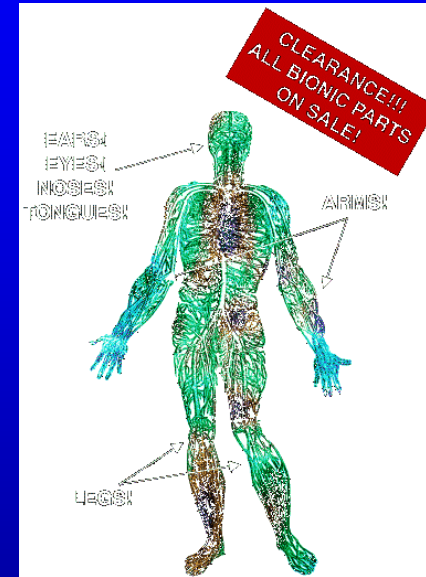


Life as a Bioengineer in Industry and Academia: Biomaterials Development for the Real World



Sujata K. Bhatia, MD, PhD, PE

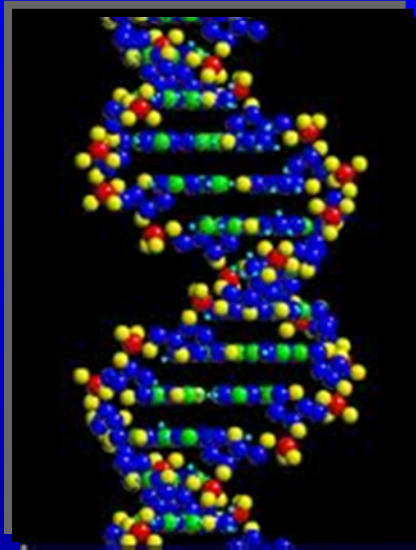
Asst Director for Undergraduate Studies in Biomedical Engineering,
Harvard University

Assistant Dean, Harvard Summer School

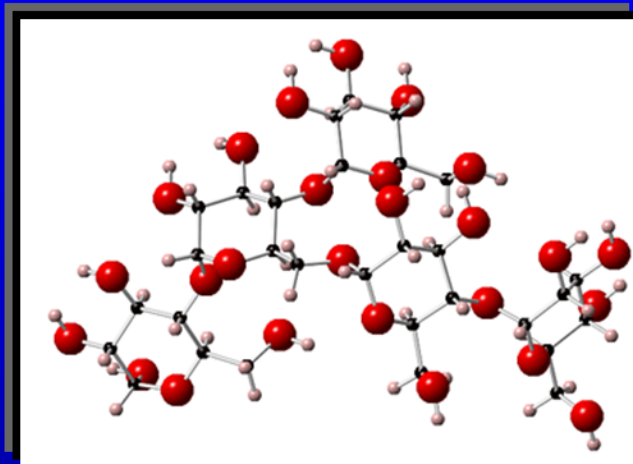
Associate, Harvard Kennedy School of Government

Polymers in the Human Body

Polymers occur naturally throughout the human body!



DNA and RNA, the body's major sources of information, are polymers of nucleotide monomers.



Polysaccharides, the body's major sources of energy, are polymers of sugar monomers.



Proteins, the body's major sources of structure and function, are polymers of amino acid monomers.

Natural Polymers in Medicine

- Innovators in *biomedical engineering* are seeking novel materials for medical devices that are optimally compatible with the human body.
- Toward the goal of a sustainable bio-economy, *biochemical engineering* is increasingly devoted to developing renewably sourced materials.
- A natural intersect exists between these areas.
- An engineering design question:

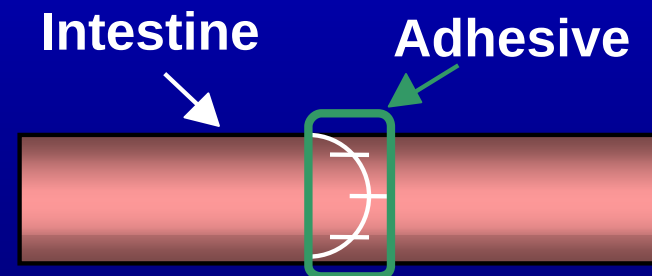
“Can bio-based polymers be utilized in biocompatible medical devices?”



An Unmet Clinical Need



- Surgical procedures create internal wounds, which surgeons close with sutures (stitches) or staples.
- Suturing and stapling are sometimes inadequate; the rate of leakage from intestinal closures is 3-15%.
- Patients with major leakage often need intensive care.
- Colorectal cancer patients with intestinal closure leakage exhibit a 20% lower 5-year survival rate, even when leakage is minor*
- Colorectal surgeons would like to utilize a sealant as an adjunct to sutures and staples in all patients.



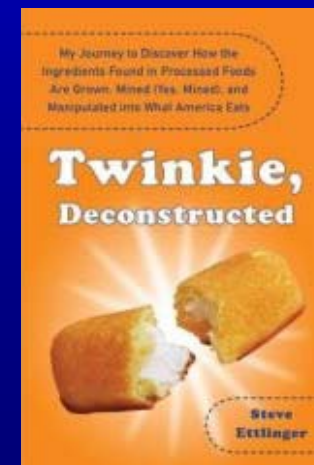
(*) Walker et al.; Annals of Surgery; V240; #2; 8 (2004)

History of Polysaccharides as Adhesives

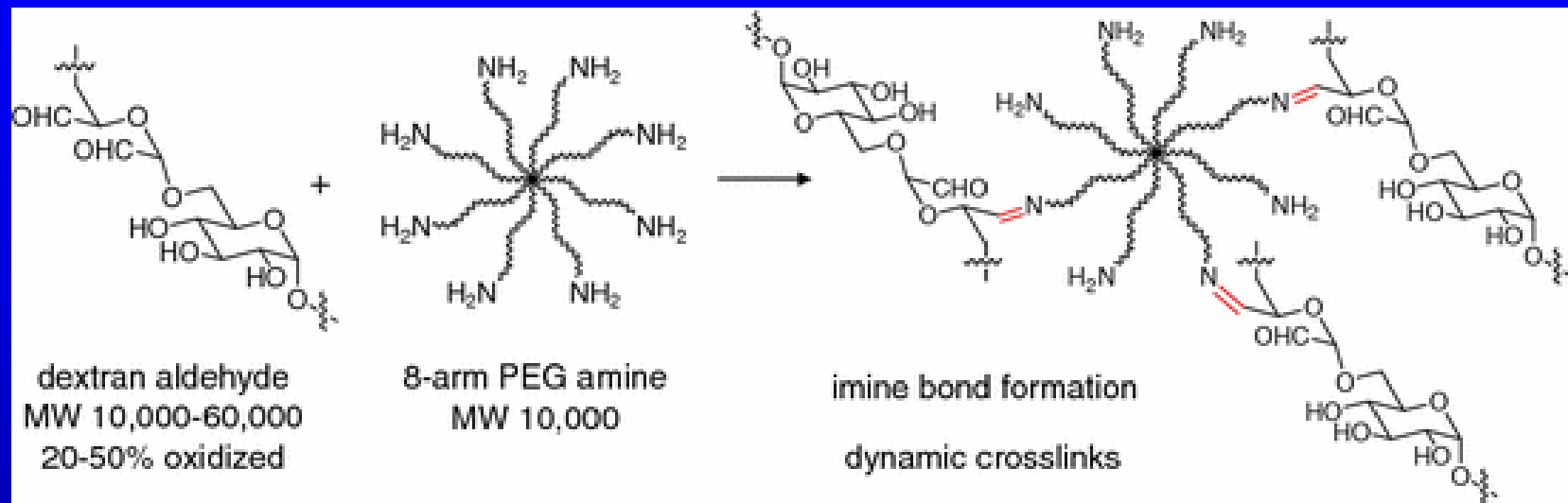
(or, Drinking and Firefighting don't mix!)

