Novel Hyaluronic Acid Derivatives to Alleviate Osteoarthritis

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Kim Fink
Objective

- To design a polymer to be used in non-surgical injections to relieve symptoms of osteoarthritis
  - Increased retention time
  - Maintain flexibility and strength
  - FDA approved
  - Reasonable cost
Overview

- Osteoarthritis
- Current Treatments
- Novel Hyaluronic Acid Derivative
- Demand
- FDA
- Conclusions
The Knee Joint
Articular Cartilage

- Transmits load from one surface to another
- 2-3 mm thick
- Components
  - Water (70%)
  - Collagen (10-20%)
  - Proteoglycans (5-10%)
  - Chondrocytes (~5%)
Synovial Fluid

- Fills gap between joints
  - Approx. 50 μm thick
    - During walking can be 0.8-1.5 μm
  - Volume ~1 ml
- Enclosed in synovial membrane
- Major components
  - Water
  - Proteoglycans
  - Hyaluronic Acid (HA)
Synovial Fluid

- Properties
  - Viscosity ~ 300-10,000 cP
  - Coefficient of friction ~ 0.02
    - Compare to 0.03 for ice-on-ice

- Main contributor to these properties
  → Hyaluronic Acid
Hyaluronic Acid (HA)

- Structure
  - Linear repeating disaccharide
    - D-glucuronic acid and N-acetyl-D-glucosamine
  - Number of units = 500 - 25,000

http://www.glycoforum.gr.jp/science/hyaluronan/HA01/HA01E.html
HA in Synovial Fluid

- Average molecular weight for healthy knee: $10^5 - 10^7$ Daltons
- Concentration for healthy adult: 3.4 mg/ml
- Non-Newtonian shear thinning
- Viscosity – variable
  - Increases with increasing molecular weight
  - High at low shear rate
  - Low at high shear rate
The Disease
Osteoarthritis – General Facts

- Over 23 million Americans affected
- Most common in people 65+
- Anyone susceptible
  - Impact injuries
  - Obesity
  - Prolonged elevated activity

- $1.5 billion/year industry in US
Osteoarthritis

- Most common in load-bearing joints
  - Knees, hip, lower back, neck
- Possibly due to decreased lubrication and load bearing properties of cartilage and synovial fluid
- Leads to degeneration of cartilage and eventually bone-on-bone contact
Normal vs. Osteoarthritic Knee

Healthy Knee in Cross Section
- Cartilage
- Synovial Fluid
- Joint Space

Osteoarthritic Knee in Cross Section
- Cartilage Damage
- Bone Spurs
- Decreased Joint Space
- Bone Cyst

www.medem.com
Symptoms

- Mild to severe pain
- Limited range of motion
- Approx. 25% of patients unable to perform daily functions

http://adam.about.com/encyclopedia/19506.htm
Current Treatments

- Physical therapy
  - exercise techniques
- Oral medication
  - Tylenol, Ibuprofen, Celebrex
  - Effective for moderate pain
- Total Knee Replacement
- Hyaluronic acid (HA) injections
Current Treatments – Total Knee Replacement

- **Advantages:**
  - Last 15-25 years

- **Disadvantages:**
  - Time away from work
    - Desk work (3-6 weeks)
    - Labor intensive work (several months)
  - Requires extensive physical therapy
  - Risk of infection
  - Cost ~ $15,000
Current Treatments – Hyaluronic Acid Injections

- Intra-articular injections of HA derivatives
  - Series of injections, must be repeated after 6 months
  - Aims to increase the viscoelasticity of the synovial fluid
Available HA Injections –

- HYALGAN®
  - Similar in structure and properties to natural hyaluronic acid
  - Mixed results

- Hylan G-F 20 (SYNVISC®)
  - Crosslinked HA
  - Viscosity and elasticity near that of healthy 18-27 year old adult
  - Last up to 6 months
  - $620 for 3-week treatment
Problems

- Current HA injections appear to degrade over time in the body.
- It has been proposed by some that the mechanism by which this degradation is occurring is through bond breaking.
  (example of mechanism shown on next slide)
Problem – Degradation

Solution – First Consideration

- CF₃ modified HA
  - Increase the dipole to increase viscosity
  - Reduce degradation rate
  - Enzyme used to initiate reaction
  - Low cost of reagents
  - Problem: Reports of toxicity
Our Solution

HYAL-VYNE®
HYAL-VYNE®

- High molecular weight hyaluronic acid derivative
  \( \sim 10^6 \text{ Da} \)
- HA modified with 2-vinyl
- New crosslinker introduced
- Forms a viscoelastic hydrogel
**Modified HA**

