and lease of the CPS instruments and from the sale of consumables (e.g., the disposable cassette that is the CPS cell culture chamber). The licensing feel will probably be rolled into the prices of these products. Aastrom plans to price the CPS so that it is competitive with PBPC therapy. PBPC therapy currently costs about $12 to $20,000 per patient. Aastrom will price the CPS in the low end of that range.

As discussed above, the CPS may come to market in 1997 in Europe and in 2000 in the U.S. However, there is considerable uncertainty associated with the regulatory process.

A.1.5 Impact of ATP Funding

Dr. Armstrong indicated that the ATP grant was very important to the development of the CPS. However, he feels that the technology is so important that if they had not been awarded the ATP grant, they would have proceeded to develop the technology, although on a different schedule. The ATP grant probably accelerated the development of the product by one to two years. ATP helped position Aastrom to obtain other sources of funding. At the time of the ATP review, Aastrom was trying to secure venture capital funding, and the ATP review probably encouraged this investment, as well as Aastrom's agreement with COBE, which was signed toward the end of the ATP project. These effects on Aastrom's cost of capital are difficult to quantify.

The ATP grant accelerated the development of the CPS by 1 to 2 years.

A.1.6 Miscellaneous

Dr. Armstrong identified two physicians that we can call for an interview:

- Dr. Randy Brown, 513-751-4448
- Dr. Sam Silver at the University of Michigan, 313-936-8561

He also suggested calling Mr. Walter Ogier, Vice President of Marketing at Aastrom, if we have additional questions.

A.2 INTEGRA LIFESCIENCES CORPORATION

We conducted a telephone interview with Richard Caruso, CEO; John Kemnitzer, Research Scientist; and Pauline Phelan, Technology and

Business Development Associate of Integra LifeSciences Corporation, and John Ricci, Research Scientist, of the Hospital for Joint Diseases, on December 18, 1996, at 10:30 a.m. RTI Project Team members Sheila A. Martin and Dan Winfield participated in the interview. This section incorporates information derived from this interview, as well as information we learned from reading project abstracts, project proposals, and other publicly available company information. Dr. Caruso has read and approved the release of this information.

Table A-3 provides a summary of the assumptions we will use in modeling the economic impact of this project.

A.2.1 Overview

> *Integra LifeSciences Corporation is dedicated to the development and manufacture of proprietary biomaterials-based applications and therapeutic products that are designed to control the behavior of cells and enable the human body to regenerate tissue that has been irreversibly lost to diseases, accident, or surgery.*
>
> *Integra LifeSciences company literature*

Table A-3. Summary: Model Assumptions for "Structurally New Biopolymers Derived from Alpha-L Amino Acids"

Application	Bioabsorbable fracture fixation devices (pins, screws, rods, plates)
Defender technology	Metal fixation devices
Applicable patient population	Patients with the following types of injuries:
	‰ Nonweight-bearing fractures (malleolus, condyles, small bones in hand or foot)
	‰ Dental and maxillofacial fractures
	‰ Weight bearing, long bone fractures
Differences in health outcomes	Reduction in stress shielding and secondary fractures due to screw holes
	Elimination of removal surgery
	Reduced potential for tissue abrasion or device loosening and migration
Differences in resource use	Eliminate need for second surgery
	May reduce length of stay
	May decrease operating room time
R&D costs to company	
ATP funds	$1,999,000
Initial project match	$469,000
Total investment to date	Same as match, plus $25,000 initial grant to Rutgers University
Expected total investment to bring to market	$600,000 to $2 million additional R&D over next 2 years
	$250,000 to manufacture prototype devices
Annual costs of production and marketing	Too early to project
Startup costs	Unknown
Average per-device costs	Unknown
Expected revenues	
Average revenue per device	Unknown
Number of devices per year	Unknown
First year of expected revenues	2000 or 2001
Impact of ATP	
Acceleration	At least 10 years
Scope effects	Significant. ATP accelerated spending on R&D at least eight times the rate they otherwise would have and attracted top talent
Availability of capital	

Integra LifeSciences received a 3-year ATP grant in 1993. The total project budget was $2.468 million; the ATP award was $1.999 million.

Integra LifeSciences, founded in 1989, is a publicly traded company, trading on the NASDAQ exchange (IART). Integra completed a public offering in January 1996, raising in excess of $35 million. The most recent quarterly earnings announcement reported revenues of $2,876,000 and an after-tax loss of $2,077,000. Their ATP project is called "Structurally New Biopolymers Derived from Alpha-L Amino Acids." It was funded in 1993 for 3 years. The total project budget was $2.468 million; the ATP award was $1.999 million.

Dr. Caruso opened the interview with a caveat that he felt that the objectives of the present ATP impact assessment project were impossible to accomplish, at least as applied to their ATP project. Integra's business strategy is to marry the range of necessary technologies for regenerative tissue engineering under the belief that this is the next great breakthrough in biotechnology applied to disease management. These necessary technologies include materials, extracellular matrices, peptides, cell seeding, growth factors, and gene therapy. He believed it would be impossible to separate out the technology development contribution from the ATP project and assess its impact in isolation from the other technologies Integra is developing. Some reasonable impact assessment can be made for the initial application of the tyrosine-based polycarbonates (i.e., fracture fixation) but the long-term impact may be much farther reaching and certainly far more difficult to assess.