“Using cornstarch as glue was accidentally discovered, the legend goes, in Dublin in 1821, during the celebration of a visit by King George IV. A fire broke out in a textile factory that used potato starch for finishing cloth. Six workers, drunk on whiskey, fell into the starch water tank while trying to man the fire pump. When they finally got out, they were stuck together, and a new use was found for starch (as well as a new image for teamwork). The official version is far less dramatic, noting only that a worker observed after a fire that this roasted, brown stuff made a thick adhesive paste when dissolved in water. No matter where the truth lies, in a slap to Irish separatists, it became known as British gums.”

-- Steve Ettlinger,
Twinkie Deconstructed (2007)



Polysaccharide-Based Tissue Sealants



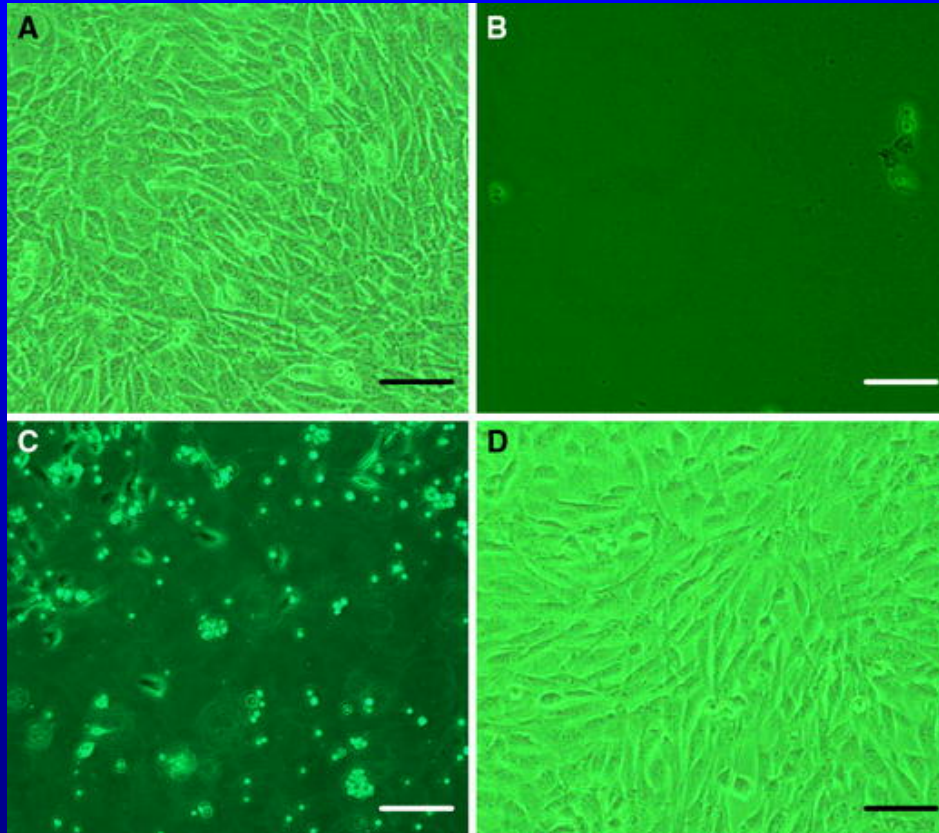
Foundation chemistry for polysaccharide-based tissue adhesives. The oxidized polysaccharide dextran aldehyde reacts with an 8-arm star PEG amine to form a crosslinked hydrogel network.

S. K. Bhatia et al. *Biotechnology Letters* (2007), 29:1645-1649.

Advantages of Polysaccharide-Based Tissue Sealants

- **No blood-derived biologic proteins → no risk of viral transmission**
- **Ready-to-use → no advance preparation required**
- **Cures rapidly (<1 min) at room temperature**
- **Crosslinks in water and adheres to moist tissue**
- **Degrades hydrolytically**
- **Based on polymers with an established history of clinical use**
 - **Plasma expanders (Dextran)**
 - **Drug delivery (PEG)**

Tissue Sealants are Non-Cytotoxic

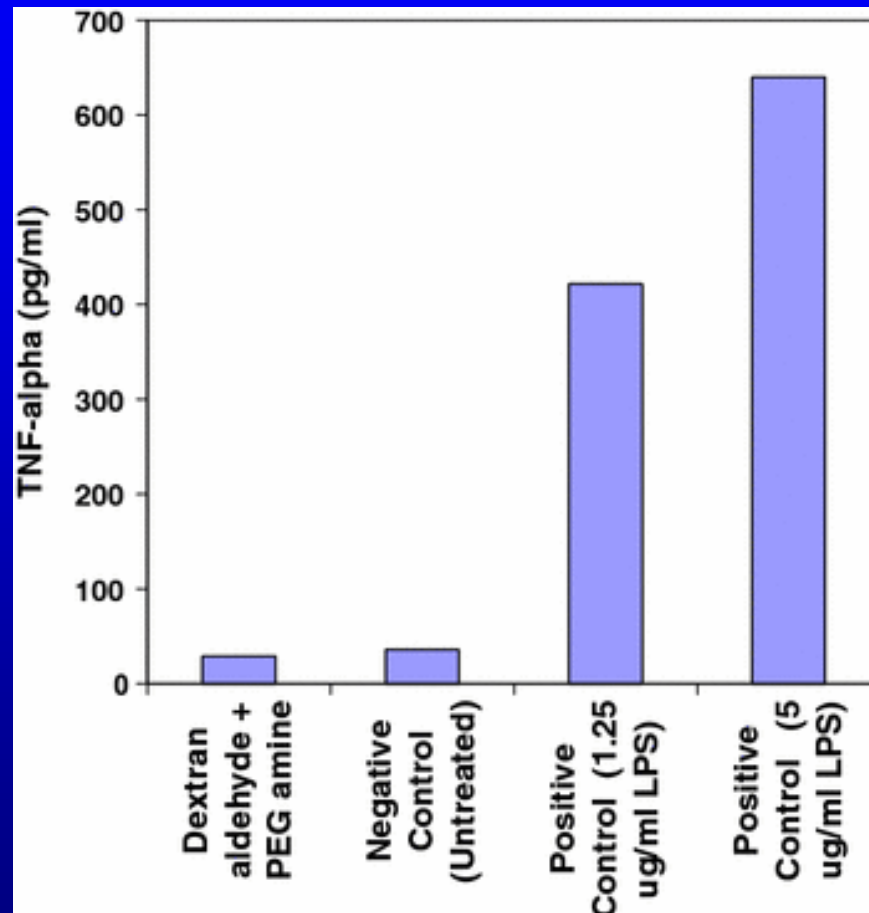


Responses of mouse 3T3 fibroblasts to tissue adhesives. Fibroblast cells were incubated in direct contact with material samples for 24 h at 37°C.

- (A) Ultra-high molecular weight polyethylene; non-cytotoxic negative control.
- (B) Organo-tin PVC; cytotoxic positive control.
- (C) Cyanoacrylate-based Dermabond tissue adhesive.
- (D) Polysaccharide-based tissue adhesive composed of dextran aldehyde (60,000 MW, 20% aldehyde conversion, 17% solids) + 8-arm PEG amine (10,000 MW, 50% solids). Scale bars = 100 μ m

S. K. Bhatia et al. *Biotechnology Letters* (2007), 29:1645-1649.

Tissue Sealants are Non-Inflammatory



Response of mouse J774 peritoneal macrophages to polysaccharide-based tissue adhesive. Macrophage cells were incubated in direct contact with material samples for 48 h at 37°C.

Following incubation, TNF- α release from macrophages was measured by ELISA.