- Hyaluronic acid polymer modified with 2-vinyl (R = -CH=CH$_2$)
  - Polymerized using Ovine Testicular HAase (OTH)
Crosslinker

- Ammonium Peroxydisulfate
  - Chemical Formula = \((NH_4)_2S_2O_8\)
  - Molecular Weight = 228.18 g/mol
  - Cost = $3.61/500g
Crosslinker

- Advantages
  - Sulfate has been proven to reduce degradation rates
  - Ability to stabilize a structure against denaturation
  - Non-toxic
Crosslinker

Crosslinking

- Provides greater stability
- Increases size of structure for higher-molecular weight
- Effects the solutions properties such as
  - strength
  - viscosity
Hydrogels

- 3D network of crosslinked hydrophilic polymer chains
- Absorb water
  - Able to retain shape upon loading and unloading
  - Able to absorb more than 20% of their own weight
HYAL-VYNE®
**HYAL-VYNE®**

- **Required concentrations (mol/ml)**
  - HA = $2.8 \times 10^{-4}$
  - Crosslinker = $5.5 \times 10^{-5}$

- **Reaction controlled by time**
HYAL-VYNE®

- Viscosity ~ 16 Pa·s
- Molecular weight ~ 3 million Daltons
- Crosslinks per polymer chain ~ 24
- Monomers per polymer chain ~ 44
- Total number of monomers ~ 6700
- Total number of crosslinks ~ 1000
Lubrication Theory

- Elastohydrodynamic Lubrication (EHL)
  - Applied in cases of low geometric conformity subject to elastic deformation
  - Applies to most biological systems
  - Synovial fluid falls into Elastic-Isoviscous Regime
  - Use theory to calculate minimum film thickness of new gel to compare to normal synovial fluid
Minimum Film Thickness

According to the Dowson-Higginson equation, the minimum film thickness for EHL is

\[ h_{\text{min}} = 1.6 \frac{\alpha^{0.6} \left( \mu_0 \tilde{u} \right)^{0.7} E'^{0.03} R^{0.43}}{w^{0.13}} \]

Where
- \( \mu_0 \) = viscosity at atmospheric pressure
- \( \tilde{u} \) = effective speed
- \( E' \) = reduced Young’s modulus
- \( R \) = effective radius
- \( w \) = load
- \( \alpha \) = material constant
Minimum Film Thickness

- Parameters:
  - \( \bar{u} = \frac{U_0}{2} = \frac{0.03+0.03}{2} = 0.03 \text{ m/s} \)
  - \( R = 0.20 \text{ m} \)
  - \( w = 2.6 \text{ MPa} \)
  - \( \alpha = 9.9 \times 10^{-9} \)
  - \( E' = 66.5 \text{ kPa} \)

<table>
<thead>
<tr>
<th></th>
<th>HYAL-VYNE®</th>
<th>Synovial Fluid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viscosity, ( \mu_0 )</td>
<td>16 Pa·s</td>
<td>15.3 Pa·s</td>
</tr>
<tr>
<td>Minimum film thickness, ( h_{min} )</td>
<td>1.54 ( \mu m )</td>
<td>1.50 ( \mu m )</td>
</tr>
</tbody>
</table>
Demand
Demand Equations

\[ p_1 d_1 + p_2 d_2 \leq Y \]
\[ p_1 d_1 \beta = \alpha p_2 d_2 \frac{d_1}{d_2} \frac{\alpha}{\beta} \]
\[ d_1 + d_2 \leq D \]

Parameters

- Product demands, \( d_1 \) and \( d_2 \) = ???
- New treatment cost, \( p_1 = $2400/\text{injection} \)
- Current treatment cost, \( p_2 = $1300/\text{year} \)
- Total market demand, \( D = 7 \text{ million} \)
- Total spent on treatment, \( Y = $1.5 \text{ billion}/\text{year} \)
- \( \alpha \rightarrow \) amount costumers know about new treatment relative to others
- \( \beta \rightarrow \) measure of how much better new treatment is compared to competitors
**Happiness Function**