A.2.1.1 Objectives

The objective of Integra's ATP-funded project is to develop a novel synthetic polymer technology using tyrosine-based monomer systems to create a cache of new bioabsorbable polymers for use in biomedical implants. The work is based on research by Dr. J. Kohn of Rutgers University, and the resulting new polymers will be designed and developed into prototype orthopedic devices in collaboration with the Hospital for Joint Diseases. The project has three major phases:

1. Polymer synthesis and characterization.
2. Polymer-tissue interactions (biocompatibility).
3. Medical device prototype development.

The concept of biodegradable medical implants has gained acceptance over the years as it has been realized that an implanted material does not have to be inert but can be degraded and/or metabolized in vivo once its function has been accomplished. This approach can alleviate some of the

problems associated with nondegradable implants, such as long-term safety and/or implant removal.

This family of polycarbonates was specifically designed to be biocompatible/bioresorbable engineering polymers, where the properties (e.g., mechanical strength, glass transition, hydrophilicity/hydrophobicity, resorption profile, cell specificity) can be systematically controlled by selecting the pendent structure in the polymer chain.

A.2.1.2 Applications

Integra's tyrosine-based polymer technology will have broad applications in orthopedics, wound care, cardiovascular repair, and drug delivery. The initial application is orthopedic fracture fixation.

Integra considers this to be a platform technology with broad applications in orthopedics (fracture fixation, cartilage and ligament repair), wound care, cardiovascular repair, and drug delivery. Ultimately, they expect to marry this technology with others under development by the company to lead to extracellular matrices for controlled tissue regeneration. However, in the near term, Integra is focusing on the orthopedic fracture fixation market to demonstrate success and generate revenue.

Bioabsorbable, fracture fixation applications, in order of adoption and market penetration, are

1. nonweight-bearing pins and screws (competing resorbable products on the market);
2. dental and maxillofacial fixation devices; and
3. weight-bearing plates, screws, and rods, for example (will require stronger material).

A.2.1.3 Factors Affecting Technical Success

Current bioabsorbable pins and screws, made of either polylactic acid or polyglycolic acid polymers, release acids upon biodegradation. The resulting acid environment leads to an inflammatory response. This response can lead to reversal of an initial healthy tissue response and ultimately result in a pocket or cyst being left where the implant was, rather than being replaced by bone as is desired. The tyrosine-based polycarbonates have been formulated to provide comparable mechanical properties and resorption rates as the polylactic acid (PLA) and polyglycolic acid (PGA) polymers and to address the inflammatory reaction problem by not releasing harmful products upon degradation. In addition to not releasing acids, the tyrosine-based polycarbonates are amorphous and thus do not break down into harmful particles.

To date, Integra has shown the ability to

- tailor resorption rates,
- tailor mechanical properties,
- manufacture quality material reliably (in small quantities), and
- stimulate a healthy bone response adjacent to the material in animal studies.

Integra will probably begin clinical trials of their fracture fixation application in 2 years.

Unanswered technical questions concern the rate of resorption, loss of mechanical strength and stiffness versus healing, and smooth transfer of load bearing from the device to the healed bone. These questions are now being addressed in a fracture fixation animal model. Clinical trials are probably 2 years from starting.

The probability of technical success is seen as very high. The 1-year bone chamber model, although not designed to assess fracture fixation, did point towards greater bone in growth and density with the tyrosine polycarbonates than with the current comparison devices.

Of importance is the likelihood that stronger and stiffer versions of the material may be required to succeed in fixation of long bone, weight-bearing fractures that account for a large percentage of the potential market.

A.2.1.4 Factors Affecting Market Success

The likelihood of market success is more difficult to accurately project. Factors that will influence market success include the following:

- Strategic partnering: Integra recognizes that it does have the orthopedic market presence necessary for success and is seeking a strategic partner.)
- Surgeon awareness and acceptance: Currently only about 10 percent of metal fixation devices are removed after healing. Will the market respond to a successful bioabsorbable alternative?)
- Price: PLA pins sell for around $90 per pin. Integra believes they can meet this price point, but tyrosine is an expensive starting material.)
- Competition: Several major orthopedic suppliers already have bioabsorbable products either on the market (J&J, Biomet, Acufex) or under development (DePuy, Wright Medical, Osteonics, Zimmer, and others).
- Liability: Biomaterials liability concerns have been raised to new heights over the past 3 to 4 years (note Dow Corning's bankruptcy case).

A.2.2 Impact on Medical Treatment and Patient Outcomes

A.2.2.1 Description of Application

Bioabsorbable orthopedic devices have the following advantages:

- reduce stress shielding,
- eliminate removal surgery, and
- minimize the potential for tissue abrasion or device loosening and migration.

Bioabsorbable, fracture fixation devices (pins, screws, rods, plates) would be used for surgical fixation of bone fractures. Segmentation of the patient population in order of likelihood of application includes the following:

1. nonweight-bearing fractures (e.g., malleolus, condyles, small bones in hand or foot);
2. dental and maxillofacial fractures; and
3. weight bearing, long bone fractures.

Bioabsorbable devices would be less likely to cause stress shielding (a condition in which the implant carries the load causing the bone to resorb since it is not being loaded); would not require a second surgery to remove the implant; and would minimize the potential for tissue abrasion or device loosening and migration.