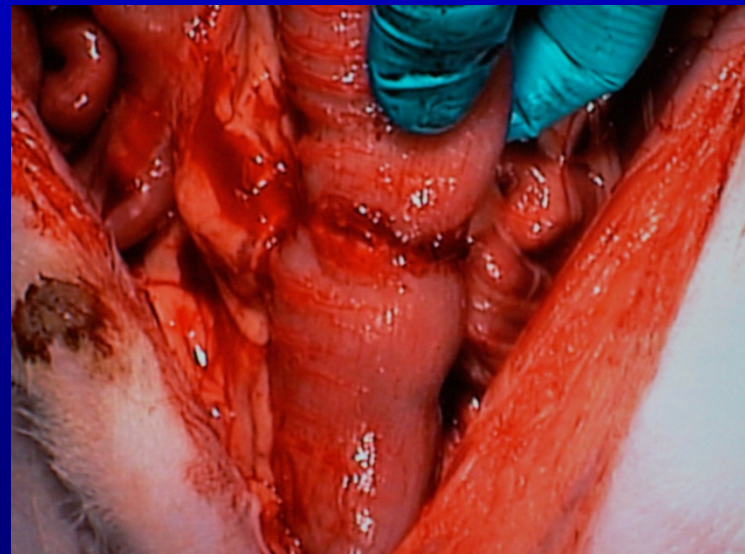
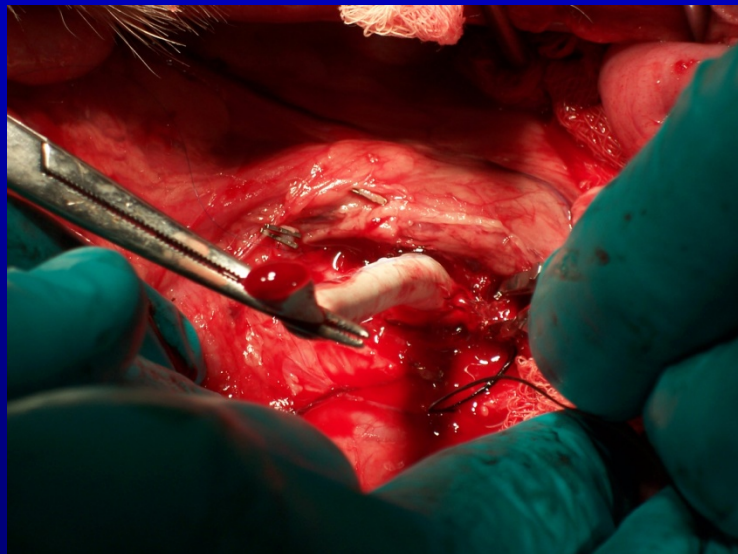
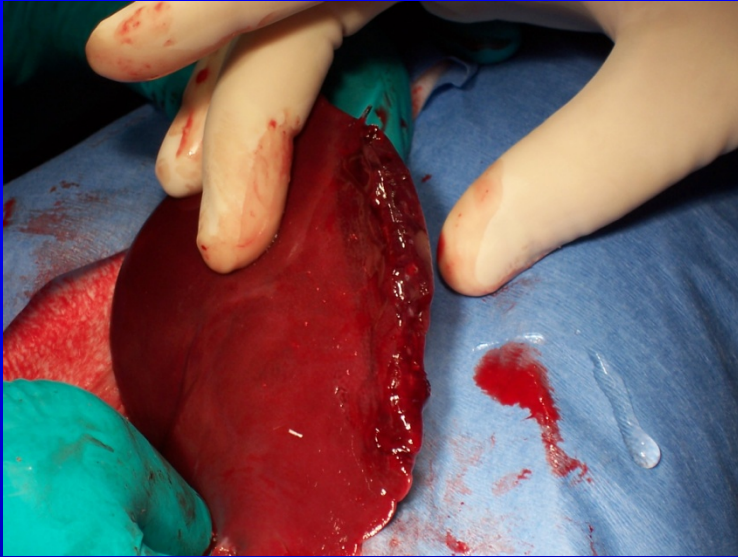
Clinical Applications of Polysaccharide Tissue Sealants

- **GI Surgery**
 - GI resections
- **Vascular Surgery**
 - Vascular grafts
- **Trauma Surgery**
 - Hemostasis
- **Ophthalmology**
 - Cataract incisions



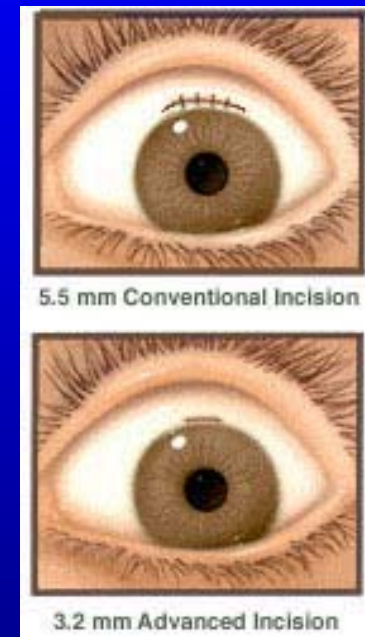
“The Agnew Clinic”
Thomas Eakins, 1889

Adheres to a Variety of Tissues

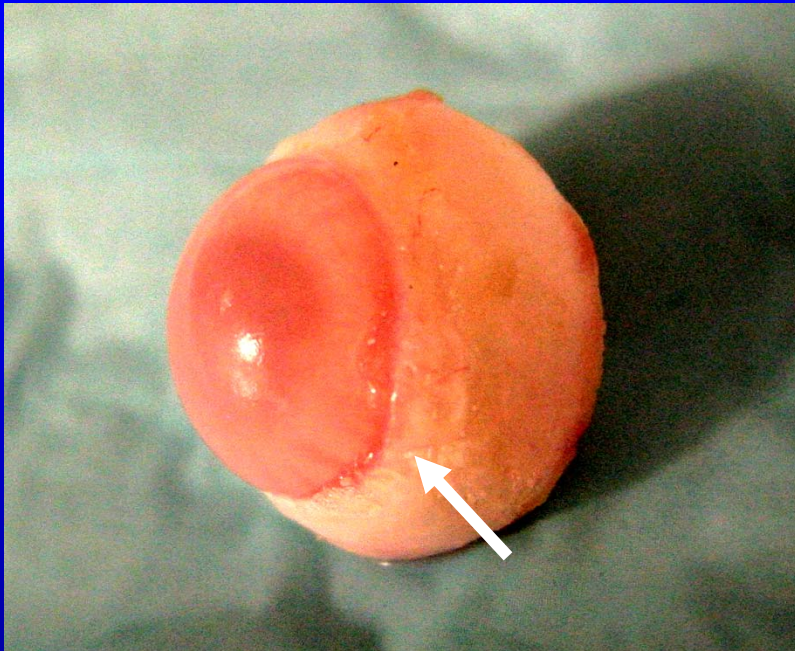


Applications in Ophthalmic Surgery

- Sutures have traditionally been used to close cataract incision wounds
 - Suturing prolongs operative time
 - Uneven tension on sutures can lead to asymmetric healing and astigmatism
- Recently, sutureless incisions have been utilized by cataract surgeons
 - Increases risk of ocular infection → partial or complete loss of vision
- Sealants are an attractive alternative to both suturing and sutureless closure of corneal wounds



Tissue Sealants for Corneal Closure



Polysaccharide-based tissue adhesives are efficacious in sealing corneal incisions.

