Biomaterials In a New Role: Treatment and Prevention of Infectious Diseases

Bob Ward
DSM PTG
Part of DSM Biomedical
Berkeley, CA

Keith McCrea
Emergence Venture Partners
ExThera Medical LLC
Berkeley, CA
Bob Ward
- Intro to DSM Biomedical Technology (for Marc Hendriks)
- New and/or improved biomaterials technology for repair, replacement and augmentation
- Polymer surface modification and characterization
  - Synthetic polymers with bioactive surfaces
  - Polymeric adsorbents with bioactive surfaces for ‘Affinity Apheresis’

Keith McCrea
- Heparin
  - Systemic use as an anticoagulant
  - Immobilized as a surface modifier for biomaterials
  - Binding capacity
    - Clotting factors
    - Pathogens and cytokines
- Use of polymeric adsorbents in future clinical applications
  - Extracorporeal therapeutic devices for the treatment of disease
A young DSM business in a high potential market

• Started in 2004 building on DSM’s skills, expertise and facilities in Life Sciences and Materials Sciences

• We supply materials and license technology to Medical Technology companies for internal body applications addressing current and future healthcare needs.
  • Medical Coatings
  • Implant Solutions
  • Drug Delivery

Broad portfolio enables crossover innovation
Building on DSM Competences

- **Technology**
  - DSM Desotech (UV-curing)
  - DSM Research (coatings)
  - DSM Resolve (analysis)
  - DSM Materials Science (performance)
  - DSM Aces (physical analysis)
  - DSM NeoResins (metal primer)

- **Antimicrobial Knowledge**
  - Life Sciences R&D Delft,
  - Life Sciences R&D Geleen

- **c-GMP production**
  - DSM Rescom (Regensburg)
  - DSM Pharma Products (Greenville)

Synergy between Life Sciences & Materials Sciences
DSM Biomedical Strategic Pathway

**BIOSTABILITY**
- Medical Coatings and Polymers

**BIOCOMPATIBILITY**
- Resorbable Polymers and Drug Delivery

**BIO-INTERACTIVE**
- Therapeutic Materials and Regenerative Medicine

- Bionate® PCU
- CarboSil® TSPCU
- ComfortCoat® coatings
- Dyneema® Purity® fiber
- Various other products and research programs

- Trancerta™ Drug Delivery
  - Preferred partner for Pharma and Medical Device Industry

- Explorative efforts in close cooperation with public and private partners
Acceleration Through Open Innovation

- Licensing
- Mergers & Acquisitions
- Venturing
- Internal Development
- Research Alliances & Cooperations
- Scientific Advisory Board

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DSM’s Biomaterials History

- **2000**: Start of Dyneema Medical Efforts
- **2002**: Medical Coatings efforts started in Desotech
- **2004**: Official launch of Dyneema Purity® orthopedic sutures
- **2006**: First sales of Dyneema Purity® for knee ligament fixation
- **2008**: EBA Biomedical launched
- **2010**: PTG Acquisition
  - First cardiovascular and ophthalmic drug delivery development agreements
  - First sales of Dyneema Purity® in cardiovascular and spinal applications

- **2006**: First sales Medical Coatings
- **2008**: Start of UH and Drug Delivery activities
- **2009**: BMM Public Private Partnership funded by Dutch government
- **2010**: Medivas technology acquisition for Drug Delivery
  - Launch of Bionate® II PCU
  - Launch of Antimicrobial Coatings
  - Launch of next generation UH product

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DSM Biomedical’s Strategy

BIOSTABILITY  ➔  BIOCOMPATIBILITY  ➔  BIO-INTERACTIVE

Medical Coatings and Polymers

Resorbable Polymers and Drug Delivery

Therapeutic Materials and Regenerative Medicine

Bionate® PCU
CarboSil® TSPCU
ComfortCoat® coatings
Dyneema Purity® fiber
Various other products and research programs

Trancerta™ Drug Delivery

Preferred partner for Pharma and Medical Device Industry

Explorative efforts in close cooperation with public and private partners
Materials Enabling Device and/or Drug Therapy

**BIOSTABILITY**

Medical Coatings and Polymers

- Examples:
  - Pacemaker leads
  - Joint replacements

- Key requirements:
  1. Durable
  2. Matching mechanical properties
  3. Design flexibility

**BIOCOMPATIBILITY**

Resorbable Polymers and Drug Delivery

- Examples:
  - Back-of-the-eye medication
  - Drug Eluting Stent

- Key requirements:
  1. Reach targeted area
  2. Elution of active drug at right dose
  3. Disappears after use
Antimicrobial coatings:

- Building on our hydrophilic platform
  - Excellent lubricity, lowest friction & stiction
  - Superior durability and wear resistance
- Silver-based for urology
- Hemocompatible, non-eluting for vascular applications

**ComfortCoat®
Antimicrobial coatings**
• Strong, thin and pliable sutures play an important role in Rotator Cuff repair:
  • Minimizes suture breakage during tightening
  • Reduces need for additional procedures
  • Reduces patient discomfort

• Switch to Dyneema Purity®

Sutures with Dyneema Purity®: the new ‘gold’ standard

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Medical Grade UHMwPE

**Easy-XL** – a novel family of UHMwPE grades with a new molecular architecture to increase crosslinking efficiency

**HALS-UH** – an Alternative Stabilizer that provides stabilization of UHMWPE powder
Incorporate dienes in growing PE chain:

Incorporation of diene in UHMWPE will leave a pendant unsaturation which is believed to make crosslinking more efficient.

This enables the use of lower radiation doses, so less radicals stay behind which will potentially reduce oxidative degradation.

Further by adapting molecular architecture we can optimize mechanical properties.
Easy-XL needs significantly less radiation for low wear

POD results show that 25 kGy irradiation (i.e. sterilization dose) resulted in a wear resistance comparable to highly XL materials.
HALS: Hindered Amine Light Stabilizer for UHMWPE

An alternative stabilizer for crosslinked UHMwPE:

• No radical scavenging during radiation
  → no interference with the crosslinking process

• Regenerative - Less stabilizer needed

• No yellowing (consistent color) because no degradation components are formed
HALS : Effective Stabilization of UHMWPE

Higher crosslink density for HALS than for Vitamin E stabilized UHMwPE

- Tested 0.05 and 0.15 wt.% Vitamin E versus 0.05 and 0.15 wt.% HALS
- No significant differences between 0.05 and 0.15 wt.% HALS

Change in Carbonyl Index as a result of ageing during 6 weeks at room temperature shows better stabilization compared to vitamin E
DSM Resorbable Polymer Platforms
-- Focus on Drug Delivery Applications

MATERIALS PORTFOLIO

Amino acid based materials
Polyester amides
Polyester urethanes
Polyester ureas
- Surface eroding
- Enzymatically degradable
- Good shelf-life stability

Polythioesters
- Crosslinkable and linear
- Low and high modulus material can be obtained
- Hydrolytic degradation

Novel Polyurethanes
- Chemistry to control degradation rate
- Crosslink density to control drug encapsulation, release and degradation
- Hydrolytic degradation

CLINICAL FOCUS

Ophthalmology
Cardio/Vascular
Pain Management
Orthopedics
α-Amino Acid Based Polymers

Amino acid based materials:
Polyester amides
Polyester urethanes
Polyester ureas

• Surface eroding
• Enzymatically degradable
• Strong shelf-life stability

Programmable properties
Promote interaction between polymer and drug to enhance incorporation and modulate release (i.e., not limited to passive entrapment)
Physical and mechanical properties (Tg, elongation, tensile strength, hydrophobicity, wettability, polarity, etc.)
Ease and density of functionalization

Controlled degradation kinetics
Enzymatic surface erosion
No acidification of micro-environment during degradation

Superior biocompatibility
Amino acid based
Clinical safety demonstrated
Designing Next-Generation Biomaterials to Enable Advancements in Device and Drug Therapies

- Utilizing structure-property relationships understanding
  - Optimizing molecular architecture of our materials enables us to find improved mechanical properties, better biocompatibility, biostability, degradability, or polymer-drug compatibility.
  - Improved and/or novel ways of processing our materials can yield unique product properties

- The breadth of our portfolio allows us to design proprietary composite materials that can uniquely address ever more demanding clinical applications

- Merging our materials science with molecular biology understanding (‘life sciences’) allows us to design ‘therapeutic materials’
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Why use a ‘new’ material?

