Technological & Financial Analysis of a Carbohydrate Vaccine for Tuberculosis

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Tuberculosis

Currently:
- Leading cause of death in developing world
- 2 billion infected
- 8 million/year - active TB
- 3 million/year die
- 10-15 million latent in U.S.

Projected:
- 37,800,000 of current HIV patients will become active and die in the U.S.
- New Cases: 1 billion 2020
- 36 million deaths from new infections

Vaccine Needed!
What is Tuberculosis?

- *Mycobacterium tuberculosis*
- Infection by inhalation
- Contagious when active
- Symptoms: weight loss, fever, appetite loss, cough, chest pain, bloody sputum
- Patients will die within weeks to months without treatment
New Drugs: Significance

- Drastic effect on population
  - Lower death rates
  - Extend life expectancy
  - Eradicate disease (small pox 1967-73)
- Financial gain
- Personal motivations

Romantic view!
New Drugs: Reality

- Average cost over $400 million from research to consumer
- Strictest protocols for drug approval in U.S.
  - Food & Drug Administration
  - Lengthy and tedious process
  - average = 15 years
  - Success rate: 5/5,000 potential drugs
A Researcher’s Concerns

- Will my procedure work?
- How accurate is my theory?
- How can I increase the product yield?
- Can this process be scaled up?
An Investor’s Concerns

- Amount to invest in research?
- How long will it take?
- Risk of losing money?
- How much can I lose?
- Expected profit?
- What timeframe?
- Failure at any FDA Phase?
- Product price?
- What is the market?
- Advertisement campaign?

We can provide simultaneous answers to these questions!
Project Overview

- Proposal

  *Carbohydrate-based tuberculosis vaccine*

- Acknowledgment of technical uncertainties

- Success estimate

- Two directions
  - How to develop vaccine
  - Decisions to be made
Vaccines

- Definition: weakened or killed pathogens or parts of polysaccharides and/or proteins that stimulate immune response

- Benefits of using parts of the organism
  - Will not cause infection with organism
  - Stimulates antibody production in body
Antibody Stimulation Goal

- Antigen recognition
- Engulfing
- Cell death & degradation
- Fragments displayed on cell surface
- Proliferation and activation of T cells
- Antibody circulation
M. Tuberculosis Cell Wall

- Cell growth
- Polysaccharide recovery
- Cleaving
- Conjugation to carrier protein
Bacterial Growth

- *Mycobacterium tuberculosis* ATCC 25177
- Inoculated in Lowenstein-Jensen (LJ) plates
  - Generation time = 6 - 8 weeks
- Transfer to LJ liquid medium
  - Generation Time = 15 hours
- Deviation: growth time
Cell Membrane Separation

- **Centrifugation**
  - Pellets: 3,000 x g for 20 min
  - Wash in phosphate-buffered saline
  - Re-suspend in distilled water

- **Sonication**
  - Weakening of the cell wall with electrical pulses
  - Three cycles of 30 s pulses
  - Carbohydrate yield: 70-80%

- **Centrifugation**
  - 3,000 x g for 20 min

- **Supernatant filtration**
  - Separation of the capsule

- **Lyophilization (optional)**

**Deviation:** sonication cycles

As presented by Stokes et al., 2004
Cell Membrane Cleaving

- Fragments between 2 and 10 kDa
  - Ensures no virulence activity
  - High titer response with less than 10 kDa
Acetolysis

- **Step 1: Acetolysate**
  - Acetic acid, acetic anhydride, and sulfuric acid
  - 8 hrs @ room temp. (RT)
  - Pour into 30 g ice water

- **Step 2: pH stabilization**
  - At RT
  - pH = 7.5 with NaOH

- **Step 3: Sugar acetate extraction**
  - Use chloroform
  - Yield = 96.3%

- **Step 4: Evaporation**
  - Dry over anhydrous sodium sulfate
Deacetylation

- **Step 5:**
  - Methanol, barium methoxide, & Dowex 50
- **Step 6:**
  - Sephadex G- 25, eluted at 10 mL/hr
- **Step 7:** Gel filtration (0.2 µm)