<table>
<thead>
<tr>
<th>Attributes</th>
<th>$W_i$</th>
<th>Design Variables</th>
<th>Min</th>
<th>Max</th>
<th>$Y_i$</th>
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</thead>
<tbody>
<tr>
<td>Frequency of Treatments</td>
<td>0.75</td>
<td>Crosslink Density</td>
<td>-10.00%</td>
<td>10.00%</td>
<td>10.00%</td>
</tr>
<tr>
<td>Pain of Injection</td>
<td>0.125</td>
<td>Molecular Weight</td>
<td>-20.00%</td>
<td>20.00%</td>
<td>20.00%</td>
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<tr>
<td>Cost</td>
<td>0.125</td>
<td>Injection Volume</td>
<td>-5.00%</td>
<td>5.00%</td>
<td>-5.00%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Viscosity</td>
<td>-10.00%</td>
<td>10.00%</td>
<td>-10.00%</td>
</tr>
</tbody>
</table>

- **Old Treatment Happiness** = 40%
- **New Treatment Happiness** = 62%
Demand

\[ \beta = \frac{\text{competition's happiness}}{\text{new treatment happiness}} \]

\[ \beta = \frac{40\%}{62\%} = 0.645 \]

- Year (0) = 0.645
- Changes over time due to improvements in competitor products
- Assume \( \alpha \) gradually increases until new product is equally known
# Demand

<table>
<thead>
<tr>
<th>Year</th>
<th>Alpha, $\alpha$</th>
<th>Beta, $\beta$</th>
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<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0.645</td>
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<tr>
<td>1</td>
<td>0.15</td>
<td>0.715</td>
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<tr>
<td>2</td>
<td>0.4</td>
<td>0.785</td>
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<tr>
<td>3</td>
<td>0.89</td>
<td>0.855</td>
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<tr>
<td>4</td>
<td>0.99</td>
<td>0.925</td>
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<tr>
<td>5</td>
<td>1</td>
<td>0.995</td>
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<td>6</td>
<td>1</td>
<td>1.065</td>
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<td>1.205</td>
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<td>9</td>
<td>1</td>
<td>1.275</td>
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<tr>
<td>10</td>
<td>1</td>
<td>1.345</td>
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</table>
Demand

- Total demand changes each year
  - Year 1 = 370,000 people
  - Year 2 = 621,000 people
  - Year 3 = 625,000 people (max)

- By Year 6 it is expected that a better treatment will be created due to the increasing competition
FDA Approval Process
FDA Approval - Outline

- Classification
- Type of Premarket Approval
- Necessary Experiments
- Possible Scenarios for success/failure
- Time and Money requirements
Drug or Device?

- Drug: used for diagnosis or treatment of disease or to affect the structure or function of the body

- Device: used for diagnosis or treatment of disease or to affect the structure or function of the body, but does not depend on metabolic process to achieve primary purpose
Product Classification

HYAL-VYNE

Medical Device
Device Classification

- **Class I: General Controls**
  - Least stringent; minimal risk

- **Class II: Special Controls**
  - More regulations than Class I; no life-threatening health risks

- **Class III: Premarket Approval**
  - Most strict control; often intended to prevent or treat disease or sustain human life; require extensive review before marketing
Premarket Approval (PMA)

- **Traditional PMA**
  - All non-clinical and clinical tests completed, then PMA submitted to FDA all at once
  - If denied, possibly have to start completely over

- **Modular PMA**
  - Non-clinical and clinical tests divided into modules, information from one module reviewed by FDA at a time
  - Allows for easier reassessment in case of denial
Modular PMA

- First a PMA shell must be submitted
  - No predetermined format, customized for particular device
  - Outlines experiments to be conducted in each module
  - Gives approximate time of completion
## HYAL-VYNE

<table>
<thead>
<tr>
<th>Module Number</th>
<th>Contents</th>
<th>Time to Complete</th>
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<tbody>
<tr>
<td>1</td>
<td>Nonclinical Laboratory Studies:</td>
<td>3 Years</td>
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<tr>
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<td>Physical and Chemical Property Tests</td>
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<td>Degradation Tests</td>
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<tr>
<td></td>
<td>Toxicity Tests</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Nonclinical Laboratory Studies:</td>
<td>3 Years</td>
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<tr>
<td></td>
<td>Animal Testing</td>
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<td>Sterilization and Packaging</td>
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<td>Injection Procedure</td>
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<tr>
<td>3</td>
<td>Clinical Studies:</td>
<td>5 Years</td>
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<td>Human Patient Testing</td>
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<td>Physician Instructions</td>
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<td>Patient Instructions</td>
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FDA Approval Process
Modeling
First-Stage Decisions

First-Stage Decision Variables
- “Here-and-Now” decisions that must be made prior to beginning a project

⇒ Number of Employees
  - PhDs and lab technicians that will manage and conduct experiments

⇒ Number of Experiments
  - Number of repeated experiments that will be performed to submit to the FDA to prove consistency of results
First-Stage Decisions:
Number of Employees and Number of Experiments