S. K. Bhatia et al. *Current Eye Research* (2007), 32:1045-1050.

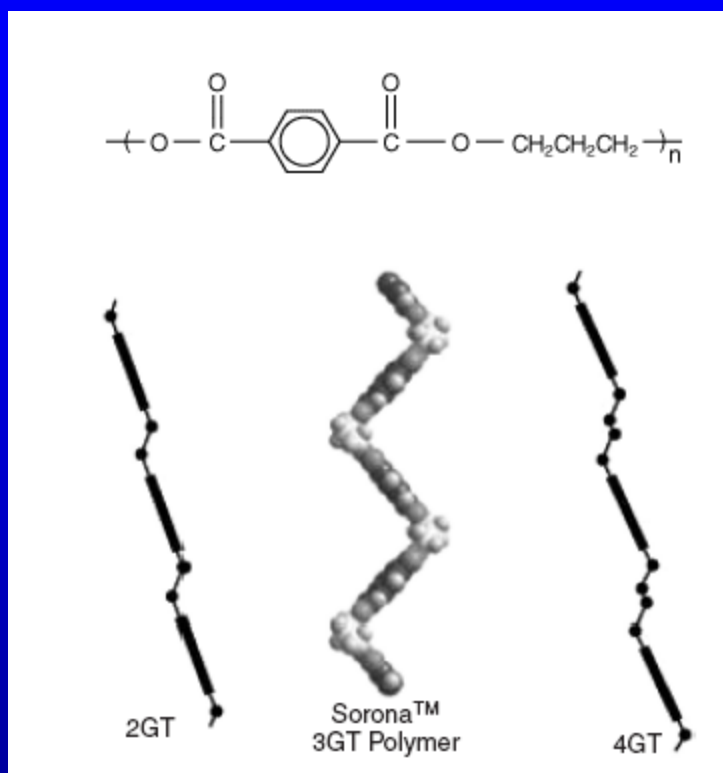
Ocular Leak Pressure Testing

Adhesive-Sealed Eyes	Leak Pressure (psi)
Trial 1	11.14
Trial 2	10.26
Trial 3	10.9
Average $\pm$ SD	10.77 $\pm$ 0.45
Non-Sealed Eyes	Leak Pressure (psi)
Trial 1	0.08
Trial 2	0.11
Trial 3	0.10
Average $\pm$ SD	0.10 $\pm$ 0.02

Polysaccharide-based tissue adhesives are efficacious in sealing corneal incisions.

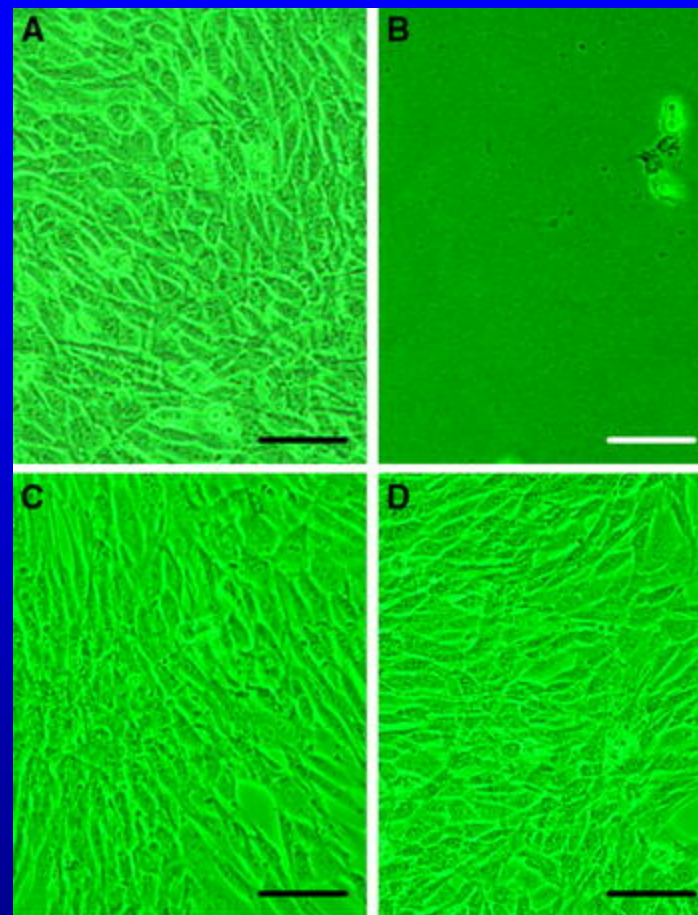
S. K. Bhatia et al. *Current Eye Research* (2007), 32:1045-1050.

Corn-Based Polymer is Non-Cytotoxic



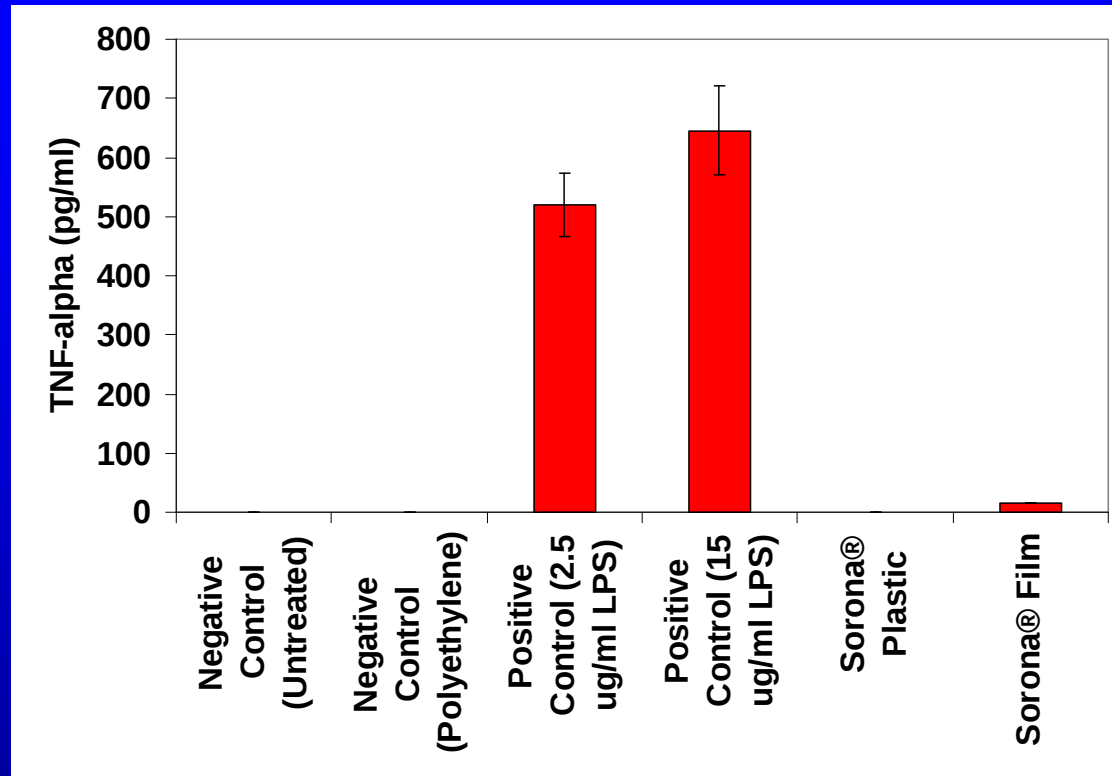
“Biological characterization of Sorona polymer from corn-derived 1,3-propanediol”

S. K. Bhatia, J. V. Kurian
Biotechnology Letters, April 2008



Response of 3T3 fibroblasts to Sorona polymer. Fibroblast cells were incubated in direct contact with samples for 24 h at 37°C. (a) Ultra-high MW polyethylene; non-cytotoxic control. (b) Organo-tin PVC; cytotoxic control. (c) Sorona plastic. (d) Sorona film. Scale bars = 100 μm

Corn-Based Polymer is Biocompatible



Response of mouse J774 peritoneal macrophages to Sorona polymers. Macrophage cells were incubated in direct contact with material samples for 48 h at 37°C. Following incubation, TNF- α release from macrophages was measured by ELISA.

