GROUP 8

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OVERVIEW

- Background/Review of current conditions
- Objective of RepliDerm
- Production plan
- FDA Approval Process
- Business/Market Plan
BACKGROUND
Problem

- 270,000 burn victims per year in the U.S. requiring hospitalization
- 1.5 million diabetic patients in the U.S. with wound ulcers
- Various narcotizing infections (flesh eating infections)
Treatments Available

- Split thickness autograft
- Donor allograft
- Synthetic allograft
- Synthetic allograft with seeded neonatal fibroblasts
- Temporary covering from biological donor
# Advantages of Existing Treatments

<table>
<thead>
<tr>
<th>Procedure (Product)</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Price/in²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Split Thickness Autograft (Surgical treatment)</td>
<td>Inexpensive No rejection</td>
<td>Extensive scarring Limited donor sites</td>
<td>$0</td>
</tr>
<tr>
<td>Donor Allograft (AlloDerm)</td>
<td>Relatively Inexpensive</td>
<td>Disease transmission 10% Rejection Small wounds only</td>
<td>$7/in²</td>
</tr>
<tr>
<td>Synthetic Allograft with Seeded Cells (Epicel)</td>
<td>No epidermal graft needed 5% Rejection</td>
<td>Fragile</td>
<td>$102/in²</td>
</tr>
<tr>
<td>Synthetic (Integra)</td>
<td>Strong &amp; supple Protective layer 5% Rejection</td>
<td>Epidermal autograft required</td>
<td>$42/in²</td>
</tr>
</tbody>
</table>
On the Market: Integra Dermal Regeneration Template
On the Market: Integra Dermal Regeneration Template
Mechanism for Angiogenesis

Angiogenesis

sprouting

mother vessel

bridging

intussusception

daughter vessels

VEGF, VEGFR2, VEGFR3, Ang1, Ang2, Tie2, HIF-1α, ARNT, VHL, α4, αvβ3, VE-Cadherin, PA, MMP, SCL, TEL, CXCR4, VCAM1
On the Market: Integra Dermal Regeneration Template
On the Market: Integra Dermal Regeneration Template
On the Market: Integra Dermal Regeneration Template
Product Objective

- To produce a synthetic dermal replacement template that increases the speed of vascularization and quality of burn and wound treatment.
Growth Factors

- Basic Fibroblast Growth Factor - BFGF
- Acidic Fibroblast Growth Factor - AFGF
- Platelets Derived Growth Factor - PDGF
- Vascular Endothelial Growth Factor - VEGF
VEGF Stimulation of Angiogenesis

VEGF

VEGFR2

PLCγ1

PI3 kinase

Morphogenesis

Cell Proliferation
Methods of Delivery

- Daily Injections
- VEGF in the crosslinked collagen matrix
- VEGF in suspension in pores of matrix
- Controlled release microparticles
Controlled Release particles

- Optimize rate of vascularization by altering:
  - Number/VEGF Concentration of Microcapsules
  - Location of Microcapsules
  - Size of Microcapsules
Microcapsule Diffusion Model

- A model of the VEGF’s motion through the implant could be created and used to create a more-effective product.
- If a model with predictive capabilities was created, then the ideal initial concentration and placement of the microbeads could be determined.
**Microcapsule Diffusion Model**

- No flux across top layer: \( \frac{\partial c}{\partial z} = 0 \) at \( z=L \)
- Bottom layer rises with time as tissue vascularizes into graft
- Living tissue carries away VEGF with a rate \( k_v f(c_3) \)
- Regions 1, 2, and 3 have a diffusion coefficient \( D_1 \)
- Region #4 has diffusion coefficient \( D_2 \)
- Molar fluxes are equal at region interfaces

Microbead region releases VEGF with rate \( r^* \) and at a concentration \( c^* \)
With the model described in the previous slide, the following expression is obtained:

\[
\frac{dy}{dt} = \frac{k g r^*}{k} e^{-y^2/\alpha_3 \sqrt{t}}
\]