First Stage Variables

Determine Number of Workers

1 PhD, 10 Lab Techs
1 PhD, 5 Lab Techs
1 PhD, 2 Lab Techs

Determine Number of Experiments

100 Experiments $170,000 100 Days
85 Experiments $150,000 90 Days
50 Experiments $100,000 65 Days

Determine Number of Experiments

100 Experiments $170,000 105 Days
85 Experiments $150,000 95 Days
50 Experiments $100,000 70 Days

Begin Pre-FDA Experimentation

Determine Number of Workers

1 PhD, 10 Lab Techs
1 PhD, 5 Lab Techs
1 PhD, 2 Lab Techs

Determine Number of Experiments

100 Experiments $170,000 100 Days
85 Experiments $150,000 90 Days
50 Experiments $100,000 65 Days

Begin FDA Approval
<table>
<thead>
<tr>
<th>Name</th>
<th>Min NPV</th>
<th>Max NPV</th>
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</thead>
<tbody>
<tr>
<td>10 workers 85 experiments</td>
<td>-396.31</td>
<td>805.83</td>
</tr>
<tr>
<td>5 workers 85 experiments</td>
<td>-554.35</td>
<td>815.63</td>
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<tr>
<td>2 workers 85 experiments</td>
<td>-415.27</td>
<td>901.93</td>
</tr>
</tbody>
</table>

**Distribution for 10 workers 85 experiments/M1060**

Mean = 206.0359

5% at -0.2121, 90% at 0.5818, 5% at 1.0000
We have assigned probabilities (0-100%) for each anticipated result after a particular module is submission to the FDA.

There are three probabilities listed for each scenario, which correspond to the number of experiments performed.

In the case of disproval, we will re-evaluate our procedures and resubmit the module.
Module 1

- Non-Clinical Testing
  - Compression/tension ratings
  - Viscosity
  - Crosslinking density
  - Product purity
  - Degradation rates
  - Toxicity
Module 1:
Non-clinical chemical and physical properties, degradation, and toxicity tests
Module 2

- Non-Clinical Animal Testing
  - Biocompatibility/Immunogenicity
  - Biodegradation
  - Infection
  - Injection procedure (large animals only)
  - Range of mobility (large animals only)
Module 3

- Clinical Trials (Human patient testing)
  - Range of motion
  - Reduction in pain
  - Lasting effects
  - Effectiveness over placebo
Conclusions
Conclusions

- The novel hydrogel HYAL-VYNE® will be hyaluronic acid modified with 2-vinyl and crosslinked with ammonium peroxysulfate
- \((\text{NH}_4)_2\text{S}_2\text{O}_8\) increases
  - Stability
  - Retention
  - Load support
Conclusions

- Expected demand of 325,000 and will reach 625,000 per year
- Expected project life of 5 years
- Total product cost ~ $210 million
- Cost per injection ~ $688
- Expected FDA approval process cost will be ~ $2 million, and will take ~ 9 years
Further Studies – Scale-up

- With the determined demand, it would required that:
  - The plant capacity for HYAL-VYNE® be approximately 1000 Liters/yr
  - The cost of the treatment to be competitive should be ~ $1500 per year or $2400 per injection
Special Thanks

- Research contacts
  - CBME
    - Miguel J. Bagajewicz
    - Alberto Striolo
  - Chemistry/Biochemistry
    - Daniel T. Glatzhofer – Organic; Polymer Chemistry
    - Vadim A. Soloshonok – Synthetic Organic Chemistry
References

- “Chemical and Other Safety Information.” The Physical and Theoretical Chemistry Laboratory, University of Oxford. 7 March 2006. http://ptcl.chem.ox.ac.uk/MSDS/#MSDS
References

References

- Langer, Robert S.; Elisseeff, Jennifer, H.; Anseth, Kristi; Sims, Derek; “Semi-interpenetrating or interpenetrating polymer networks for drug delivery and tissue engineering” May 3, 1997.
- Uebelhart, Daniel MD.; Williams, James M. PhD.; Current Opinion in Rheumatology 1999, 11(5), 427.
- Soltos, L. and Mendichi, R. Biomedical Chromatography 2003, 17, 376-384.
- Waddell, D. MD; Rein, A. MS; Panarites, C. PhD; Coleman, M. MD; Weiss, C. MD; The American Journal of Managed Care 2001, 7(10), 981-991.
- Han, T. Journal Zhejiang University SCI 2004, 5(8), 928-931.
Questions?