The use of SIBS for Glaucoma Drainage Tubes and Intraocular Lenses
Plus Angioplasty Balloons

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American Chemical Society, Polymers in Biology and
Medicine. October 11, 2013
Small Caliber Vascular Grafts
Technology: Spinning Polyurethane Fibers onto a Rotating Mandril

Ortech International & Corvita
Spun Polyether urethane Vascular Graft

1 Month in Animal Pellethane 2363 80A
Entrepreneur’s nightmare

- Product degraded.
- Product occluded.
- Out of money.
- No one would finance us.
- Board decided that we would close up.
Nylon Chemistry (Polyamide)

$$\text{HOOC---R---COOH} + \text{H}_2\text{N---R'---NH}_2$$

$$\text{HOOC---R---C\text{---N---R'---NH}_2}$$

Amide Linkage
Development of the Angioplasty Balloon: Nylon (Polyamide)

- Nylon 6,6 – machined parts
- Nylon 4,4 – Pantyhose, stockings
- Nylon 4,6
- Nylon 6 – Power tool housings
- Nylon 11 – Carpet, guitar strings
- Nylon 12
Nylon 12: Cyclolaurolactam
Ring opening
Nylon 12: Poly(laurolactam)
Nylon 12: Poly(laurolactam)
Untwisting the 12 member ring
Untwisting the 12 member ring
Axial Orientation of Nylon 12
Biaxial Orientation of Nylon 12
Stress Strain curve for Nylon 12

Stress (force)

Strain (Elongation)
First Angioplasty (PTCA) and Valvuloplasty Catheters made (1987)

Leonard Pinchuk, Ph.D.
Small Profile is Key
Nylon 12 Angioplasty Catheters

- Sold patents to Cordis Corporation in 1987
- Became #1 seller in every major country in the world
- Held this position since 1988
- Johnson and Johnson licensed the Palmaz patents.
- Nylon 12 was the only balloon that would deploy a Palmaz stent.
- JnJ does a hostile takeover of Cordis to get access to Nylon 12 patents
Polyetherurethane: 1 Month In Vivo
Inflammation with Attraction of PMNs in 8-Week Subcutaneous Implant
12 Weeks (in Cornea)
HE staining, 100X

M. Fukuda et al, Kinki University School of Medicine, Osaka, Japan
Polyurethane phagocytosed by macrophage.

21 Weeks (in Cornea), TEM

Courtesy of M. Fukuda et al, Kinki University School of Medicine, Osaka, Japan
Hypothesis

- Surface tension characteristics of the polymer may dictate the acute foreign body reaction
- The long-term foreign body reaction is a function of the inertness and cleanliness of the polymer
Early 1990’s Need to Fix Polyurethanes

\[-(\text{CH}_2-\text{CH}_2-\text{O}-\text{CH}_2-\text{CH}_2)_n-\]
Polyether Soft Segment

\[-(\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{O}-\text{C}=\text{O}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2)_n-\]
Polycarbonate Soft Segment
Deploying a Stent-Graft
Fate of polycarbonate urethanes

- Corvita patented the polycarbonate urethanes for implant applications.
- Pfizer would not close $85 MM acquisition of Corvita’s stent-graft business unless Corethane was divested.
- Gave patents to PTG - Became known as “Bionate.”
- Thermedics/Lubrizol never had license to use PCU for implant applications – sold it under the Tradename Carbothane
Slow Persistent Degradation of Polycarbonate Urethanes

Two Year Implant Duration
Need to Fix Polyurethanes Again

CH₂–CH₂–O–CH₂–CH₂)–
Soft Segment

-(CH₂–CH₂–CH₂–CH₂–CH₂–)
Polycarbonate Segment

Corethane, Bionate, Carbothane
State of the art implantable biomaterials in the mid 1990’s

- Most elastomeric materials slowly degrade in the body which result in low grade inflammation and capsule formation.
- Need a new elastomer that is biostable and non-inflammatory.
  - Backbone must not oxidize, hydrolyze or embrittle in the body.
  - Side groups must not cleave.
- Uses include long-term implants in contact with metals, in sub-micron embodiments and adjacent to sensitive tissues.
Strategy: No degradable bonds
Theory: Polyethylene

S.M. Kurtz, et al, 2006 Otto Aufranc award paper:
Significance of in vivo degradation for polyethylene
Theory: Polypropylene

Theory: Polyisobutylene

The structure shows a polymer chain with a secondary carbon labeled and a quaternary carbon labeled. The text "Will Not Oxidize!" is prominently displayed inside a red stop sign-like shape.
Theory: Polyisobutylene

Secondary Carbon

C

C

C

C

Quaternary Carbon

C
Polymerization of Isobutylene
Using Living End Carbocationic Chemistry

J.P. Kennedy, University of Akron
Polymerization of Isobutylene and Styrene Using Living End Carbocationic Chemistry

J.P. Kennedy, University of Akron
Poly(Styrene-block-IsoButylene-block-Styrene)