- Satisfy both the bulk and surface property requirements of a (new) device or implant
- Obtain a performance advantage (over competitive devices)
- Replace an unreliable or unwilling supplier
  - Improve lot-to-lot consistency
  - Allow a chronic implant application
- Improve device manufacturing process
  - Reduce Costs
- Strengthen IP position
- Facilitate regulatory approval
  - Establish(ed) FDA Master File
  - ISO and cGMP Quality Systems
DSM PTG Biomedical Polymer Capabilities

- Vertically Integrated R&D/Manufacturing for Materials-Intensive Medical Device Applications
  - Design of Biostable or Bioresorbable Polymers
  - Lab and Pilot-Scale Polymer Synthesis
  - Batch and Continuous Production-Scale Synthesis
  - Polymer Conversion and Processing
  - Characterization and Testing
  - Cleanroom Device Assembly

- Custom Synthesis of Polymers and Precursors
  - Monomers
  - Oligomers
  - Polymers

Surface Modification Without Additives: Block Copolymers with Surface-Active, Self-Assembling Monolayer End Groups (SAME® technology)

SAME — Polymer Backbone

Surface Properties
- = SAME # 1
- = SAME # 2

Bulk Properties
- = Soft Segment # 1
- = Soft Segment # 2
- = Hard Block

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Unlimited. DSM
Application Examples

• **Contact Lenses**
  • Silicone-Hydrogels: wettability and high $O_2$ permeability

• **Orthopedic Implants (Compliant Bearings)**
  • Dynamic Spinal Fixation
  • Prosthetic Spinal Discs
  • Hip and Knee Joint Replacement
  • Cartilage Repair Devices

• **Glucose Sensors**
  • Membranes with Independent Control of Glucose and $O_2$ Permeability
  • Barrier Membranes for Blocking Competitive Analytes

• **Cardiac Assist Devices**
  • Artificial Hearts and VADS
    • Pulsatile Diaphragm and Sac-Type
    • Continuous Axial Flow Pumps

• **Pacemaker and Neuro-Stimulation Leads and Components**

• **Post-Surgical Adhesion Prevention**

• **Wound Dressings**

• **Drug Delivery Devices**
A Typical DSM PTG Materials-Intensive Project: From Concept to Commercialization

- Interactive Creation of Material / Device Specification
- Proposal Writing
  - Technical Approach, Budget, Timeline, References, Credentials
- (In-house) Test Method Development
- Iterative Development with Design Control Documentation
  - Lab-Scale Material Synthesis and Characterization
    - Interactive Specification Modification*
  - Device or Component Prototype Fabrication
    - Testing by Client
    - Interactive Device Design Modification*
  - Material and Design Freeze
- Scale Up of Polymer Manufacturing
- Pilot Device Manufacturing
  - Write and Approve SOPs
  - Build Preclinical Units
  - Build Clinical Units
- Wait for Clinical Trials Results and Regulatory Approval ………
- Begin Full-Scale Manufacturing Under Quality Systems

* Beware of Creeping Specifications!
Visible Light or UV-Initiated Crosslinking
High Purity
Controlled Permeability
Phase Mixing In Amphipathic Systems
39 Years of Cardiovascular Applications: Polyurethanes in Chronic Implants

AVCO IAB 1971
Jarvik III TAH
Abiocor TAH
Abiomed BVS
Thoratec PVAD and IVAD

TCS HeartMate® LVAD
Vector™ Vascular Graft

Thoratec HeartMate II
Jarvik 2000
Pacemakers (Various)

Sunshine Heart C-Pulse™ 2009
Polyurethane hard segment formed by reacting diisocyanates with low-MW diols ($R^1$ may be ‘aromatic’ or ‘aliphatic’):

Diisocyanate $O=\text{C}=N-R^1-N=\text{C}=O + \text{HO}--R^2--\text{OH} + O=\text{C}=N-R^1-N=\text{C}=O + \text{HO}--R^2--\text{OH} \rightarrow \cdots$

repeats

$\cdots$ $\text{C}--\text{N}--R^1\text{N}--\text{C}--\text{O}--R^2\text{O}--\text{C}--\text{N}--R^1\text{N}--\text{C}--\text{O}--R^2\text{O}--\cdots$ repeats

Urethane

Urethane

Urea formed by reacting a diisocyanate with an amine:

Isocyanate $R-N=\text{C}=O + R-N\text{H}_2 \rightarrow Urea$
Many Possibilities with Polyurethanes: ‘The most versatile biomaterial’

**Widest range of possible bulk and surface properties:**

- **Large number of possible reactants**
  - **Hard Segments**
    - Diisocyanates
    - Diols » urethane and/or diamines » urea
  - **Soft Segments**
    - Single Polyol Chemistry
    - Mixed Polyols
  - **End groups**
  - **Pendant groups**

- **Many possible structures**
  - **Linear**
  - Linear with pendant groups or end groups
  - Branched or dendritic
  - Crosslinked

- **Easily synthesized by batch or continuous polymerization**
- **May be designed for biostability or bio-resorption!**
Common Diisocyanates for Synthesis of Biomedical Polyurethanes: Reaction w. low MW diol or diamine → polyurethane or polyurea ‘hard segment’