**Deviations:**

Cleaving, size, yield, and reaction
Carbohydrate Attachment

- **Step 1- Amination of polysaccharides (PS)**
  - Deviation: insufficient amino substitution
    \[ \text{PS-CHO} + \text{NH}_4\text{Cl} \rightarrow \text{PS-NH}_2 \]

- **Step 2- Thiolation of PS with 2-iminothiolane**
  \[ \text{PS-NH}_2 + \text{NH}_2^+\text{Cl}^- \rightarrow \text{PS-NH-C(NH}_2^+\text{Cl}^-)_(\text{CH}_2)_3\text{-SH} \]
Carbohydrate Attachment

- Step 3- Bromoacetylation of tetanus toxoid (TT)
  - Deviation: contamination in tetanus sample

\[
\text{TT-NH}_2 + \text{NHS-CO-CH}_2-\text{Br} \rightarrow \text{TT-NH-CO-CH}_2-\text{Br}
\]

As presented by Pawlowski, et al, 1999
Carbohydrate Attachment

- Step 4- Conjugation activated PS and TT
  - Deviation: incomplete conjugation

Step 2 product + Step 3 product →

\[
\text{TT-NH-CO-CH}_2\text{-S-(CH}_2\text{)}_3\text{-C(NH}_2^+\text{Cl}^-\text{-NH-PS}
\]

- Step 5- Separation: product from free reactants
  - Deviation: contaminants, pH variation
Research and Pre-FDA

- Laboratory research
  - Create the vaccine
  - Improve the product yield
  - Create the deliverable drug

- Animal testing
  - Test biological activity and safety
FDA Approval Process

- **Phase I**
  - Metabolic and pharmacologic effects in humans
  - Dosing effects
  - Effectiveness

- **Phase II**
  - Effectiveness of the drug
  - Short-term side effects
  - Health risks

- **Phase III**
  - Overall benefit-risk relationship

- **Applications and Committees**

- **Conditions of Failure**
  - Design failure in research
  - Clinical hold in FDA
What do technical deviations mean in ???
Goals

- Directed at risk taker, risk averter, or risk average

- Aid with critical decisions
  - Research and investment
  - Failed FDA phase

- Market strategies and demand models

- Risk assessment

- Success and profit estimation
Decision- Making

- First Stage or “Here and Now” Decisions
  - There will be consequences for “things that I do today”
  - Example: buying a house

- Second Stage or “Wait and See” Decisions
  - Made in response to the realization of uncertainty
  - Need to be addressed, not made
  - Example: opening an umbrella when it rains
## Decision- Making

<table>
<thead>
<tr>
<th>First Stage Decision</th>
<th>Second Stage Decisions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focus processes in pre-FDA research</td>
<td>- Time to begin plant construction</td>
</tr>
<tr>
<td>- Protein/ polysaccharide conjugation</td>
<td>- Time to begin marketing campaign</td>
</tr>
<tr>
<td>- Capsule cleaving/ recovery</td>
<td>- Additional research after failed FDA stage</td>
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<tr>
<td>- Bacterial growth</td>
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</tbody>
</table>
Financial Definitions

**Market** – brings together buyers and sellers

**Demand** – schedule with various amounts of a product consumers are willing/able to purchase at a price

**Risk** - uncertainty of project and associated financial loss or gain

**Net Present Value (NPV)** – how much the project is worth at a point in time; indicative of favorable venture
Market

- Diverse target groups
  - Melanoma patients in the U.S.
  - Cancer world wide
- Tuberculosis
  - 12 million hospital personnel
  - 1.4 million military personnel
- Depends on resources of investors
Economics

**Definitions:**
- $\alpha =$ Measurement of customer knowledge of product
- $\beta =$ Measurement of customer preference
- $d_1 =$ Amounts of a product at a price that consumers are willing to purchase