(“SIBS”)  

Ultrastable backbone with no ability for side groups to come off

J.P. Kennedy, University of Akron
Nitric Acid Test

HNO₃
65% Concentration
At Boil
Nitric Acid Test: Results

- Polyurethane < 10 Sec.
- Dacron < 10 Sec.
- Natural rubber < 50 Sec.
- Crosslinked PCU Very Brittle
- PEEKEK Very Brittle
- Silicone rubber Very Brittle
- Polyethylene LD Very Brittle
- Polypropylene No Change
- PMMA No Change
- Polystyrene No Change
- Teflon No Change
- Sty-PIB-Sty-46A No Change
2 Year implant duration

Explanted Consortemer CEG
2 years follow-up, Study C-33 Pilot
T.S. #2516 Lt. Iliac, HPS x20

From Gregory Wilson MD
Granulocytes were not identified in any of the sections representing the graft.

2 Year implant duration

From Gregory Wilson MD
Microfiber Explants of SIBS Showing No Biodegradation

Pre-implant | 6 Months | 2 years

(B) 10 μm (400x)
**In Vivo** Biostability of SIBS as a Coating on a Coronary Stent in Pigs up to 2 Years (MWt Determined by GPC)

*Slope = 0.23: no biodegradation!*

Courtesy of Boston Scientific
The Drug Eluting Stent

Marker

Stent on Inflated Balloon

Delivery catheter
Taxus® Stent with Polycarbonate Urethane Coating

Bare Stent Polyurethane-coated stent showing severe inflammation (2 months)

BSC In Collaboration w/Drs. Rogers and Edelman, MIT (normal porcine coronary model)
Vascular Compatibility of SIBS
No Polymorphonuclear Leukocytes
TAXUS (Boston Scientific Corporation)

SIBS: poly(styrene-b-isobutylene-b-styrene)

Stent Strut

Paclitaxel
First Medical Use of SIBS: Boston Scientific’s Drug Eluting Coronary Stent: The TAXUS® Stent

• Sales > $3 Billion in first year
• Largest product launch in the history of medical devices
Stenting in the Eye

Can we Stop Glaucoma?
The Discovery:
Rabbit Studies at the
University of Miami’s
Miller School of Medicine, Bascom Palmer Eye Institute
(SIBS and silicone rubber implanted sub-Tenons for 2 months)

Silicone Rubber Disk

Silicon Rubber

De Novo Collagen

Myofibroblasts (scar tissue)

SIBS Disk

SIBS does not provoke neovascularization and capsule formation

No Myofibroblasts!

Silicone Rubber routinely provokes neovascularization and capsule formation

Courtesy: Edgar Espana, MD & Carolina Acosta, MD
Encapsulation of polymers

Silicone versus SIBS in subconjunctival implantation

*Rabbit @ 3 months*

Encapsulation thickness is function of the polymer’s biocompatibility

*Courtesy: Sander Dubovy, MD*
The Eye
Drainage in the eye

- Cornea
- Lens
- Conjunctiva
- Schlemm’s Canal
- Ciliary Body
- Iris
- Lens
Drainage in the eye

- Cornea
- Sclera
- Schlemm’s Canal
- Ciliary Body
- Conjunctiva
- Iris
- Lens
Drainage in the eye

Corneal IRIS Lens Sclera Conjunctiva Trabecular Meshwork Schlemm’s Canal Anterior Chamber Tenon’s Capsule Ciliary Body Choroid
Glaucoma: Increased intraocular pressure (IOP) due to fluid buildup causing poor blood flow to the optic nerve, ultimately damaging the nerve.
Advanced Glaucoma Intervention Study (AGIS)*

IOP must be ≤ 14 mmHg in individual patients to prevent vision loss

*AGIS 7 Study, Am J Ophthalmology 2000;130:429-440
The “Right” mechanism of action - How to get to 14mm/Hg

Ciliary Body (inflow)

Uveo-scleral

Trabecular Meshwork

To Schlemm’s Canal (drain plate)

Venous Resistance to the head

Transcend
SOLX
Glaukos II

Glaukos I
Ivantis
iScience
NeoMedix
The “Right” mechanism of action - How to get to 14mm/Hg

Achieving IOP of ≤14mm/Hg requires bypassing the trabecular meshwork and the venous resistance and the use of Mitomycin C.
The Device: The InnFocus MicroShunt™
AKA The MIDI Arrow

- Matches the compliance of ocular tissue
- Conforms to the curvature of the eye
- Does not require a cadaver patch
  - Soft, flexible, rubbery, no erosion
- Atraumatic fins prevent
  - Migration
  - Peri-annular leakage
- No MRI interference
- Outer diameter is 350 µm
- Lumen diameter is 70 µm and 8.5 mm long to drop IOP

Hagen-Poiseuille Equation:

\[
D = 4 \sqrt{\frac{2.547 \times 10^{-6} \frac{QL}{P_0 - P_L}}}
\]
Need to preserve the permeability of the microcysts in the conjunctiva