`4,4'-diisocyanatodicyclohexylmethane`

`Diphenylmethane diisocyanate (MDI)`
- Pure isomer available commercially
- High cohesive energy density hard segment with best phase separation
- Most biostable
- Best physical-mechanical properties

`Hydrogenated MDI’ (HMDI)`
- Only isomeric mixtures available
- Lower cohesive energy / less phase separation
- Lower flex life
- Reduced biostability in chronic implantation
Candidate Diisocyanates for Synthesis of Bioresorbable Polyurethanes

1,6-diisocyanatohexane

‘Hexamethylene diisocyanate or HDI’
Pure isomer available commercially
Both –NCOs have equal reactivity
Aliphatic (can’t form aromatic amines upon degradation)
Rarely used in biostable biomaterials

5-isocyanato-1-(isocyanatomethyl)-1,3,3-trimethyl-cyclohexane

‘Isophorone diisocyanate or IPDI’
Cycloaliphatic (can’t form aromatic amines upon degradation)
Cis and trans isomers available commercially
Secondary isocyanate group is more reactive than primary -NCO
First Generation Polyurethane Soft Segments: Polyethylene and polybutylene adipate (esters)

\[
\left[ \text{O-CH}_2\text{CH}_2-\text{O-} \right] \left[ \text{C-CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-\text{C} \right]_n
\]

<table>
<thead>
<tr>
<th>formula</th>
<th>([\text{OCH}_2\text{CH}_2\text{O}_2\text{C(CH}_2\text{)}_4\text{CO}]_n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>compound formula</td>
<td>(\text{C}<em>8\text{H}</em>{16}\text{O}_6)</td>
</tr>
<tr>
<td>name</td>
<td>poly(ethylene adipate)</td>
</tr>
<tr>
<td>IUPAC name</td>
<td>adipic acid; ethylene glycol</td>
</tr>
</tbody>
</table>

\[
\left[ \text{O-(CH}_2\text{CH}_2)_2\text{-O-} \right] \left[ \text{C-CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-\text{C} \right]_n
\]

<table>
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<tr>
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</tr>
<tr>
<td>name</td>
<td>poly(tetramethylene adipate)</td>
</tr>
<tr>
<td>IUPAC name</td>
<td>adipic acid; butane-1,4-diol</td>
</tr>
</tbody>
</table>

- **\(T_g \approx -70^\circ C\)**
- **Biodegradable:** hydrolyzes with self-catalyzing acid degradation product
- Poly(tetramethylene adipate) is more hydrophobic.: *somewhat* more hydrolytically stable than poly(ethylene adipate)
- Produces high strength TPUs
2nd Generation Polyurethane Soft Segments: ‘Caprolactone’

- \( T_g \approx -60 \, ^\circ C \)
- Slowly biodegradable (no acid degradation product)
- More hydrolytically stable than poly(adipate esters)
- Produces high-strength TPUs
### Common Polyurethane Soft Segments: Polyalkylene oxides

<table>
<thead>
<tr>
<th>Polyethylene oxide (PEO, PEG)</th>
<th>Polypropylene oxide (PPO)</th>
<th>Polytetramethylene oxide (PTMO, PTMEG)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="PEO structure" /></td>
<td><img src="image" alt="PPO structure" /></td>
<td><img src="image" alt="PTMO structure" /></td>
</tr>
<tr>
<td>Tg ≈ -60 °C</td>
<td>Tg ≈ -66 °C</td>
<td>Tg ≈ -75 °C</td>
</tr>
<tr>
<td>Primary -OH</td>
<td>Secondary –OH</td>
<td>Hydrolytic Stability</td>
</tr>
<tr>
<td>Very hydrophilic</td>
<td>No strain-induced</td>
<td>Exc. Hydrolytic Stability</td>
</tr>
<tr>
<td>Oxidizes <em>in vivo</em></td>
<td>crystallization</td>
<td>Reversible strain-induced crystallization</td>
</tr>
</tbody>
</table>

*Note: Tg represents the glass transition temperature.*
Common Polyurethane Soft Segments: **Aliphatic Polycarbonate**

- Oxidatively stable when (Ether-free™)
- Low permeability
- Degradation limited to surface region
- Gives very high tensile strength TPUs
- Polyol is commercially available

**NOT!**

- Bisphenol-A monomer: *a hormone-like ‘endocrine disruptor’*
Synthesis of Ether-Free Polycarbonate Diol from Ethylene Carbonate

At low Temperatures: 140-145 °C

Removal of ethylene glycol in final stage drives the equilibrium from C-2 to form C-6 carbonate
At higher Temperatures > 150 °C
Side Reaction Form Ether linkages:
Effect of Ether ‘Contaminant’ on Oxidative Stability Polyhexmethylene carbonate-urethane