**Purpose**
- Price
- Return on Investment (ROI)
- Production schedule

\[ d_1 = \left[ \frac{\alpha P_2}{\beta P_1} \left( \frac{Y}{P_2} - \frac{P_1}{P_2} d_1 \right)^{1-\beta} \right]^{1/(1-\alpha)} \]
Demand Model

Iterative Calculation – 82% Market

New Product 3.5 times better

d1 = New drug
\( \alpha = \text{varied} \)
\( \beta = 0.29 \)

\( P2 = $115.09 \)
\( P1 = $140.00 \)

D = 13.4 million units
### α Function Model

<table>
<thead>
<tr>
<th>Year</th>
<th>Market Target</th>
<th>Installations Visited</th>
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<tbody>
<tr>
<td>0</td>
<td>2 %</td>
<td>170</td>
</tr>
<tr>
<td>0 to 1</td>
<td>10 – 15 %</td>
<td>760</td>
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<tr>
<td>1 to 2</td>
<td>35 – 40 %</td>
<td>1,940</td>
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<tr>
<td>2 to 3</td>
<td>70 – 75 %</td>
<td>2,690</td>
</tr>
<tr>
<td>3 to 4</td>
<td>90 – 95 %</td>
<td>1,520</td>
</tr>
<tr>
<td>4 to 5</td>
<td>95 – 100 %</td>
<td>170</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>7,250</strong></td>
</tr>
</tbody>
</table>

- Increased with advertisement
- Aggressiveness of marketing campaign
## β Parameter

<table>
<thead>
<tr>
<th>Property</th>
<th>Description</th>
<th>Weight (w)</th>
<th>New Product (y₁)</th>
<th>Existing Product (y₂)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>New product more effective than existent one</td>
<td>0.7</td>
<td>0.8</td>
<td>0.2</td>
</tr>
<tr>
<td>Side Effects</td>
<td>New product has less side effects than existent one</td>
<td>0.3</td>
<td>0.7</td>
<td>0.3</td>
</tr>
<tr>
<td>Delivery Method</td>
<td>Currently, only available via injection</td>
<td>0</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Availability</td>
<td>Target institutions, not public</td>
<td>0.05</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Brand</td>
<td>No similar product</td>
<td>0.05</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

β = measurement customer preference

\[
H = \Sigma (w * y₁) = 0.77
\]

\[
\beta = \frac{H_2}{H_1} = 0.23
\]

\[
\beta = 0.29
\]
Price & Demand Relation

- Higher demand for lower priced product

Demand at Different Prices

- Time (years) axis
- Demand (million units) axis
- Different price lines for $100/unit, $120/unit, $135/unit, $140/unit, $145/unit, $170/unit, and $200/unit
Profit Results

Different profits depending on $\alpha$ and $d_1$. 

Cumulative Profit for Different Prices

- $100/unit
- $120/unit
- $135/unit
- $140/unit
- $145/unit
- $170/unit
- $200/unit

Profit ($millions$)

Time (years)
Price Optimization

NPV as a Function of Price

- Higher NPV preferred
- Discounted rates, etc. (later)
Return on Investment

ROI = Profit/FCI; approx. 3 years

Maximum ROI = 29.08%
Demand and Risk Relation

- Selected values of $\alpha$, $\beta$, price, and demand
  - $\alpha$ varies with time
  - $\beta = 0.29$
  - $P_{\text{opt}} = $140.00
  - Demand = 13.4 million units

- Risk calculated accordingly
What is Risk?