\(y(t)\) (the “rate of healing”) can be approximated from the above model.
PRODUCTION PROCESS
REPLIDERM PRODUCTION PROCESS

Add Bovine Tendecn Collagen Dispersion
REPLIDERM PRODUCTION

- Raw material needed
- Equipments needed
- Description of process
- Human labor needed
- Facility layout
REPLIDERM Production

- Raw materials needed
- Equipments needed
- Description of process
- Human labor needed
- Facility layout
## REPLIDERM Production (Raw materials)

<table>
<thead>
<tr>
<th>Procedure (Product)</th>
<th>Description</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bovine Collagen</td>
<td>Extracellular protein</td>
<td>Support and structure of matrix</td>
</tr>
<tr>
<td>Chondroitin 6-Sulfate</td>
<td>Glycoproteins known as proteoglycans found in shark cartilage</td>
<td>forms the ground substance in the extracellular matrix of connective tissue.</td>
</tr>
<tr>
<td>Silastic</td>
<td>Silicon layer</td>
<td>Used as a temporary barrier to protect against infection</td>
</tr>
<tr>
<td>PLGA (polylactic glycolic acid)</td>
<td>Biodegradable, biocompatible polyester</td>
<td>Manufacture of microspheres</td>
</tr>
<tr>
<td>PEG (Polyethylene-glycol)</td>
<td>Polymer</td>
<td>Speeds up degradation of the microbeads. It also forms the sphere shape of the beads</td>
</tr>
<tr>
<td>VEGF</td>
<td>As described earlier</td>
<td>A protein growth factor</td>
</tr>
</tbody>
</table>
REPLIDERM Production

- Raw material needed
- Equipments needed
- Description of Process
- Human labor needed
- Facility layout
Repliderm Production
(Equipments Needed)

- Small Equipment
- Batch processes

Blender

Tissue Homogenizer

Vacuum oven

Vortex

Centrifuge
REPLIDERM Production

- Raw material needed
- Equipments needed

- Description of Process
  - Human labor needed
  - Facility layout
REPLIDERM PRODUCTION PROCESS

Add Bovine Tendone Collagen Dispersion
Before Microbead addition...

Add Bovine Tendon Collagen Dispersion
REPLIDERM PRODUCTION PROCESS

Add Bovine Tendelon Collagen Dispersion
After Microbead addition...

ADD MICROBEADS HERE

FROM VACCUM

Application of silastic top layer using mechanical spreader

Bath Suspension of Glutaraldehyde on a plate shaker

Elution of Aldehyde with water

Freeze Drying

To Packaging
Microcapsule Production

- Raw materials -
  - PLGA Poly(lactic-co-glycolic) acid (50:50)
  - PEG (Polyethylene-glycol)
  - VEGF (Vascular endothelial growth factor)
  - Albumin
  - PVA (polyvinyl alcohol)
  - Isopropanol
REPLIDERM Production

- Human Labor Needed
  - Minimum – 1 PhD, 3 technical assistants

- Facility Layout (30,000 sq-ft)
  - 1 cryo room, Storage, Offices, Animal storage, Laboratory testing, 2 Production rooms
Quality Control

• 1% of all sheets produced to be selected at random and tested for quality assurances
  – All of sheets to be tested are halved. Half of each sheet are tested on a chorioallantoic membrane.
  – The remaining halves are tested in vitro with vascular endothelial cells
FDA PROCESS
FDA Approval Process

- Most costly and time consuming step in bringing a new product to market.
- REPLIDERM is a Class III medical device. Class III medical devices are those that are implanted into a patient and left in the body.
  - Non-clinical testing
  - Manufacturing and facility testing
  - Clinical testing
FDA Approval Process

• Modular Pre-Market Approval Process
  • Module 1: Non-clinical Trials
  • Module 2: Manufacturing & Facility Testing
  • Module 3: Human Clinical Trials
FDA Testing

- Historically FDA testing requires $200,000,000 to $300,000,000 and can last 10-15 years.
- It is this cost and time delay the FDA testing is the most critical step in bringing a new product to the market.
First Stage Variables