A.2.2.2 Description of Status Quo Defender Technology

Because current bioabsorbable fixation devices have not achieved widespread acceptance to date, the defender technology remains the use of metal fixation devices such as pins, rods, plates, and screws. These devices are surgically placed after reduction of the fracture to maintain alignment and provide stability for the fracture segments. A small proportion of these devices (10 percent at Integra's estimate) are later removed at a second surgery after complete healing. Removal is most common in the ankle area where the threat of abrasion is highest because of the limited soft tissue coverage in this region. Stress shielding is also a significant concern and motivator for removal. Regions that are more difficult to access surgically (e.g., the hip) are least likely for secondary device removal. Depending on fracture location, metal fixation devices can also have an adverse effect on the growth and maturity of bones in children; thus, the use of bioabsorbable devices may have special merit in children.

A.2.2.3 Differences in Treatment between Defender and New Technology

Patient Outcomes. The use of bioabsorbable fixation devices should minimize or eliminate the need for a secondary surgery to remove the implant, which eliminates the attendant hazards of such a surgery. In addition, if the device works as anticipated (i.e., eventually being

completely replaced by bone), it should reduce the likelihood of secondary fractures resulting from the stress-shielding effect or the presence of screws holes that serve as stress concentrators.

Integra indicated that current competing bioabsorbable products experience 8 to 15 percent complication rates. Information on patient outcomes using these devices may be valuable for comparison.

Resource Use. Bioabsorbable fixation devices will minimize the need for a second surgery and eliminate these costs. In addition, they may reduce overall procedural costs by decreasing the length of stay and operating room time.

A.2.3 Costs to the Company

A.2.3.1 R&D Costs

Integra's R&D costs have generally followed the budget plan outlined in the ATP proposal.

Integra's initial cost in the technology was a small grant ($25,000) to Rutgers University at the time Integra took an option on the technology. Upon receiving the ATP grant, Integra exercised the license option, and Integra's R&D costs have generally followed the budget plan outlined in the ATP proposal.

Integra's plans call for investing $600,000 to $2 million in R&D for this technology over the next 12 to 24 months. In addition, they expect to spend $250,000 over the next 24 months on manufacturing prototype devices.

A.2.3.2 Production and Marketing Costs

It is too early to project these costs.

A.2.4 Revenues to the Company

The commercial potential of the total absorbable polymer medical products market is estimated to be well over $500 million in 1998, with projected growth of over $1 billion by 2001.

Integra provided market figures from a 1995 Frost & Sullivan market report. The absorbable rod and pin market is projected to have an annual growth rate over 12 percent to the year 2001, with expected revenues of $15 million. The absorbable screw market is expected to grow at 40 percent per year to 2001, with expected revenues of $13 million. The commercial potential of the total absorbable polymer medical products market is estimated to be well over $500 million in 1998, with projected growth of over $1 billion by 2001. Absorbable rods and screws currently account for only 2.8 percent of this market but are expected to reach 14.2 percent by 1998 and 16.7 percent by 2001. In a recent press release, Integra quoted NIST, saying the U.S. market for absorbable medical products is approximately $400 million and is projected to grow to $1 billion by the turn of the century.[4]

A.2.4.1 Expected Adoption of Technology

Integra does not expect the first products to reach the market for 3 to 4 years, perhaps longer depending on clinical trials and the FDA approval process.

Integra again provided data from the Frost & Sullivan report showing that, in 1996, the total patient population who elected absorbable fixation was over 93,000, and the projected population usage is estimated to be over 350,000 by 2001.[5]

A.2.4.2 Expected Revenues from Sales of Goods or Services

Integra did not provide any estimates of projected sales and licensing revenues from products based on the tyrosine-based polycarbonate technology. Their business strategy is to locate an orthopedic partner to assist in further development and commercialization of the technology. At this point, they anticipate being a manufacturer of devices but may later choose to license manufacturing rights to their future orthopedic partner.

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[4]The 1995 *Medical & Healthcare Marketplace Guide* estimates the worldwide, fracture fixation market at $456.2 million and projects it to grow steadily through the remainder of the decade. Just over 50 percent of 7 million fractures each year in the U.S. are surgically treated. The cost to the U.S. health care system for treatment of fractures exceeds $20 billion per year.

[5]Other data indicate about 3.5 million fractures treated surgically each year. Using the above numbers, market penetration can be estimated to be 2.6 percent presently and 10 percent by 2001.

A.2.5 Impact of ATP Funding

Integra believes that, in the absence of the ATP grant, the rate of their research in this area would have been much slower.

Integra strongly and repeatedly stated the importance of the ATP funding to their progress on this project. They stated that if they had not received ATP funding, they would still be funding the project at only a small level (approximately $50,000 to $100,000 per year). At least as important, the ATP funding allowed them to attract top-notch talent like Dr. George Brode and Dr. John Kemnitzer for this project. Because of the progress allowed by the ATP project, major companies, such as Johnson & Johnson (J&J) and Union Carbide who had turned down an option to this technology earlier, are now interested.

A.3 VIVORX, INC.

We conducted a telephone interview with Glen Spaulding and Derek Brown of VivoRx, Inc., on December 17, 1996, at 12:30 p.m. RTI Project Team members Sheila A. Martin, Dan Winfield, John Farris, Anne Kenyon, and Mohan Bala participated in the interview. This section incorporates information derived from this interview, as well as information we gathered from reading project abstracts, project proposals, and other publicly available company information. Mr. Brown has read and approved the release of this information.

Table A-4 provides a summary of the assumptions we will use in modeling the economic impact of this project.