“Biological characterization of Sorona polymer from corn-derived 1,3-propanediol”

S. K. Bhatia, J. V. Kurian

Biotechnology Letters, April 2008

Bio-Based Materials in Medicine



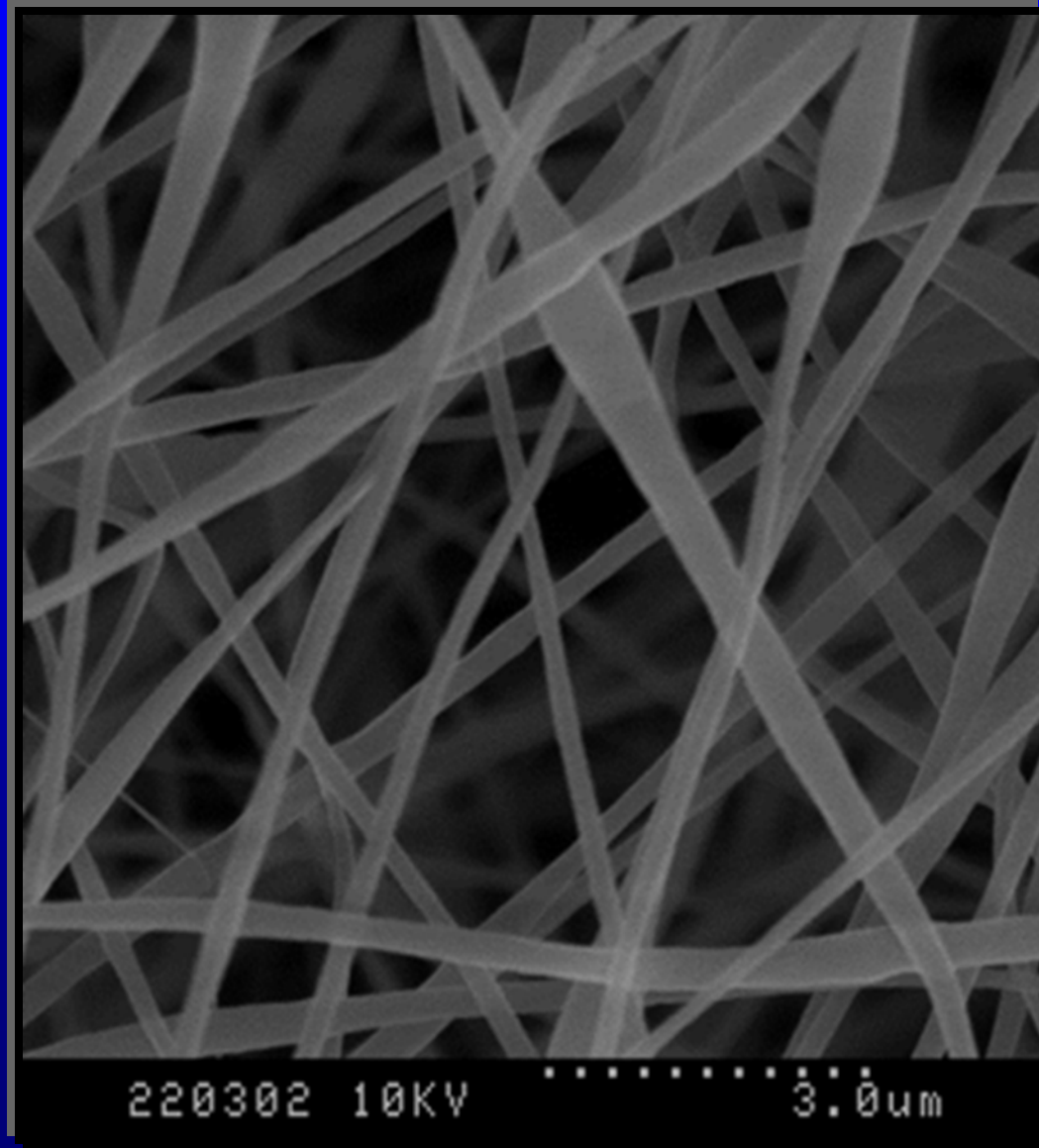
“Bio-Based Materials Step Into the Operating Room”

S. K. Bhatia

Chemical Engineering Progress, September 2012

- **Polysaccharide-based tissue glues**
- **Soy-based bone fillers**
- **Silk-based tissue scaffolding**
- **Corn-based 1,3-propanediol**

SEM of Electrospun Corn-Derived Poly-L-Lactic Acid



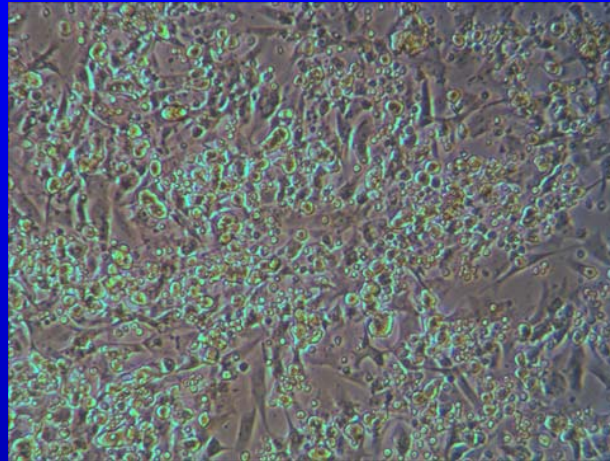
Cardiac Myocytes with Corn-Derived Poly-L-Lactic Acid



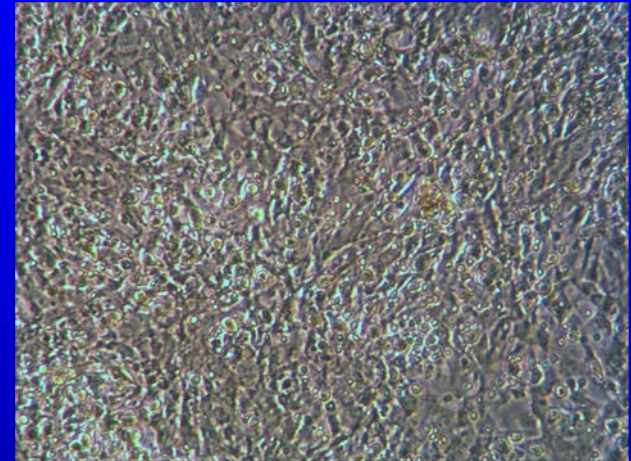
Leslie Rea

**6% corn-
derived
PLLA**

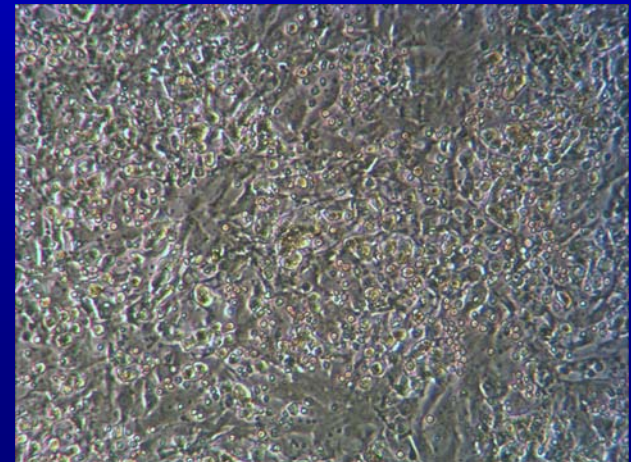
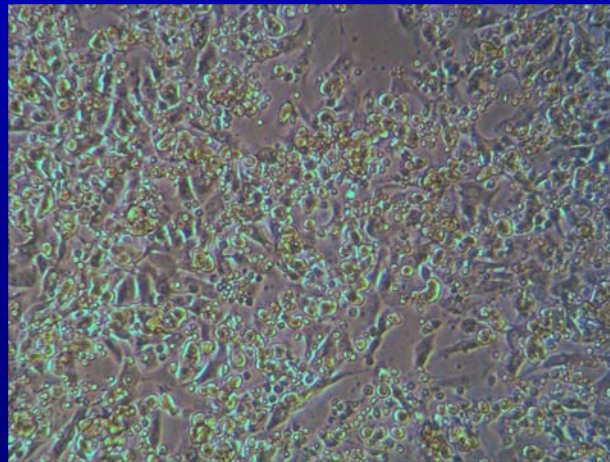
24 hours