- Predictor of the product’s success
- A collection of paths that vary with first stage decision
  - Research time invested: 6, 8, or 10 years
Cumulative Probabilities and Costs

- Pathways
  - All possibilities considered
  - Realistic probability assigned
- Probabilities compounded and costs summed over a particular path
- Risk and net present values calculated
Sample Pathway

1. Reaction to Vaccine:
   - 30-20-15%
   - 70-80-85%

2. Titer Measurements:
   - 0.5 years
   - 90-80-75%
   - 10-20-25%

3. Booster Administration:
   - $1.3 million - $1.3 million - $2.2 million
   - 1.5 - 1.5 - 2.5 years
   - 20-10-5%
   - 40-45-45%
   - 40-45-50%

4. Titer Levels:
   - Insufficient Titer
   - Sufficient Titer Levels as BCG Vaccine
   - High Titer

5. Titer Levels:
   - Low Titer Levels than BCG Vaccine
   - High Titer

6. Reaction Detection in Animal Testing:
   - 70-80-90%

7. Adverse Reaction:
   - Back to R&D

8. Satisfactory or No Reaction:
   - $1.8 million - $2.6 million - $3.5 million
   - 2-3-4 years
   - 30-20-10%

9. Vaccine Proceeds!!
## Sample Pathway

<table>
<thead>
<tr>
<th>Characteristics of Example Path</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Possibility of Occurrence</td>
<td>0.259%</td>
</tr>
<tr>
<td>Cost of Pathway (millions)</td>
<td>$49.0</td>
</tr>
<tr>
<td>Time in Research (years)</td>
<td>6</td>
</tr>
<tr>
<td>Time in FDA (years)</td>
<td>10</td>
</tr>
<tr>
<td>Net Present Value (millions)</td>
<td>$605</td>
</tr>
</tbody>
</table>
This is a very risky project!

What can we do?
FDA: Attempt #2

- Where drug was abandoned before, return to research for one year

- Continue in FDA at same phase

- Expect higher probability of success
Comparison of Risk Analyses

<table>
<thead>
<tr>
<th>Summary of Pathways in Risk Analysis</th>
<th>Initial</th>
<th>&quot;Second Chance&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Pathways</td>
<td>71</td>
<td>443</td>
</tr>
<tr>
<td>Successful Pathways</td>
<td>12</td>
<td>96</td>
</tr>
<tr>
<td>Percent Success (6 year path)</td>
<td>9.2%</td>
<td>23.3%</td>
</tr>
</tbody>
</table>
# Risk Summary: TB Vaccine

<table>
<thead>
<tr>
<th>First Stage Decision- Time Invested in Research</th>
<th>6 Years</th>
<th>8 Years</th>
<th>10 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single trip Through FDA</td>
<td>Risk</td>
<td>90.8%</td>
<td>78.1%</td>
</tr>
<tr>
<td></td>
<td>Expected Worth (millions)</td>
<td>$555.43</td>
<td>$494.43</td>
</tr>
<tr>
<td>Recycle Through FDA</td>
<td>Risk</td>
<td>76.7%</td>
<td>65.3%</td>
</tr>
<tr>
<td></td>
<td>Expected Worth (millions)</td>
<td>$485.97</td>
<td>$428.16</td>
</tr>
</tbody>
</table>
Conclusions

- **1st stage decision**
  - 6, 8, or 10 years pre-FDA research

- **Price optimization**
  - $140/unit
  - ROI = 29% (5 years)

- **FDA risks based on 1st stage decision**
  - From 54% to 91%

- **Risks based on 2nd stage decision to re-cycle drug**
  - Decreased to 47% to 77%
  - Decreased Expected Worth

- **Pre- FDA research**
  - Significantly increases success probability
  - Decreases Expected Worth
General Conclusions

- New drug analysis outcome
  - General form of pre-FDA research & FDA approval process
  - Market analysis
  - Demand and pricing models
  - Risk analysis
  - Expected worth estimation
  - Assistance in critical decision-making
Tuberculosis Vaccine

Questions?
Appendix
Antibody Stimulation: Goal

- Use parts of *Mycobacterium tuberculosis* capsule and force the body to create antibodies against it
- Replicate ‘natural’ antibody production process
- Stimulate response for future and current infection
Method Benefits

- Has the highest yield and the most documentation
- Modeled for all saccharide-protein conjugate vaccines
- Researched with Tetanus Toxoid
Antibody Suppression