A.3.1 Overview

VivoRx, Inc., a development-stage biopharmaceutical company, is developing a new treatment for diabetes. The treatment will consist of transplanting human islets that have been encapsulated in immunoprotective membrane consisting of a novel material. This material protects the cells from the host's immune response. The treatment will apply to all Type I (insulin-dependent) diabetes patients and about 15 to 20 percent of Type II (insulin-resistant) diabetes patients. It will eliminate the need for daily insulin injections and will enable patients to achieve tight glycemic control, reducing the risk of the common complications of diabetes. This technology also has potential applications for liver disease, thyroid

Table A-4. Summary: Model Assumptions for "Treatment of Diabetes by Proliferated Human Islets in Photocrosslinkable Alginate Capsules"

Application	Diabetes	
Defender technology	Daily insulin injections	
Applicable patient population	All Type I diabetics; insulin-dependent Type II diabetics	
Differences in health outcomes	As noted by the DCCT study (DCCTRG, 1996).	
Differences in resource use	Daily insulin injections	BetaRx-PR
Annual cost of treatment	$2,500	$20,000 to $30,000[a]
Annual cost of complications[b]	To be determined by model	To be determined by model
R&D costs to company (for BetaRx-PR)		
ATP funds	$2,000,000	
Initial project match	$14,925,000	
Total investment to date	$25 to $30 million[c]	
Expected total investment to bring to market	Unknown	
Annual costs of production and marketing	Unknown	
Startup costs	$60 to $80 million, plus land and buildings	
Per-patient costs	Unknown	
Expected revenues		
Revenue per treatment	Unknown	
Number of treatments per years	To be determined by physician interviews and diffusion modeling	
First year of expected revenues	Unknown[d]	
Impact of ATP		
Acceleration	5 to 7 years	
Scope effects	None	
Availability of capital	Nonquantifiable effects	

[a]This is the current cost of islet cell transplants based on cells obtained from cadavers and a replacement dose every 6 months. If proliferation technology is successful, the per-treatment cost will be less, and the patient will only need an injection once per year or once every 2 years.

[b]We will estimate these expected costs based on the probability of health outcomes and how they change when tight glycemic control is achieved, as found by DCCTRG (1996). The model will incorporate the current cost of treating each of these complications.

[c]This figure was quoted in the interview for all research in islet cell encapsulation, not simply BetaRx-PR.

[d]Although VivoRx expects to bring BetaRx-P to market in 1997, they did not estimate an expected date for commercializing proliferated human cells (BetaRx-PR).

disease, Parkinson's disease, Alzheimer's disease, and myocardial infarction. However, the most immediate application is for diabetes.

VivoRx's 3-year ATP project was funded in 1994. The total project budget was $16.925 million. The ATP provided $2 million.

To make this therapy widely available, VivoRx, Inc., must find a source of human islet cells. With ATP support, VivoRx proposed to develop the culture conditions and methods for proliferating human islets. They also proposed to perfect the polymers and biomaterials that are required to achieve immunoprotection and biocompatibility for the encapsulation technology.

The ATP award was made in 1994 for a period of 3 years for $2 million. The total project budget was $16.925 million.

A.3.1.1 Objectives

The objectives of the grant project were to

- develop a technique for proliferating human islet cells in sufficient quantity for commercial production while maintaining the cells' ability to function properly (e.g., producing insulin and sensing glucose) and
- achieve immunoprotection and biocompatibility through an encapsulation technology that is feasible on a commercial scale.

A.3.1.2 Applications

This technology will replace daily insulin injections for Type I and some Type II diabetic patients.

Although achieving proliferation of human islet cells will have far-reaching impacts, it is appropriate to focus on the potential benefits of this technology to diabetic patients. This technology will be used in place of daily insulin injections and can be used by Type I diabetic patients and about 15 to 20 percent of Type II diabetic

patients. In total, about 30 percent of the total diabetes population may benefit from this treatment (Soon-Shiong, 1996).[6]

A.3.1.3 Factors Affecting Technical Success

The most important challenge to technical success of this project is achieving proliferation of islet cells that function properly; that is, they produce insulin and sense glucose. While VivoRx and other researchers have had some success proliferating cells, VivoRx's challenge is to identify the growth factors and cofactors that will overcome this problem

[6]Our model will incorporate the most recently available data from the American Diabetes Association (ADA). We will include ADA's estimate of the total number of Type I diabetics plus the total number of Type II diabetics that currently depend on insulin injections.

and enable VivoRx to proliferate enough fully functional cells to accommodate the many patients who might benefit from this treatment.

The second challenge is to perfect the polymers used to encapsulate the cells. Even when human cells are transplanted, patients might experience an inflammatory reaction. Preventing this response with an appropriate encapsulation material is important.

VivoRx has several related research programs currently underway. In 1993, VivoRx began testing its encapsulated human islets (BetaRx-H) using islet cells isolated from human cadaver pancreata. The patients receiving this treatment have achieved insulin independence and tight glucose control. This trial provided a proof of concept.

In 1995, FDA approved Phase I/II clinical trials using proliferated *human islets (BetaRx-PR).*

In 1995, FDA approved Phase I/II clinical trials using *proliferated* human islets (BetaRx-PR). This trial will determine the correct dosage of these cells for a typical patient and the frequency with which the cells will have to be replaced. In July 1996, VivoRx received approval to begin Phase I/II trials using porcine islets (BetaRx-P). The porcine cells represent VivoRx's fallback position in the event that the human proliferation technology is not feasible on a commercial scale.

A.3.1.4 Factors Affecting Market Success

A number of companies are working on similar competing technologies. However, VivoRx believes they are the leader in this technology, having 3 years of effectiveness data and FDA approval for clinical trials.