- A 1st Stage Variable is a decision that must be made before any production begins.
- For our project, we have two 1st Stage Variables:
  - The number of personnel to hire
  - The number of experiments to run before submitting our product to FDA evaluation.
Second Stage Variables

- A 2\textsuperscript{nd} Stage Variable is a decision that is made after an outcome.
- For our project, we have several 2\textsuperscript{nd} Stage Variables:
  - Each 2\textsuperscript{nd} Stage Variable is a choice on whether or not to continue after an FDA Failure.
  - The chance of having an FDA Failure is dependent on the amount of tests conducted prior to FDA review.
First Stage Variable

- **Number of Personnel Options:**
  - 1 Ph.D. and 3 Lab Technicians
  - 1 Ph.D. and 5 Lab Technicians
  - 1 Ph.D. and 7 Lab Technicians

- **Number of Experiments to Run Prior to submission to FDA review:**

<table>
<thead>
<tr>
<th>Set</th>
<th>Cell Tests</th>
<th>CAM Tests</th>
<th>Nude Mice</th>
<th>Guinea Pigs</th>
<th>Pigs</th>
<th>Dogs</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>B</td>
<td>100</td>
<td>100</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>C</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>25</td>
<td>25</td>
</tr>
</tbody>
</table>
### Second Decision (First Stage Variable)

<table>
<thead>
<tr>
<th>Set</th>
<th>Description</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Set A</td>
<td>100 Cell Flask, 100 CAM, 100 Nude Mice, 100 Guinea Pig, 100 Pig, 100 Dog Tests</td>
<td>More time and money spent up front, but higher likelihood of passing FDA trials on 1&lt;sup&gt;st&lt;/sup&gt; try.</td>
</tr>
<tr>
<td>Set B</td>
<td>100 Cell Flask, 100 CAM, 50 Nude Mice, 50 Guinea Pig, 50 Pig, 50 Dog Tests</td>
<td>Compromise on time and money, but the chances of passing FDA are less than A.</td>
</tr>
<tr>
<td>Set C</td>
<td>50 Cell Flask, 50 CAM, 50 Nude Mice, 50 Guinea Pig, 25 Pig, 25 Dog Tests</td>
<td>Lest costly, but higher likelihood of being forced to repeat some FDA trials.</td>
</tr>
</tbody>
</table>
The initial amount of grant money that we obtain will be the deciding factor in which employment option and which testing option we choose.

Initial grant money will be obtained from the NIH, NSF, CDC, and other various government granting agencies.
FDA APPROVAL

1 PhD & 3 Technicians
Salary: $205,000/yr
Working hr: 24hrs/day

1 PhD & 5 Technicians
Salary: $275,000/yr
Working hr: 40hrs/day

1 PhD & 7 Technicians
Salary: $345,000/yr
Working hr: 56hrs/day

Number of experiments run
100 Cell-Flask Tests
100 CAM Tests
Days: 270

50 Cell-Flask Tests
100 CAM Tests
Days: 220

50 Cell-Flask Tests
50 CAM Tests
Days: 145

Number of experiments run
100 Cell-Flask Tests
100 CAM Tests
Days: 160

50 Cell-Flask Tests
100 CAM Tests
Days: 130

50 Cell-Flask Tests
50 CAM Tests
Days: 90

Pre-Market Application Review
Cost: $50,000
Time: 55 Days

Approval
90% chance
Failure Due to Market Limitations
5%
Failure Due to Vagueness of Application
5%

Reapply for PMAR?
Grant > $50,000
Yes

Scrap Project
Cost: $0

Pre-Market Application
Approval
99% chance
Failure
1%

File PMAR Application
Cost: $0
Time: 0 Days

Scrap Project

Modular Testing
Cost: $500,000
Time: 2 Years

Appraisal
70%

Change concentration of VEGF
Cost: $6000
Time: 2 days

Failure due to number of microbead
10%

Failure due to the location of the bead
10%

Continue?
Grant > $500,000

Scrap

Continue?
Grant > $500,000

Scrap
First Decision (First Stage Variable)
Selection of Employees

- Decision is based on the amount of initial grant money available.
- The more technicians the shorter the time required to run the same amount of test.
Second Decision (First Stage Variable)
Selection of Experiments

- **Set A** - more experiments run concurrently, more in-depth testing and increasing the chances of passing the FDA trials on the 1st try.