TB multiplies inside macrophages

- Binds to macrophage surface protein (C3b) - receptor for complement cascade
  - No guidance to site of infection
- Prevents formation of phagolysosome
Carbohydrate Attachment

- Step 1- Amination of polysaccharides (PS)
  - Deviation: insufficient amino substitution

\[
\text{PS-CHO} + \text{NH}_4\text{Cl} \xrightarrow{\text{NaBH}_3\text{CN}} \text{PS-NH}_2
\]

- solid sodium cyanoborohydride

PS + solid ammonium chloride $\rightarrow$ aminated PS
Carbohydrate Attachment

- Step 2- Thiolation of aminated polysaccharides with 2-iminothiolane

\[ \text{PS-NH}_2 + \text{S} - \text{NH}_2^+\text{Cl}^- \rightarrow \text{PS-NH-C(NH}_2^+\text{Cl}^-)-(\text{CH}_2)_3\text{-SH} \]

Aminated PS + 2-iminothiolane $\rightarrow$ thiolated PS
Carbohydrate Attachment

- Step 3- Bromoacetylation of tetanus toxoid (TT)
  - Deviation: contamination in tetanus sample

\[ \text{TT-NH}_2 + \text{NHS-CO-CH}_2-\text{Br} \rightarrow \text{TT-NH-CO-CH}_2-\text{Br} \]

Stock TT + solid N-hydroxysuccinimide ester of bromoacetic acid \( \rightarrow \) bromoacetylated TT
Carbohydrate Attachment

- **Step 4**: Conjugation of thiolated polysaccharides with bromoacetylated tetanus toxoid
  - Deviation: incomplete conjugation

\[
\text{PS-NH-C}(\text{NH}_2^+\text{Cl}^-)-(\text{CH}_2)_3-\text{SH} + \text{TT-NH-CO-CH}_2-\text{Br} \rightarrow \\
\text{TT-NH-CO-CH}_2-\text{S-(CH}_2)_3-\text{C}(\text{NH}_2^+\text{Cl}^-)-\text{NH-PS}
\]

- **Step 5**: Separation of conjugates from free reactants
  - Deviation: contaminants, pH variation
General Technological Risks

- Experimental failure
- Unexpected outcomes
- Lack of chemical reactivity
- Deviations in product recovery
  - Methodology or instrumentation
- Unavailability of resources or test subjects
- Risk to human health
TB Vaccine Risks & Deviations

- Growth on plates not determined
- Non-effective sonication
- Yield of cell membrane (pellets) uncertain
- Carbohydrate cleaving inaccurate
  - Over 10 kDa or less than 2 kDa capsule fragments
  - Deacetylation not achieved – lower yield
TB Vaccine Risks & Deviations (cont’d)

- Insufficient amino substitution of polysaccharide
- No sulfhydryl groups after reduction of disulfides
- Residual salts and impurities in tetanus toxoid
- Incomplete bromoacetylation reaction - no activated amino group
- Incomplete conjugation of polysaccharide and tetanus toxoid
- pH variance at any step
- Contamination by free reactants
Vaccine Components

- 25ug polysaccharide- tetanus toxoid conjugate
- Sodium Phosphate Buffer
- 0.9% Sodium Chloride Saline
Animal Testing Procedures

- 80 male BALB/c inbred mice injected with complex
- 10 mice injected with saline, 10 with carbohydrates as controls
- Mice immunized subcutaneously at 0 and 28 days with 1 ug of conjugates in 0.25 mL phosphate-buffered physiological saline (PBS)
- Blood samples collected every 7 days for 120-day period
Animal Testing Procedures

- Serum titers measured when samples are sent to testing facility
- IgG levels monitored periodically
Business Plan
Competition

**Crucell & Aeras Global TB Vaccine Foundation**

- Bill & Melissa Gates Foundation
  - $82.9 million to Aeras
- $2.9 million to Crucell
- Improve on BCG vaccine
- Phase I clinical trials in 5 years + 8 yrs FDA
- Earliest distribution Year 2019!
Production Capacity