Furthermore, VivoRx believes that proliferation of human cells is the best source of cells for transplantation. Although VivoRx and other companies have pursued the idea of using porcine islet cells, porcine sources have several problems, including

- the availability of disease-free pigs and
- the antigenicity of the insulin, hormones, and other biological products of the pig islets that may penetrate the microcapsules and produce an immune response.

The market for this technology (in this application) is Type I diabetics and 15 to 20 percent of Type II diabetics (who are insulin dependent).[7]

[7]The Health Interview Survey indicated that a total of 2.9 million insulin-dependent diabetics are in the United States. Of these, 700,000 are Type I; the remainder are Type II (ADA, 1996).

VivoRx thinks that, if the treatment is a technical success, they will eventually capture virtually all of the market (compared to daily insulin injections) because the results are so good that physicians would be negligent if they did not prescribe this treatment. In the first few years, they expect approximately 15 percent of the market to switch from daily insulin injections to proliferated human cell transplant.[8]

VivoRx does not believe that third-party payers will be a serious issue. Hospitals are currently focusing on capitation and determining the best treatment for a patient based on long-term outcomes. Given this trend, VivoRx thinks that many hospitals and health maintenance organizations (HMOs) will adopt the transplant technology. They are currently working to develop Centers of Excellence in hospitals to treat diabetic patients. VivoRx will work through these hospitals to administer this therapy.

A.3.2 Impact on Medical Treatment and Patient Outcomes

A.3.2.1 Description of Application

Encapsulated human islet cells are injected into the patient's peritoneal cavity. The patient will receive an injection once a year or once every 2 years.

The application will involve an outpatient procedure and a local anesthetic. Proliferated, encapsulated human islet cells are injected into the peritoneal cavity. The patient then waits in the office for several hours before leaving. Because beta cells are constantly dying and being replenished, the patient will receive an injection once per year or perhaps once every 2 years. The dose and frequency of treatment have not yet been finalized but will be determined during the current Phase I/Phase II trials.

In this early stage of development of this therapy, the patient is required to see the physician about once a month to verify the treatment's effectiveness.

A.3.2.2 Description of Status Quo Defender Technology

Currently, the status quo technology is daily insulin injections. This treatment is the appropriate treatment of comparison for calculating the benefits of the transplant technology.

Another treatment, pancreatic transplant, has a high failure rate and an insufficient number of donors. A third treatment is insulin pumps, which

[8]We will interview physicians to verify VivoRx's expectations about the percentage of the market they expect to capture.

have been available for 20 years, but they do not provide sufficient feedback to maintain tight glycemic control. Thus, neither of these is a suitable defender technology.

A.3.2.3 Differences in Treatment between Defender and New Technology

Daily insulin injections require that patients inject themselves each day with insulin and monitor their insulin level. The transplant technology will require only a once per year (or maybe once per 2 years) outpatient procedure, plus a follow-up visit of once per month, at least at the beginning.

A.3.2.4 Differences in Patient Outcomes between Defender and New Technology

The health benefits of this technology will be similar to those achieved by the intensive insulin therapy, as documented in the DCCT.

With the transplants, the patient achieves tight glycemic control. The health benefits of this type of control are documented in the Diabetes Control and Complications Trial (DCCT). VivoRx believes that the transplant therapy will lead to similar changes in risk of complications of diabetes. (However, the intense insulin therapy tested in the DCCT has some side effects, such as an increase in the incidence of severe hypoglycemia, that would not apply to the transplant technology.)

A.3.2.5 Differences in Resource Use between Defender and New Technology

The most important source of resource savings associated with islet cell transplants will be due to the reduced risk of complications. Every person with Type I diabetes will have complications and in 30 years will be in some end-stage health state. In 1992, diabetics had an average health care cost of $2,500 for patient materials, such as insulin and needles, plus $11,200 per patient per year for treating complications. The total cost of treating diabetes and its complications in 1995, according the National Institute of Health (NIH), is $105 billion, or 1 in 7 health care dollars.

According to VivoRx, the current cost of transplant is between $20,000 and $30,000 per patient per year. However, this cost will fall if the proliferation technology is successful; the cost will depend on how well the cells proliferate (see Section A.3.4.3).

A.3.3 Costs to the Company

A.3.3.1 R&D Costs

The research effort for this project began with Dr. Soon-Shiong's work in the mid-to-late 1980s. After working with pancreatic transplants, he decided that pancreatic transplants would not provide a solution to diabetes, and he began to research cellular therapy.

VivoRx, Inc., began in the early 1990s and has invested between $25 and $30 million in R&D in this area since that time. (The project proposal estimated that the entire project would cost almost $17 million; ATP funds were $2 million.)

VivoRx is currently experiencing no capital shortages. Although they have had the opportunity to go public, they feel that would distract them from their primary research program, but they may do so in the future.

A.3.3.2 Production and Marketing Costs

It will be very important to locate many human islet processing centers throughout the U.S. so that cells used in transplants are fresh. VivoRx expects that, throughout the 50 states, they will build 20 processing centers, which will include a laboratory, a production room, and office space. They expect that the fixed costs of setting up each site will be between $3 and $4 million, not including the acquisition of buildings and land. They expect to staff each center with a production team of about 20 people per shift. These people will be highly skilled, including a manager, a supervisor, quality control people, laboratory technicians, inventory control technicians, and cell culture technicians.