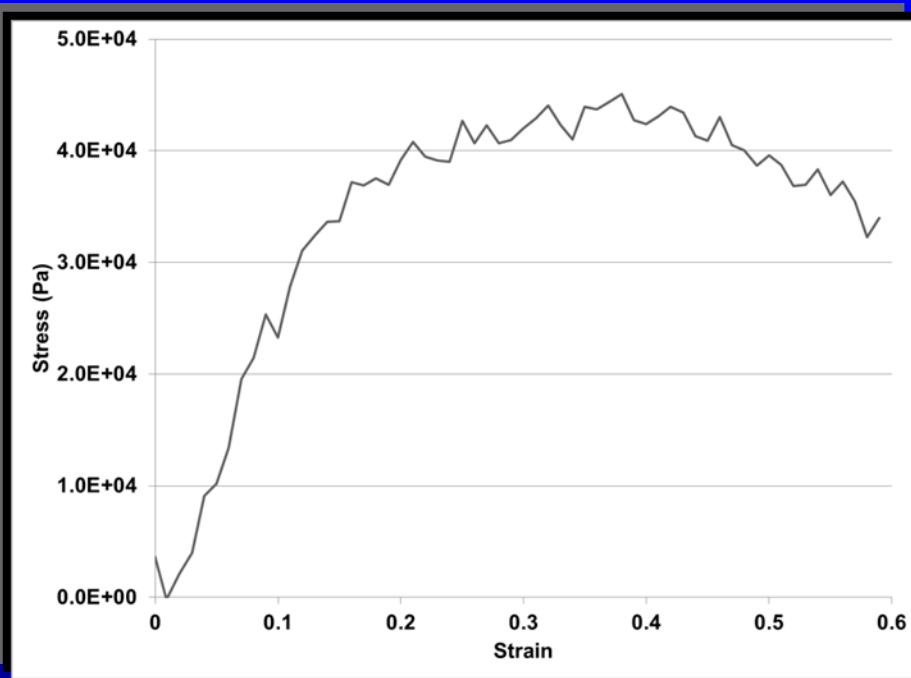
48 hours



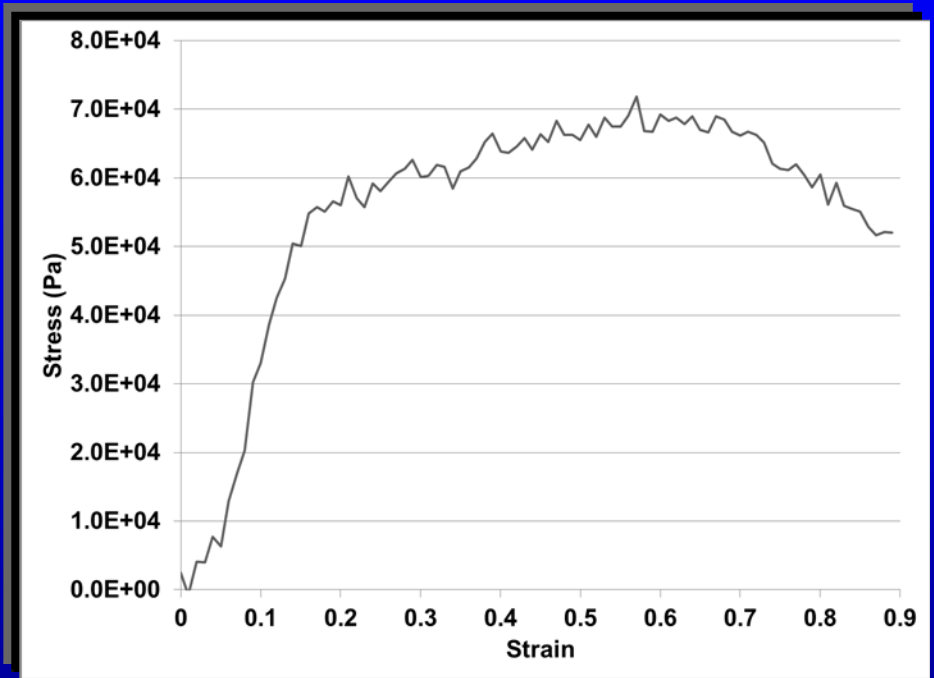
**7-8% corn-
derived
PLLA**



Tensile Testing of Corn-Derived Poly-L-Lactic Acid



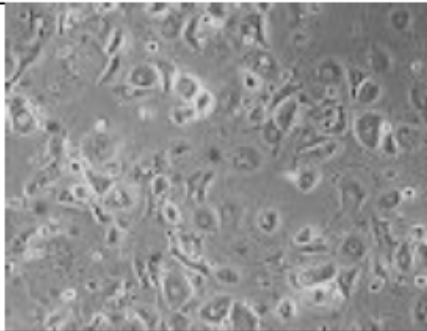
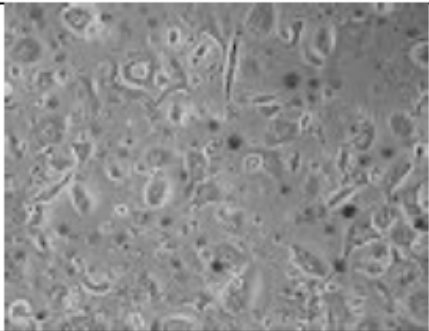
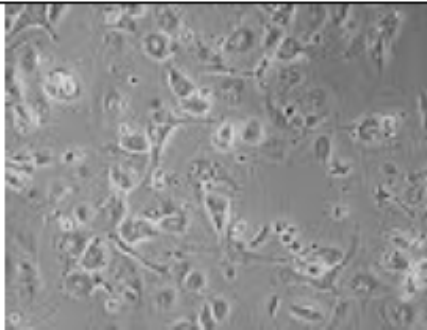
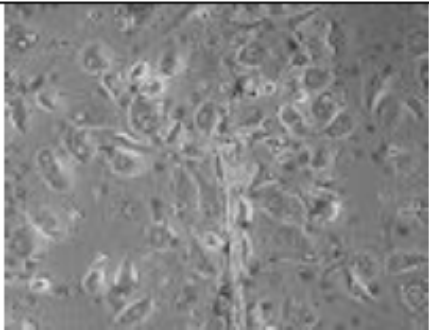
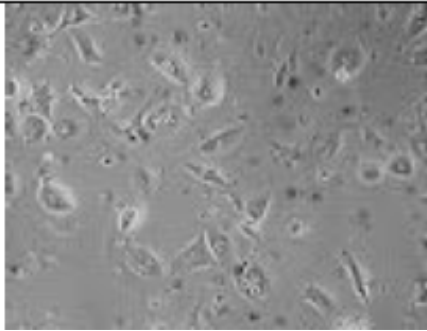
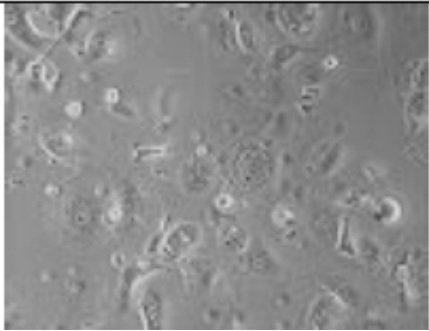
**6% corn-
derived
PLLA**