With Ether:

\[
\text{HO-CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{O-C-O-CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{O-C-O-CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CH}_2\text{OH}
\]

Resulting polyurethane may be prone to minor surface oxidation and stress cracking that does not penetrate the bulk beyond 100 µM

Ether-free™:

\[
\text{HO-CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{O-C-O-CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}
\]

Extremely tough polyurethanes are more resistant to surface and bulk oxidation
Specialty Polyurethane Soft Segments: Polydimethylsiloxane

- Presents methyl groups in surface
- Silicone rubber analog: no H-bonding with hard segment
- Oxidatively and hydrolytically stable
- End groups on silicone oligomer determines reactivity with isocyanate to form urea or urethane bond:
  - Amine or ‘Carbinol’ > Yes
  - Silanol > No!
- -Si-C- bonds are hydrolytically stable, Si-O-C bond aren’t

NO!: → Siloxane + polyurea
Specialty Polyurethane Soft Segments: Polyisobutylene

- Presents methyl groups in surface
- Butyl rubber analog: low permeability, no H-bonding
- T_g = -73 °C
- Extremely stable to oxidation and hydrolysis
- Polyurethanes have lower strength than polyether or polycarbonate urethanes of otherwise similar composition. (Second soft segment needed?)
- No commercial source for oligomeric diols
Continual Improvement of Thermoplastic Polyurethanes for Chronic Implants

Platform Compositions

- **Aromatic (MDI) Polyether-urethane**
  - Strong and hydrolytically stable
- **Aromatic (MDI) Polycarbonate-urethanes**
  - Very strong and oxidatively stable (when Ether-free™)

DSM PTG Enhancements

Via Composition Changes

- Mixed Soft Segments: Silicone-urethane copolymers with enhanced biostability (Proven within NIH SBIR 1989)
- Use of surface activity and self assembly (of end groups) for surface modification:
  - Ether-free polycarbonate soft segments
    - Improved oxidative stability
    - Increased toughness
Some DSM PTG Thermoplastic Polyurethanes

Bionate®  
- **CarboSil®** silicone-polycarbonate-urethane
- **CarboSil® AL** aliphatic silicone-polycarbonate-urethane
- **Bionate® II** polycarbonate-urethane (PCU) with SAME® technology

Elasthane™  
- **PurSil®** silicone-polyether-urethane
- **PurSil® AL** aliphatic silicone-polyether-urethane
- **Elasthane™ II** polyether-urethane with SAME® technology*

Note: All polymer families have FDA Master Files

* Developmental material
Mechanisms of Interfacial Energy Minimization in Liquids and Solids

- **Surface Area Minimization**
  - Formation of Spherical Drops
  - Fire Polishing and Solvent Polishing

- **Minimization of Unit Interfacial Energy**
  - Migration of Bulk of Components to the Surface: ‘Surface-Activity’
  - Spontaneous Ordering of Surface Molecules: ‘Self-Assembly’
    - Exchange of Surface Molecules Under an Adsorbate
  - Surface Chemical Reactions
  - Adsorption / Contamination from the Environment
Surface-activity: The process in which a substance, dispersed as a minor ingredient in the bulk of a liquid or solid, populates the surface in a concentration (much) greater than its concentration in the bulk.

Self-assembly: The processes in which a disordered system of components forms an organized structure as a result of specific, localized interactions among the components themselves, without external direction.
Surface Activity in a Two-Component System

**Typical Low-MW Solution**

- +++
- ++
- +

**Polymer-Polymer Blend**

- No Surface Activity

Surface Concentration vs. Bulk Concentration graphs for different systems.
Monolayers Matter: Using Surface Activity and Self Assembly to Modify Polymer Surface Properties in Biomedical Applications

1. Passive Thrombo-resistance
2. Enhanced Biostability
3. Improved Abrasion Resistance
4. Reduced Self Adhesion of Device Surfaces
5. Enhanced Lubricity
6. Antimicrobial Activity
7. Covalently-Bonded (Non-Leaching) Processing Aids: e.g. Bionate® II PCU
Some DSM PTG Biomedical Polyurethanes

- Bionate® polycarbonate-urethane
- Bionate® II polycarbonate-urethane with SAME® technology
- CarboSil® silicone-polycarbonate-urethane
- CarboSil® AL aliphatic silicone-polycarbonate-urethane
- Elasthane™ polyether-urethane with low-MW wax additive
- Elasthane™ II polyether-urethane with SAME® processing aid
- PurSil® silicone-polyether-urethane
- PurSil® AL aliphatic silicone-polyether-urethane
- BioSpan® segmented polyether-urethane-urea