A.3.4 Revenues to the Company

A.3.4.1 Expected Adoption of Technology

VivoRx expects the transplant of proliferated human islets to become the standard treatment for diabetes once the trials have been completed and the proliferation technology has been perfected.

As mentioned earlier, VivoRx expects the transplant of proliferated human islets to become the standard treatment for diabetes once the trials have been completed and the proliferation technology has been perfected. In the first few years after introduction, VivoRx expects 15 percent of insulin-dependent patients to switch to transplants. The long-term results of transplants are so much better than the status quo treatment (daily insulin injection) that doctors would be negligent if they did not prescribe this therapy. Furthermore, hospitals and HMOs will see transplants as a way to keep down long-term costs of treating diabetic patients.

As explained earlier, proliferated human islets is the best among the possible sources of cells, because they solve the problems associated with obtaining cadaver cells and the possible antigenicity problems associated with porcine cells.

A.3.4.2 Expected Revenues from Licenses

VivoRx may distribute its technology through a number of hospitals that could become Centers of Excellence for the treatment of diabetes. These centers will train physicians in this therapy.

They expect to bring encapsulated porcine cells, BetaRx-P, to market and begin generating revenue once the Phase I/II trials are over, which could take as long as a year. They are currently recruiting hospitals to participate in the Phase I/II trials. VivoRx expects that FDA will wave the Phase III trials because of the level of success they are having with the Phase I/II trials.

A.3.4.3 Expected Revenues from Sales of Goods or Services

The cost of the VivoRx-PR therapy will depend on the proliferation rate of the human islet cells.

VivoRx plans to charge a per-treatment fee for encapsulated human islets just as any other injectable is priced. They are focusing on the U.S. market by developing agreements with hospitals and HMOs for Centers of Excellence for treating diabetes. However, they also have developed an agreement with a Korean company that has right of first refusal for licensing the technology.

They are not sure how the therapy will be priced; it will depend on the relative ease or difficulty of proliferating cells. For example, if the

proliferation rate is only ten cells for every cell they harvest, the cost will be substantially higher than if the proliferation rate is 100,000 to 1.

A.3.5 Impact of ATP Funding

ATP funding accelerated the VivoRx research program by at least 5 years.

ATP funding was invaluable but difficult to quantify. Prior to winning the ATP grant, VivoRx expected that their first transplants of proliferated human cells would occur sometime between 2002 and 2004. With ATP, they are now planning on their first transplants in 1997. Thus, the ATP award accelerated the research program by at least 5 years.

Although the project would have begun more slowly, VivoRx feels that, even in the absence of ATP funds, the project would have evolved with a similar scope.

A.3.6 Miscellaneous

Derek Brown said that he would send us the names of physicians that we can contact regarding their willingness to prescribe this therapy. He also promised to send an information packet.

A.4 BIOHYBRID TECHNOLOGIES, INC.

We conducted a telephone interview with John (Jack) Hayes, Chief Financial Officer of BioHybrid Technologies on December 19, 1996, at 3:00 p.m. RTI Project Team members Dan Winfield, Anne Kenyon, Mohan Bala, and John Farris participated in the interview. These notes incorporate information derived from this interview, as well as information we learned from reading project abstracts, project proposals, and other publicly available company information. Jack Hayes has read and approved the release of this information.

Table A-5 provides a summary of the assumptions we will use in modeling the economic impact of this project.

A.4.1 Overview

BioHybrid's ATP project was funded in 1993 for 3 years. The total project budget was $8.525 million; the ATP provided $4.262 million.

BioHybrid's ATP project, entitled "Disease Treatment Using Living Implantable Microreactors," was a 3-year project, funded in 1993 for $4.262 million; total project funds were estimated in the ATP project proposal at $8.525 million.

A.4.1.1 Objectives

The objective of the ATP project was to develop the capability to implant specific cells into the human body that produce hormones or other bioactive agents that the patient cannot produce or is not producing in sufficient quantity. The approach is to encase the transplanted cells in microspheres to isolate them from the immune system. These "microreactors" have pores large enough to permit glucose; nutrients; electrolytes; oxygen; and bioactive products, like insulin, to pass, but small enough to block immunocytes and other relatively large molecules involved in transplant rejection. Isolating the implanted cells from the immune system opens up the possibility of using cells from animal sources, such as porcine pancreatic cells for diabetes treatment.

A.4.1.2 Applications

This "microreactor" technology has the potential to be applied to a number of therapeutic applications, including hemophilia, Huntington's Chorea, Parkinson's disease, Alzheimer's disease, hepatic failure, AIDS, and cancer. However, the most immediate

Table A-5. Summary: Model Assumptions for "Disease Treatment Using Living Implantable Microreactors"

Application	Diabetes	
Defender technology	Daily insulin injections	
Differences in health outcomes	Use a range: bottom as noted by the DCCT study (DCCTRG, 1996); top using zero complications	
Differences in resource use	Daily Insulin Injections	BioHybrid Microreactors
Annual cost of treatment	$2,500	$5,000 to $20,000 $12,000 initial implant; $6,000 booster implant; plus weekly blood glucose measurements and monthly office visits
Annual cost of complications	Estimated at $17,500 to $20,000 direct health care costs. To be determined by model	To be determined by model using range of DCCT data and zero complications
Applicable patient population	All Type I diabetics; insulin-dependent Type II diabetics	
R&D costs to company		
Amount of ATP grant	$4,263,000	
Initial project match (from company)	$4,262,000	
Total investment to date	$19 million including ATP grant ($22 million once all ATP project funds have been spent)	
Expected total investment to bring to market	Additional $125 to $200 million	
Annual costs of production and marketing	Unknown	
Expected revenues	Will depend on market penetration; see model provided by BioHybrid for estimates	
First year of expected revenues	$60 million (year 2000)	
Impact of ATP		
Acceleration	2 to 3 years	
Scope effects	None	
Availability of capital	Nonquantifiable effects on the availability of capital	

application is for diabetic patients who are unable to produce insulin to achieve control of blood glucose. This technology would be used in place of multiple daily insulin injections.