- Minimize scar tissue
- Biocompatible Ocular Biomaterial
  - SIBS
- Safe application of Mitomycin C
- Minimal fibrin in the bleb
Global Glaucoma Market:
Diagnosed and Undiagnosed Glaucoma Patients Worldwide

- 2nd leading cause of blindness affecting 64M WW
- 74% of glaucoma cases are undiagnosed
- 60 million patients diagnosed with glaucoma WW yearly
- 60 million blind due to glaucoma
Dominican Republic Study:
(9 of 23 Patients are combo procedures with cataract surgery)

IOP = 23.8 ± 5.3 mmHg (n=23)

100% Success Rate for 2 years, 96% success rate thereafter

87% patients totally off glaucoma meds!

Courtesy J. Batlle et al

October 6, 2013
Eyes at 1-year: **No encapsulation of tube in the anterior chamber**
SIBS-BASED INTRAOCULAR LENSES (IOL)
Next Generation Intraocular Lens (IOL) Material

Can we eliminate reading glasses, glare, halos, etc. after cataract surgery?

3-Piece IOL

1-Piece IOL
IOL History

- **Began with PMMA (plexiglas during WW2)**
- **6-8 mm incision, required sutures**
  - Led to astigmatism and specialty ophthalmologists
- **Replaced with foldable IOL using silicone rubber**
  - low RI, thick lenses, but smaller incision
- **Next generation of acrylic IOLS**
  - higher RI, stiff and small incision (3.2mm)
Why a new IOL Biomaterial?

- **Main trend in cataract surgery is microincision**
  - Femtosecond laser – small incisions
  - Need an IOL that can go through a microincision

- **Need a new material for ultra-long-term use**
  - Pediatric applications

- **Need larger lenses to prevent halos and other artifacts (dysphotopsia)**

- **Need a lens that changes shape with contraction of the ciliary muscle**
  - Eliminate reading glasses

- **Need to prevent glistening and whitening**
Co-polymerization of Crosslinker

Yonghua Zhou, Ph.D.
Co-polymerization of Crosslinker
Ring Opening Reaction with Heat

Yonghua Zhou, Ph.D.
8-Member Ring-Forming Reaction to Crosslink

No byproducts from this reaction!

Yonghua Zhou, Ph.D.
Crosslinked xPIB
Cataract Surgery: Femtosecond Laser

Diagram showing the various structures of the eye, including:
- Cornea
- Sclera
- Cornea
- Lens
- Conjunctiva
- Schlemm’s Canal
- Ciliary Body
- IRIS
- Lens
Cataract Surgery: Femtosecond Laser
Cataract Surgery: Femtosecond Laser
Low modulus to enable the ciliary muscle to stretch and compress to change focal point.
Glistening and Whitening

- Virtually all IOLs demonstrate glistening or whitening.
- Not considered of major clinical significance.
  - Affects contrast sensitivity at night
- Ophthalmologists and regulators don’t like to see it.
Glistening and soluble particles

- **Acrylic IOLs are polymerized into IOLs with initiators and unreacted species remaining in the matrix**
  - Post-extraction leaves vacuoles
  - Vacuoles imbibe water and haze

- **xPIB gum is ultra-purified before polymerization**
  - Crosslinking is heat-initiated
  - Nothing to extract – no vacuoles
Glistening and insoluble particles

- **Acrylic IOLs:** Insoluble salts or crosslinked oligomer cannot be extracted from the IOL matrix.
  - Insoluble particles separate from the IOL matrix depending upon polymer stresses and can cause glistening
  - Voids around particles imbibe water
- **SIBS** is filtered of all insoluble particles before crosslinking.
Why no glistening in SIBS IOLs

- No byproducts from polymerization
- No soluble particles
- No insoluble particles
- No post extraction required
  - No holes remaining to pool water
- No side groups that can dissociate with time and draw in water
Hydroxylating end groups on PIB of molecular weight 60,000
Acrylics – most common IOL

R = CH₃, PMMA  R = CH₂-CH₂-OH, p(HEMA)
R = CH₂CH₂-
Acrylics – most common IOL

Esters: hydrolyze, and slow Sn-1 reactions cleave

Acid groups are extremely hydrophilic and it only takes a couple per mole to whiten
The slow hydrolysis of the ester group in the acrylic moiety can result in glistening and whitening.
Conclusions:

- SIBS-based medical devices will continue to show less inflammation than other known elastomers.
- SIBS-based MicroShunts in the eye function well
  - The InnFocus MicroShunt™ has stopped glaucoma
  - Will change the course of glaucoma surgery
- SIBS-based IOLs can be placed through 1.5 mm cannulas and will be less traumatic to the patient.
  - Less skill to place
  - More procedures done due to less suturing required
- SIBS-based IOLs do not glisten or whiten with time.
- IOLs that remain stable and eliminate glasses are evolving
- And this is only the beginning!
Thank You!

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