- **Set C** - costs the least, begins the FDA testing quicker, but a higher likelihood of failure.

- All sets of experiments perform the same types of tests.

1 PhD & 3 Technicians
Salary: $205,000/yr
Working hr: 24hrs/day
Failure in FDA Approval (Second Stage Decision)
Example: Module 1 Failure

Module 1 (Non testing)

Collagen Matrix &

Collagen Matrix F

Microbead Failure

Approval
Fixing a Failure with the Concentration of VEGF in the Microbeads

Cost of Fixing:
- $12,000 total
- $6,000 for beads themselves
- $2,000 for cell and CAM tests
- $2,000 for small animal tests
- $2,000 for labor

Time required is 14 days:
- Cell, CAM, and small animal tests will be run concurrently
Example: Pathway
FDA Decision

- 9 decisions
- Each decision contains 738 pathways
- Total pathways: 6642 pathway
- Calculated by Excel
- Each pathway contains its cost, duration and probability
Comparison of different set of experiments

- Set C
- Set B
- Set A
Comparison of different number of personnel

- 3 Tech. Set A
- 5 Tech. Set B
- 7 Tech. Set C

NPW

Probability

$450,000,000$ $350,000,000$ $250,000,000$ $150,000,000$ $50,000,000$ $0$ $50,000,000$ $150,000,000$ $250,000,000$ $350,000,000$ $0$
Option to Choose

- 1 Ph.D. and 7 technicians
- Perform test set A
Justification

- Different kinds of failure may occur.
- The easiest problem to fix is one that does not occur.
- Costs escalate rapidly with every time a product must be re-evaluated by the FDA.
Cost Evaluation

- Direct cost - $8,960,000
  Equipment cost, Installation cost, Building & facility cost, Service charges, Raw material cost, Quality control

- Indirect cost - $350,120,000
  FDA cost, Engineering and supervision

FCI $359,079,000
Business Goal

- Obtain the major part of research cost from following sources
  - NIH, NSF, CDC
- Production of new allograft Repliderm with the rate of 2220 sheets/month
- Breakeven in 2-3 years
Demand in the Market

- Burn
- Wound
- Ulcers
- Production

Year 1: Required sheets/year
Year 2: Required sheets/year
Year 3: Required sheets/year
Year 4: Required sheets/year
Year 5: Required sheets/year
Current Market Demand

- Market Demand Model

\[ \beta(t, x) p_1 d_1 = p_2 (D - d_1) \alpha(t, x) \]

D – Total Production Demand – 500,000

d_1 – REPLIDERM Demand

p_1 – REPLIDERM Price/sheet

p_2 – Competitor's Price/sheet

x - Marketing
Production rate & sale price

\[ \sum_{i=1}^{3} p_i d_{1i} - PC = FC_i \]

Product price = $1870 / sheet
Production rate = 2220 sheets / month (1st yr)
Marketing

- Product distribution
  - 56 hospitals every six months
- 3 national conferences annually
- 2 International conferences annually
- Tradeshows and fellowship
Cumulative Cash Position

- Increase in production rate following the model
  - Initially 26645 sheet / year
- Increase in staff by 25%
- Increase Marketing by 10-20%
Cumulative Cash Position Forecast
Location Selection

- Factors considered
  - NIH funding
  - Employment in Biotech companies
  - Cost of living
  - Number of private biotech companies
  - Number of Hospitals
  - Corporate tax rate
- Fairfield, CA
Conclusion

- Control release delivery system
- Pre-FDA testing by 8 personnel
- Testing Set A
- Sale price $1870 / sheet
- Production rate 27000 sheets / year
Acknowledgements

- Dr. Bagajewicz
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QUESTIONS???????