A.4.1.3 Factors Affecting Technical Success

The principal factors affecting technical success are

- how long these implanted cells will survive in the human body;
- how long they will remain protected from the immune system; and
- how long they will continue to produce therapeutic quantities of insulin, appropriately regulated by blood glucose levels.

BioHybrid expects to begin human clinical trials by late 1997 or early 1998.

Exhaustive animal studies in mice, rats, rabbits, and dogs have been extremely promising. Experimental data indicate that the cells should remain viable and productive for at least 3 months. BioHybrid hopes that within 5 years the cells will survive for 6 to 12 months. BioHybrid expects to begin human clinical trials by late 1997 or early 1998. They are technically ready to begin these trials now, but safety testing and good manufacturing practice (GMP) development are required before receiving FDA Investigational New Drug (IND) approval.

A.4.1.4 Factors Affecting Market Success

BioHybrid believes the market for this technology includes all Type I diabetics (those who cannot produce insulin) and most Type II diabetics who take daily insulin injections. BioHybrid estimates that 14 million diabetics live in the U.S., of which 7.5 million have been diagnosed. Of these, 800,000 to 900,000 are Type I. Of the remaining Type II, 28 percent take daily insulin injections (this figure is lower in less-developed countries). This provides an estimated U.S. market of 2.5 to 2.8 million patients and an estimated worldwide market of approximately three times the U.S. market.[1]

BioHybrid believes that its therapy will attract customers because it provides near normal blood glucose control, which will significantly reduce or eliminate the many complications that currently result from inadequate glucose control in diabetics. Many patients will also be attracted to the therapy because of its impact on a patient's quality of life, as described in Section A.4.2.4.

[1] we will use the most recently available data from the American Diabetes Association to estimate the potential size of the market.

The key factor in BioHybrid's market success will be the timing of required re-injections of transplanted cells.

The key market factor will be the timing of the required re-injections of transplanted cells. If the timing is too frequent, it will not only become inconvenient for the patient but far too expensive as well. BioHybrid is confident they will be able to achieve one or two transplants per year, which will allow them to easily remain competitive with current health care costs for diabetes. Third-party payers will be attracted to the therapy's impact on the insulin therapy-related costs, as explained in Section A.4.2.5.

A number of companies are working on similar competing technologies:

- Neocrin—porcine islet cells in a proprietary hydrogel membrane;
- W. R. Grace & Co.—Phase I clinicals with a bioartificial pancreas;
- Metablex—alginate microcapsules with multilayer coatings;
- BetaGene—engineered cell lines; and
- VivoRx—islet cell proliferation and encapsulation.

A.4.2 Impact on Medical Treatment and Patient Outcomes

A.4.2.1 Description of Application

The application will involve an outpatient procedure and a local anesthetic. Encapsulated porcine islet cells are injected into the peritoneal cavity under ultrasound control in a procedure similar to an amniocentesis. Because the transplanted islet cells have a finite life, the patient will receive an injection once or twice a year. The dose and frequency of treatment have not yet been finalized but will be determined during the planned clinical trials.

In this early stage of development of this therapy, the patient is required to see the physician about once a month to verify the treatment's effectiveness. This frequency will decrease once the treatment effectiveness is verified. Patients will monitor blood glucose once per week.

A.4.2.2 Description of Status Quo Defender Technology

Currently, the status quo technology is daily insulin injections. This is the appropriate treatment of comparison for calculating the benefits of the transplant technology. Daily insulin injections require patients to inject themselves, on the average, one to three times each day with

insulin[2] and monitor their blood glucose levels daily. Monitoring blood glucose requires a pin prick to obtain a small drop of blood for use in a portable diagnostic instrument that patients must carry with them.

A.4.2.3 Differences in Treatment between Defender and New Technology

BioHybrid's transplant technology will require an outpatient transplant procedure once or twice a year. Patients will monitor glucose once a week.

The transplant technology differs from the defender technology in two ways: rather than daily insulin injections, the patient will receive a once or twice per year outpatient procedure, plus a follow-up visit once a month, at least at the beginning of therapy. Second, patients will monitor blood glucose only once a week rather than daily.

Implantable microreactors for diabetes offer the following advantages over daily insulin injections and other alternatives:

- automatic insulin response to glucose,
- no immunosuppression required,
- elimination of daily injections,
- simple to administer,
- minimal glucose monitoring,
- abundant supply, and
- reduced complications.