All polymer families have FDA Master Files
N, N’-ethylene bis-stearamide: Waxy processing aid present at 0.25-0.5 wt% in many ‘biomedical’ TPUs

Synthesis: 2 stearic acid + 1 ethylene diamine

Melting Point: 138 °C

Use: Surface active (presents methyl groups in surface) mold release, internal or external lubricant and/or processing aid for molding, extrusion and calendaring

Cons: Low MW wax (580 d): leachable, can interfere with bonding
Measurement of Water & Methylene Iodide Contact Angles: Solid Surface Tension Calculated from Geometric Mean
Sum Frequency Generation (SFG) Vibrational Spectroscopy: Analysis of the outer-most molecular monolayer ‘wet or dry’
Solid Surface Tension Reduction of a Polymer by a Surface Modifying Polymeric Additive Correlates with Surface Concentration Increase* of the Surface Modifying Additive in a Compatible Base Polymer (measured by SFG)


* Shown as decreasing surface concentration of base polymer
• **Modify Surface Properties**
  - Control Biological Interactions
    - Affect protein adsorption
    - Affect cellular interactions
    - Improve thromboresistance
    - Provide antimicrobial properties
  - Increase Biostability
  - Affect wettability / contact angle
  - Reduce coefficient of friction
  - Increase abrasion resistance

• **Improve Consistency**
  - Mono-functional end groups are chain stoppers
    - Concentration in reaction mixture determines MW

• **Improve Thermoplastic Processing**
  - By limiting molecular weight
  - Via internal lubrication **without** the use of low MW additives
  - By improving mold release and reducing self adhesion
Self-Assembled Thiol Monolayers on Gold: A Useful Research Tool

Comparison of Model SAME and SAM Monomers: C\textsubscript{18} Alkane (with Methyl Head Group)

**SAM Monomer**
- **Head Group**
- **Alkane Spacer**
- **Reactive Group = Thiol**
- Thiol reacts with gold to form a (fragile) gold-sulfur bond on gold-plated surfaces

**SAME Monomers**
- **Head Group**
- **Alkane Spacer**
- **Reactive Group = Hydroxyl**
- Hydroxyl reacts to form a stable covalent bond to the polymer backbone, e.g. urethane

* Can be: non-reactive, reactive and/or biologically active
Surface Analysis by Sum Frequency Generation (SFG): Polyurethane with Octadecane SAME vs. Control

The red trace is a Bionate® PCU 55D control sample without any additives or SAMEs.

Two main peaks are observed at 2850 and 2910 cm\(^{-1}\) and are assigned to the symmetric and asymmetric stretches of the polycarbonate soft-segment methylenes (-CH\(_2\)-\(_6\)) , respectively.

The black trace is the Bionate® 55D with octadecane SAMEs. This material also contains no additives.

The two main peaks appear at 2875 and 2940 cm\(^{-1}\) and are assigned to the symmetric and fermi resonance of the terminal methyl head groups on the octadecane SAME.
The simulated SAM spectrum (from spectral fitting parameters) is compared to Bionate 55D SAME polymer. The dominant peaks for both materials are very similar: methyl groups. Note: The only methyl group in the polymer is on the head group on the SAME.
Water Contact Angle: Bionate® PCU vs. Bionate® II PCU

<table>
<thead>
<tr>
<th>POLYMER</th>
<th>Mean CA [°]</th>
<th>Std. Dev.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bionate® PCU 55D</td>
<td>78.3</td>
<td>1.6</td>
</tr>
<tr>
<td>Bionate® PCU 90A</td>
<td>78.2</td>
<td>.8</td>
</tr>
<tr>
<td>Bionate® PCU 80A</td>
<td>76.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Bionate® II PCU 55D</td>
<td>97.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Bionate® II PCU 90A</td>
<td>98.8</td>
<td>2.3</td>
</tr>
<tr>
<td>Bionate® II PCU 80A</td>
<td>97.2</td>
<td>1.3</td>
</tr>
<tr>
<td>UHMWPE</td>
<td>104</td>
<td>2.6</td>
</tr>
</tbody>
</table>

Bionate II PCU is Hydrophobic  
Bionate PCU is Hydrophilic

All measurements made with glass-distilled water.
Improving Biostability with (Fluorocarbon) End Groups: Polyetherurethanes: Intramuscular Rabbit Implants @ 400 % Strain