**7-8% corn-
derived
PLLA**

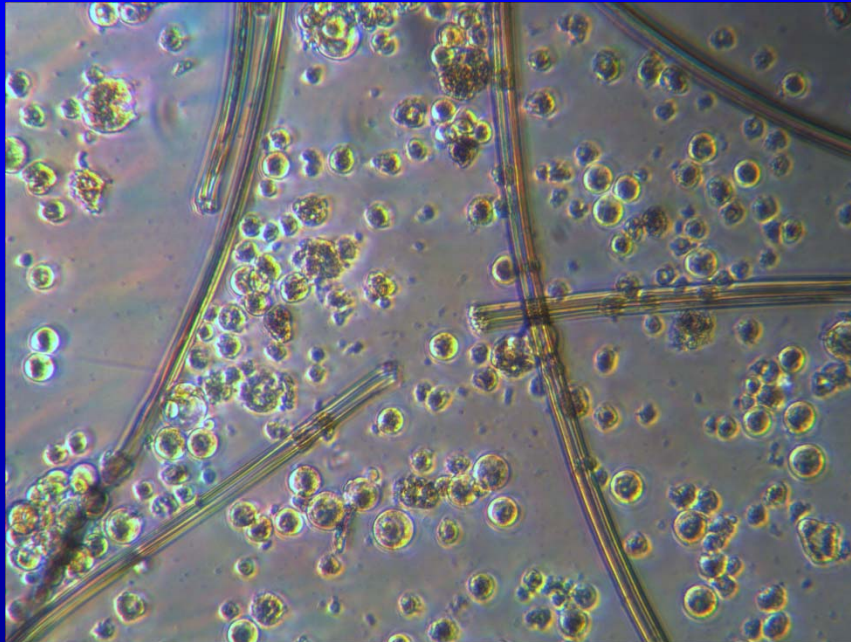
Corneal Endothelial Cells with Soybean Fibers



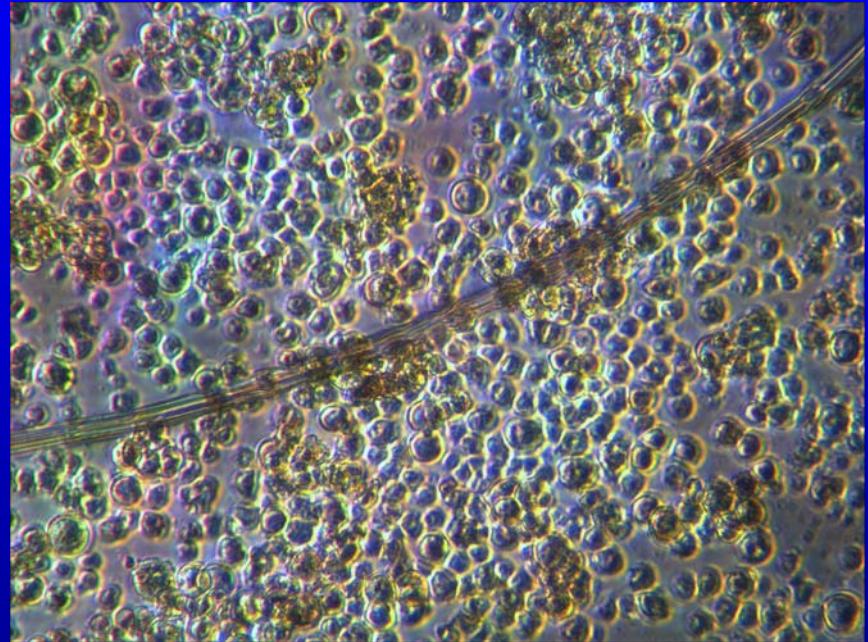
BCE C/D-1b	Control (10x)	36% Soybean Fiber (10x)
24 hours		
48 hours		
72 hours		

Bamboo Viscose Fibers with Neural Stem Cells

48 hours



72 hours



Scott
Yim

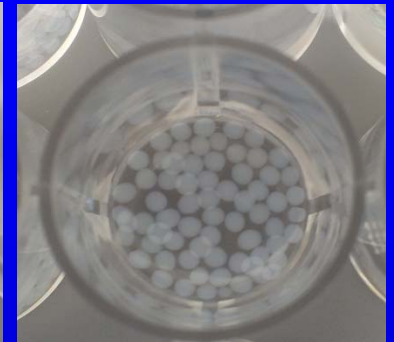
Bamboo viscose fibers

Alginate Microspheres

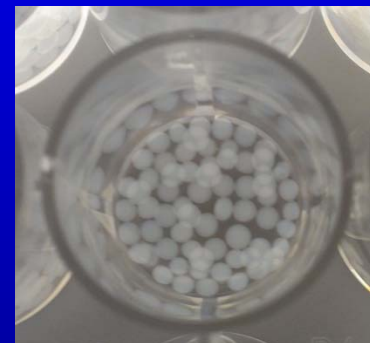
- Alginate is a carbohydrate derived from brown seaweed.
- Microsphere structures ideal for loading and release of drugs.
- Plan use for transport of stem cells.
- Dehydrate with time, depending on media and the amount of spheres.
- Strength can be enhanced with pectin.
- Carbon nanobrushes can be incorporated into microspheres to impart electrical conductivity.



0.5wt% alginate



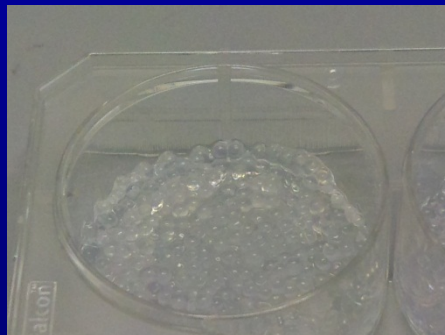
1wt% alginate



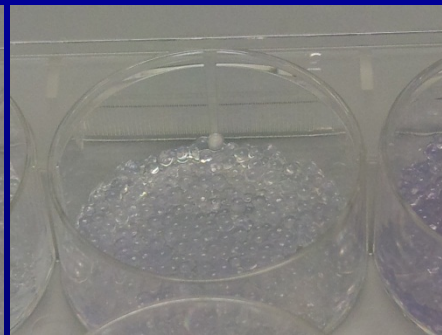
2wt% alginate



1wt% alginate, 1 vol% CNB



1% alginate + 0.1% CNB



1% alginate + 0.5% CNB



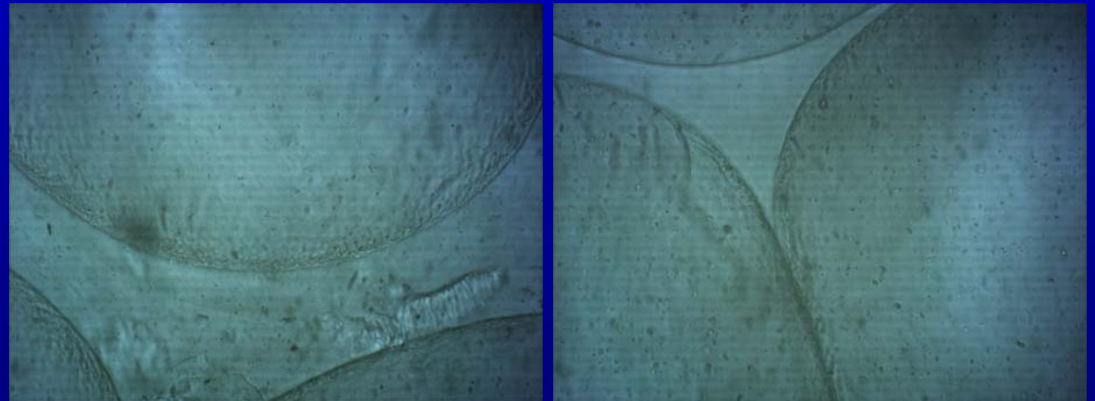
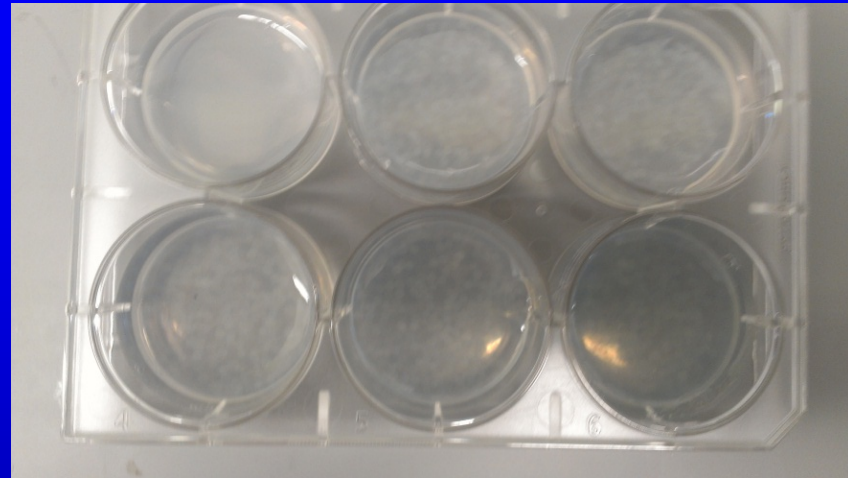
1% alginate + 1% CNB