A.4.2.4 Differences in Patient Outcomes between Defender and New Technology

With the transplants, the patient achieves tight glycemic control. The health benefits of this type of control are documented in the DCCT. BioHybrid believes that the transplant therapy will reduce risk of complications of diabetes even more than the DCCT indicates. In the DCCT, only 5 percent of patients achieved normal blood glucose as defined by glycosylated hemoglobin measurements. That is, all populations achieved better control of blood glucose, but few were in the normal range. If the implanted microreactors achieve normal glycemic control, one can expect even greater reduction in complication rate, if not elimination of complications. In addition, the intense insulin therapy tested in the DCCT has some side effects, such as an increase in the incidence of severe hypoglycemia, that would not apply to the transplant technology because of its self-regulating feature. The transplant therapy will also provide an improvement in the patient's quality of life. Patients

[2]The intensive insulin therapy used in the DCCT involved five to six injections of insulin per day as well as frequent glucose monitoring.

will be free from daily injections and frequent monitoring; they also will have more freedom with respect to their diet. For example, many diabetics eat the same meals repeatedly because they can predict the effect on blood glucose.

A.4.2.5 Differences in Resource Use between Defender and New Technology

BioHybrid estimates that the procedure will cost $1,000, and the transplant will cost $12,000 for the initial transplant and $6,000 per year for boosters.

For estimating procedural costs for the outpatient transplant injection, the most similar medical procedure is amniocentesis under ultrasound guidance (estimated at $600 to $700 by BioHybrid). BioHybrid is currently projecting a procedure cost of $1,000. Their initial estimate of the cost of the transplant itself is approximately $12,000 for the initial implant and $6,000 per year for booster injections regardless of the number required. They anticipate the patient will need to perform an at-home blood glucose measurement about once a week and, at least initially, will require one office visit per month for a glycosylated hemoglobin test.

This therapy offers two sources of resource savings. The first, most immediate savings are those directly related to insulin therapy, such as the elimination of injections, less frequent monitoring, and fewer emergency room visits. These savings will be very important to third-party payers who must justify the expense of the transplant.

The second source of resource savings associated with porcine islet cell transplants will be a result of the reduced risk of complications. Under conventional therapy, every person with Type I diabetes will have complications and within 30 years will be in some end-stage health state. In 1992, diabetics had an average-per-patient health care cost of $2,500 for patient materials such as insulin and needles, plus $11,200 per year for treating complications.

BioHybrid provided the following figures on the cost of diabetes in the U.S. (American Diabetes Association, 1996):

- Direct and indirect costs: includes short-term morbidity, long-term disability, and mortality — $109 billion
- Direct costs: inpatient and outpatient costs — $55 billion
- Products and office visits: physician, hospital outpatient, and ER visits — $9.9 billion

- Therapeutic products: includes insulin, insulin therapy supplies, glucose monitors, and reagent strips, for example — $4.8 billion

On a per-patient basis, BioHybrid provides the following estimates for annual cost per diabetic taking insulin:

Patient products	$1,250 – $1,500
Direct outpatient costs	$3,000 – $3,500
Direct health care system costs	$17,500 – $20,000
Total costs	$30,000 – $35,000

For intensive insulin therapy, such as that used in the DCCT, the total cost of patient products is between $3,500 and $5,000.

A.4.3 Costs to the Company

A.4.3.1 R&D Costs

BioHybrid indicated that they have invested the $4.263 million cost-share match as included in the ATP proposal. They have invested $19 million to date, including the ATP grant, on this technology. They plan to spend $3 million more ATP project funds. They expect to spend an additional $125 and $200 million total on this technology by the time it is brought to market.

A.4.3.2 Production and Marketing Costs

BioHybrid believes that it is premature to develop actual estimates of production and marketing costs.

BioHybrid believes that it is premature to develop actual estimates of production and marketing costs. Their market assessment indicates that their technology must be able to provide comparable or better health outcomes at between $5,000 and $20,000 annual health care costs per patient. Their analysis of their production methods indicates they should have no trouble pricing the technology within these targets.

A.4.4 Revenues to the Company

BioHybrid provided RTI with one market penetration model they have used to attract investment (see Table A-6). This model assumes a very conservative estimate of market penetration, achieving only 8 percent of the available market by the year 2005. Even at this conservative estimate, they are able to project significant revenues. Based on their knowledge of the current market and expected cost, they plan to price the initial implant at $12,000, with booster implants at about $6,000 per year per patient. This estimate is subject to considerable uncertainty.

A.4.5 Impact of ATP Funding

BioHybrid estimates that the ATP funding has accelerated their efforts by at least 2 to 3 years.

The principal effect of ATP funding has been in BioHybrid's ability to attract capital in a market sector that is underfinanced. In recent years the private equity market has not been excited about early, development-stage, high-risk biotechnology companies. ATP funding was important in their ability to secure the $4.25 million private funding as cost share for the ATP project. ATP funding and the progress they have been able to make under this project have been essential in establishing a dialog with prospective investors to provide the $50 to $200 million that will be required to get this technology to market. BioHybrid estimates that the ATP funding has accelerated their efforts by at least 2 to 3 years.

Table A-6. Market Penetration Scenario/U.S. Only
Pricing: initial implant $12,000; booster implant $6,000[a]

Patients Implants	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**
Initial Implants	5,000	10,000	20,000	40,000	70,000	122,500
Booster Implants	0	5,000	15,000	35,000	75,000	145,000
Total Implants	5,000	15,000	35,000	75,000	145,000	267,500
Total Implants Percentage of Market	0.2%	0.6%	1.3%	2.3%	4.7%	8.0%
Revenue (millions $)						
Initial Implant	$60	$120	$240	$480	$840	$1,470
Booster Implant	$0	$30	$60	$210	$450	$870
Total Implant Revenue	$60	$150	$330	$690	$1,290	$2,340

[a]Actual pricing has not been set.