Polyether-urethane Control: 3-month explant

Polyether-urethane with fluorocarbon end groups: 6-month explant
Improving Accelerated *In Vitro* Stability with C$_{18}$ End Groups (?): Polycarbonate urethanes after 407 Hours of Stokes Testing

Polycarbonate-urethane Control: **407 hours** exposure

Ether-free™ Polycarbonate-urethane with 0.6 wt % Stearyl End Groups: **407 hours** exposure
### Bionate® II PCU Property Summary

**Molecular Weight [kg/mole]**
- 80A: 243
- 90A: 253
- 55D: 231

**Melt Flow Rate [g/10min] @ 224 °C, 2160g load**
- 80A: 25
- 90A: 18
- 55D: 36

**Ultimate Tensile Strength (TS) [psi]**
- 80A: 8231
- 90A: 8499
- 55D: 8960

**Ultimate Elongation (UE) [%]**
- 80A: 518
- 90A: 385
- 55D: 372

**Tensile Stress vs. Strain**
- **Bionate® II PCU 55D**
- 17% Tougher: Avg for 3 grades

© DSM 4/10
Antimicrobial Activity: Surface Active, Self Assembling Covalently-Bonded Alkylammonium Halide End Groups Impart Antimicrobial Activity to Thermoplastic Polycarbonate-urethanes

\[ \begin{align*}
R_1: & \quad (\text{CH} \quad \text{CH} \quad \text{O})_m \\
R_2: & \quad (\text{CH})_n \text{CH} \\
\text{PCU: Polycarbonate urethane} & \quad \text{spacer} \quad \text{end group}
\end{align*} \]
## Physical properties of Bionate® PCU 80A and Bionate® PCU 80A w. SAME Quats

<table>
<thead>
<tr>
<th>Polymer with SAME Quats:</th>
<th>Wt% Quat</th>
<th>Mw (Dalton)</th>
<th>Ult. Tensile (psi)</th>
<th>Ult. Elong. (%)</th>
<th>50% Sec. Mod. (psi)</th>
<th>Water uptake %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bionate® PCU 80A control</td>
<td>0</td>
<td>216891</td>
<td>7267</td>
<td>504</td>
<td>1423</td>
<td>0.71</td>
</tr>
<tr>
<td>$\text{C}<em>{18}\text{H}</em>{37}\text{N}^+\text{Me}_2\text{EtOH Cl}^-$</td>
<td>0.5</td>
<td>191415</td>
<td>6132</td>
<td>525</td>
<td>1506</td>
<td>0.74</td>
</tr>
<tr>
<td>$\text{C}<em>{18}\text{H}</em>{37}\text{N}^+\text{Me}_2\text{EtOH Br}^-$</td>
<td>0.5</td>
<td>172785</td>
<td>6543</td>
<td>575</td>
<td>1570</td>
<td>0.60</td>
</tr>
<tr>
<td>$\text{C}<em>{18}\text{H}</em>{37}\text{N}^+\text{Me}_2(\text{EtO})_3\text{H Cl}^-$</td>
<td>1.0</td>
<td>254663</td>
<td>6706</td>
<td>509</td>
<td>1519</td>
<td>0.40</td>
</tr>
<tr>
<td>$\text{C}<em>{12}\text{H}</em>{25}\text{N}^+\text{Me}_2(\text{EtO})_2\text{H Cl}^-$</td>
<td>0.5</td>
<td>283006</td>
<td>7294</td>
<td>535</td>
<td>1461</td>
<td>0.79</td>
</tr>
</tbody>
</table>

EtO: Ethylene oxide
SFG Confirms Surface Activity & Self Assembly of SAME Quats on Polycarbonate-urethane

Sum Frequency Generation Spectroscopy (SFG)

Bionate® PCU Tubing with SAME Quat:
- 2870 cm\(^{-1}\) = CH\(_3\) Sym. Stretch of Methyl Head Groups
- 2935 cm\(^{-1}\) = CH\(_3\) Fermi Resonance

Bionate® PCU 80A Control Tubing:
- 2845 cm\(^{-1}\) = CH\(_2\) Sym. Stretch of Backbone Methylene
- 2905 cm\(^{-1}\) = CH\(_2\) Asymmetric Stretch
## Antimicrobial Properties (Per ASTM E2180)