- Current Market = 2.68 million/year
- 3.5% Market Growth - linked to hospitals
## α Function Model

<table>
<thead>
<tr>
<th>Range (Years)</th>
<th>Advertisement Method</th>
<th>Expenses</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Word of mouth, Presentations, FDA Results, Journals, Visits (2 sales reps)</td>
<td>$121,584.00</td>
</tr>
<tr>
<td>0 to 1</td>
<td>Visits + Website + Television (9 sales reps)</td>
<td>$1,361,768.00</td>
</tr>
<tr>
<td>1 to 2</td>
<td>Visits + Website + Television (23 sales reps)</td>
<td>$2,212,865.00</td>
</tr>
<tr>
<td>2 to 3</td>
<td>Visits + Website + Television (32 sales reps)</td>
<td>$2,759,984.00</td>
</tr>
<tr>
<td>3 to 4</td>
<td>Visits (18 sales reps)</td>
<td>$1,094,256.00</td>
</tr>
<tr>
<td>4 to 5</td>
<td>Visits (2 sales reps)</td>
<td>$121,584.00</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>$7,672,032.00</strong></td>
</tr>
</tbody>
</table>

- First 3 years – most costly
## Advertisement: Methods & Costs

<table>
<thead>
<tr>
<th>Method &amp; Description</th>
<th>Cost ($/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sales Representative (84 installations)</strong></td>
<td></td>
</tr>
<tr>
<td>• Salary</td>
<td>45,000.00</td>
</tr>
<tr>
<td>• Transportation, car, plane tickets</td>
<td>13,440.00</td>
</tr>
<tr>
<td>• Misc., meals, reimbursements, other</td>
<td>2,352.00</td>
</tr>
<tr>
<td><strong>World Wide Web</strong></td>
<td></td>
</tr>
<tr>
<td>• Web Page</td>
<td>2,400.00</td>
</tr>
<tr>
<td>• Web Master salary</td>
<td>32,000.00</td>
</tr>
<tr>
<td>• Fee, other</td>
<td>240.00</td>
</tr>
<tr>
<td><strong>Television</strong></td>
<td></td>
</tr>
<tr>
<td>• 30 second commercial 3 times/day</td>
<td>780,000.00</td>
</tr>
</tbody>
</table>
Demand Equation

\[ \beta p_1 d_1 = \alpha p_2 d_2 \left( \frac{d_1^\alpha}{d_2^\beta} \right) \]

\[ \beta = \frac{S_2}{S_1} \]

\( \alpha = \text{awareness of product} \)

\( p_1 = \text{our price} \)

\( p_2 = \text{competitor's price} \)

\( d_1 = \text{our demand} \)

\( d_2 = \text{competitor's demand} \)

\[ Y = p_1 d_1 + p_2 d_2 \]

\[ \Rightarrow d_2 = \frac{Y - p_1 d_1}{p_2} \]

\[ \therefore d_1 = \left( \frac{\alpha p_2}{\beta p_1} \right) \left( \frac{Y - p_1 d_1}{p_2} \right)^{1-\beta} \cdot d_1^\alpha \]
Risk Analysis

- Probability
- Net Present Value (millions)

- 6 years
- 8 years
- 10 years
Detail of Losses

Net Present Value (millions)

Probability

-14 -12 -10 -8 -6 -4 -2 0 1

6 years 8 years 10 years

Net Present Value (millions)
## Timeline: 2\textsuperscript{nd} Stage Decisions

<table>
<thead>
<tr>
<th>Year</th>
<th>Research</th>
<th>Animal Testing</th>
<th>FDA: Phase I</th>
<th>FDA: Phase II</th>
<th>FDA: Phase III</th>
<th>FDA: Applications</th>
<th>Plant Construction</th>
<th>Marketing</th>
<th>Production</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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