Godwin
Abiola

Alginate Microspheres in Agar

- Agar is a polysaccharide sugar derived from red algae
- Agar previously shown to support growth of cardiac fibroblasts
- No visible dehydration after a week
- Spheres are completely immobilized



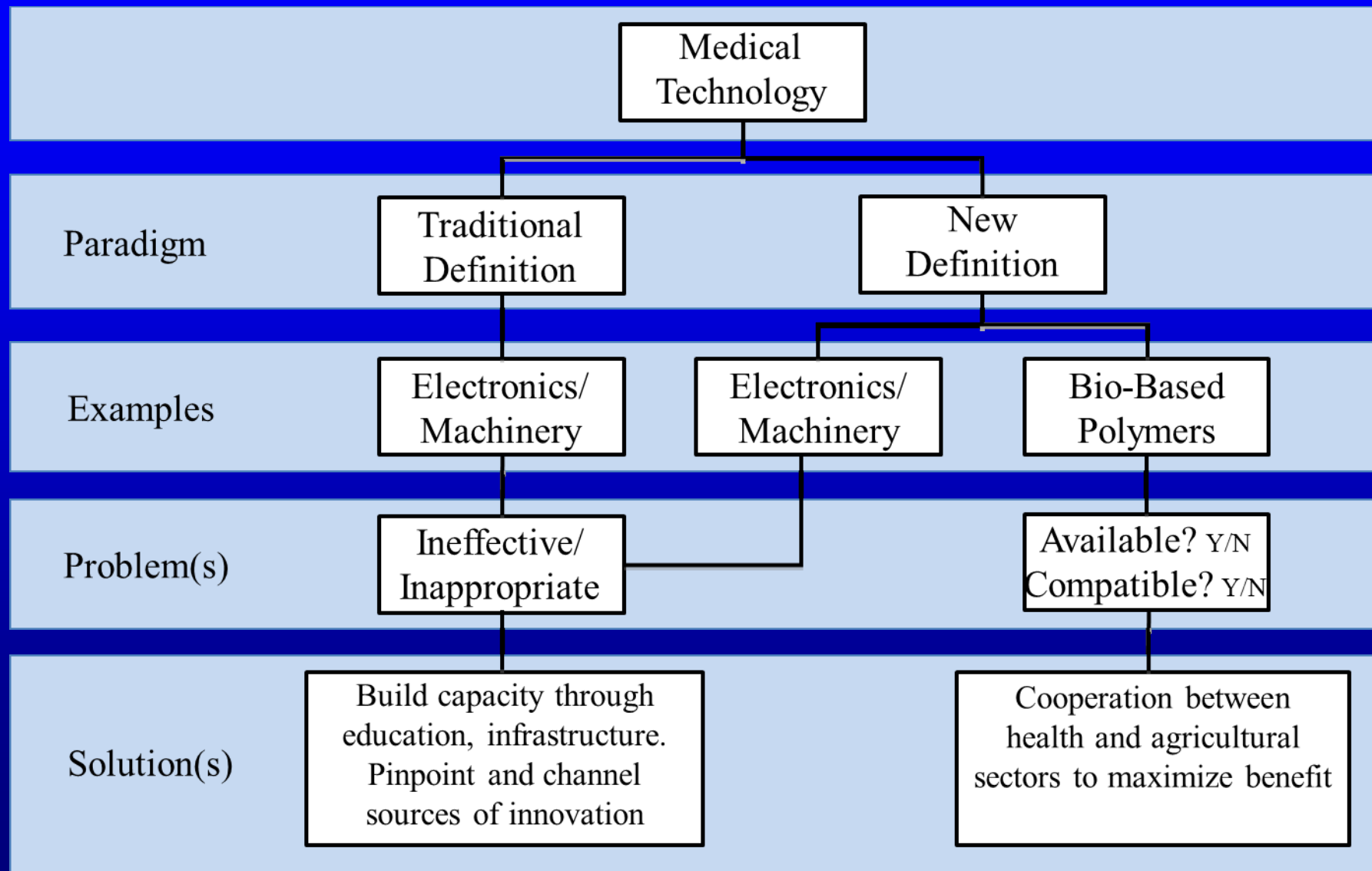
Advantages of this Approach

- Bio-based polymers can be derived from numerous raw material sources → *versatility*
- Bio-based polymers can naturally interface with human cells and tissues → *biocompatibility*
- Bio-based polymers can be modified to meet mechanical requirements of implants → *tunability*

Potential for this Approach

- Naturally-derived polymers can allow developing nations to join in the biomedical revolution in ways that were not previously possible.
- Bio-based polymers can **empower** developing countries to leverage their own agricultural capabilities to enter the biomedical revolution.

How Does This All Fit Together?



Reframing the Conversation

- Criteria for appropriateness of equipment are inherently different in the developed and developing world
- If we adopt a new definition of technology, we see that developing world countries actually have a lot to contribute to the development of novel technologies
- One way is through the use of **BIO-BASED POLYMERS**

Traditional Definition

Technological advance has come to be synonymous with computerization, digitization, and building of machines that do things faster and smaller, yet last longer and on a much larger scale.



New Definition

Technology is the use of scientific knowledge to manipulate materials, manmade or otherwise, for the benefit and increased capability of society .

In other words...

- 1. It is clear that medical equipment (in general) is ineffective in the developing world, limiting the maximum possible quality of care available. We claim that part of the reason for the continued limitation is the dependence of the developing world on equipment developed for and originating from the developing world, where the criteria for appropriateness are inherently different.**
- 2. We want to challenge the idea, which is supported by this one-way flow, that there is no potential for the developing world to contribute to the advancement of technology. This is where the “changing our definition of technology” point comes in. We recognize that a challenge that must be overcome in order for them to realize their possible contribution is the improvement of capacity within their overall development program.**
- 3. While these nations continue to develop the infrastructure needed to support production of their own machinery/traditional medical equipment, they should also look at the resources that they already have in place. By doing so, they uncover potential (such as in the use of naturally derived and scientifically optimized, or syntheto-natural, biomaterials) to advance the frontier of science, which can help both the developed AND the developing world.**



***“I’m a doctor,
not an engineer.”***

“Now, you’re an engineer.”



“Go see the human beings who are suffering, and then ask yourself, is the work I did today relevant to human suffering? Did I do something that is going to help change somebody’s life, maybe not today but sometime soon?”

- Christopher Reeve, 2001



Useful Resources

- Biomedical Engineering Society - www.bmes.org
- Society for Biomaterials - www.biomaterials.org
- Advanced Medical Technology - www.advamed.org