<table>
<thead>
<tr>
<th>Bionate® PCU 80A with SAME Quats:</th>
<th>Wt. % SAME Quat in Polymer</th>
<th>24 hour % Cell Reduction Relative to Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>Staphylococcus aureus (+)</strong></td>
</tr>
<tr>
<td>Bionate® PCU 80A control</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$C_{8}H_{17}N^{+}(Me)_{2}EtOH\ Cl^{-}$</td>
<td>0.5</td>
<td>99.8</td>
</tr>
<tr>
<td>$C_{18}H_{37}N^{+}(Me)_{2}EtOH\ Cl^{-}$</td>
<td>0.5</td>
<td>99.8</td>
</tr>
<tr>
<td>$C_{18}H_{37}N^{+}(Me)<em>{2}(EtO)</em>{3}H\ Cl^{-}$</td>
<td>0.5</td>
<td>&gt;99.999999</td>
</tr>
<tr>
<td><strong>$C_{18}H_{37}N^{+}(Me)<em>{2}(EtO)</em>{3}H\ Cl^{-}$</strong></td>
<td><strong>1.0</strong></td>
<td><strong>&gt;99.999999</strong></td>
</tr>
<tr>
<td>$C_{18}H_{37}N^{+}(Me)_{2}EtOH\ Br^{-}$</td>
<td>0.5</td>
<td>&gt;99.999999</td>
</tr>
<tr>
<td>$C_{18}H_{37}N^{+}(Me)_{2}EtOH\ Br^{-}$</td>
<td>1.0</td>
<td>&gt;99.999999</td>
</tr>
</tbody>
</table>

Very Effective Against Gram Positive *Staph a.*
Extruded Polycarbonate-urethane Tubing with Non-leaching Antimicrobial SAME

Bionate® PCU 80A Control Tubing

Bionate® PCU Tubing with 0.5 wt% Antimicrobial End Groups

Zone of Inhibition Indicates No Leaching:

Test Organism: Staphylococcus aureus (ATCC 6538)
Self Assembly on Extruded Polyurethane Tubing

1. Extrusion of Polymer with SAME® Technology

2. End Groups @ t=0

3. Surface-Active End Groups Concentrate at Tubing Surface

4. End Groups Self Assemble

Schematic only. Not to scale
New Device Possibilities with End-Group-Modified Thermoplastics

• Biomaterials must satisfy bulk and surface property requirements

• PUs with Self Assembling Monolayer End Groups (SAME® technology) are a ‘Biomaterials Toolkit’ for independently optimizing bulk and surface properties

• SAME® technology combined with minor (but significant) composition changes and processing improvements created a step improvement in a well-established biomaterial: Bionate® II PCU is stronger, more oxidatively stable, more constant and more easily processed

• Polymers modified with SAME® technology can be easily integrated into medical device manufacturing e.g. as structural materials:
  • No post fabrication treatments necessary
  • Wide variety of surface modifications possible
    • Antimicrobial (Quats)
    • Hydrophilic (PEG)
    • Hydrophobic (fluorinated)
    • Ionic (sulfonate)
    • Selective adsorption
Apheresis for Extracorporeal Therapy

The process of removing specific components from whole blood that are inherently harmful (e.g., pathogens) or harmful because of an acute increase in their concentration (e.g., cytokines), by passing it through an adsorption bed and returning the treated blood to the patient.
Requirements for Safe and Effective Affinity Apheresis Therapy

- Non-thrombogenic and non-leaching adsorption media
- Adequate adsorption capacity with minimum hold-up volume
- Good hemodynamics
- Selective adsorption of ligands
  - Cytokines
  - Pathogens
- Adsorption kinetics compatible with typical flow rates of extracorporeal circuits
- Scale-able for different clinical applications
  - Larger for therapeutic applications
  - Smaller for prophylactic use
- Robust manufacturing process for adsorption media and columns
  - Consistent and measurable adsorption capacity
  - Consistent flow rate/pressure drop
- Reasonable COGs
Thank You

Additional information available at SFB Booth 201

www.dsmbiomedical.com

DSM PTG, Part of DSM Biomedical
2810 7th Street
Berkeley, CA 94710
(510)841-8800
ExThera Medical, formed in 2007, is a joint venture between Emergence Venture Partners, Berkeley, CA and ExThera AB, a technology transfer company at the Karolinska Institute, Stockholm, Sweden.

ExThera AB is a technology-focused R&D firm based on the life work of Professor Olle Larm, a pioneer in the study of heparin and its many attributes.

The Company is preparing for first in man clinical trials for an extracorporeal therapy in 2010.
Seraph (Selective Removal by Apheresis)

- Exthera Medical has developed a novel affinity apheresis blood filter to down-regulate the inflammatory response
- The technology is based on covalently end-point attached heparin
  - Surface bound heparin provides improved blood compatibility
  - Surface bound heparin provides mode of action for binding inflammatory molecules, pathogens, and virulence factors present in blood