

**Frequently Asked Questions**

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**Press Coverage**

- [Tissue Engineers Steering Stem Cells to Produce Bones, Cartilage](#)
- [Technology Review Hails Johns Hopkins Researcher as Pioneer in Tissue Engineering. One of the Top Ten Emerging Technologies](#)

**Selected Publications:**

["Transdermal Photopolymerization for Minimally Invasive Implantation"](#), Proc. Nat. Acad. Sci., USA

["Transdermal Photopolymerization of PEO-Based Injectable Hydrogels for Tissue Engineering Cartilage"](#), Plastic and Reconstructive Surgery

"Synthesis and Characterization of Photocrosslinked Polymers Based on Poly(L-lactic acid-co-L-aspartic acid)", Macromolecules

"Cogelation of Hydrolyzable Cross-Liners and Poly(ethylene oxide) Dimethacrylate and Their Use as Controlled Release Vehicles", Intelligent Materials for Controlled Release, ACS Symposium

["Photoencapsulation of chondrocytes in Poly\(ethylene oxide\)-based Semi Interpenetrating Networks"](#), Journal of Biomedical Materials Research, 51(2):164-71, 2000

"Controlled Released IGF-I and TGF-b on Bovine Chondrocytes Encapsulated in a Photopolymerizing Hydrogel", accepted to the Journal of Orthopedic Research.

"Transtissue Photopolymerization of Poly(Vinyl Alcohol) Hydrogels" The Wiley Polymer Networks Group Review Series, vol. 2, B.T. Stokke (ed.), in press

**Introduction:**



**Dr. Jennifer Elisseeff**

Over 15 million people worldwide suffer from knee-joint failure each year due to the breakdown of surrounding cartilage in the joint and the inability of this cartilage to repair itself through the natural regenerative processes of healing in the body.

Tissue engineering has emerged as a field to replace tissues and organs lost by disease, trauma, or congenital abnormalities. Attempts have been made to engineer many tissues including skin, cartilage, bone, nerve, cardiovascular valves and conduits, and liver. Dr. Jennifer Elisseeff and her colleagues have pioneered the regeneration of cartilage for the repair of joints such as the knee.

First, some background on the field...

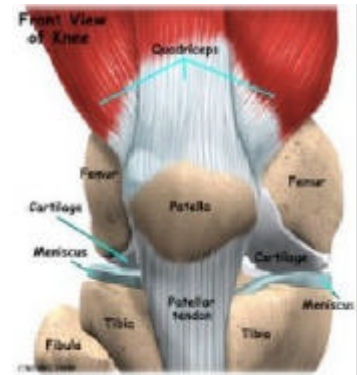
About ten years ago, doctors in Sweden began to surgically remove samples of healthy articular cartilage from the knees of patients with cartilage defects and use it to grow new cartilage in tissue culture. Once they had enough material, they went back into the patient's knees, removed the damaged cartilage, and inserted the test tube cells, called chondrocytes, in its place. The results were promising.

Today, there are three main types of transplants:

- The meniscal transplant - the cartilage shock absorber in the knee joint. If for some reason that is torn, it has to be surgically removed and a donated cartilage disk is transplanted into the knee.
- Articular cartilage is laminated to the ends of the bones that are inside the joints. There are a few different ways to transplant that kind of cartilage. One is to take plugs

**The Technology:**

The knee joint is very complex. It is composed of four bones, the ligaments that hold them together, the articular and meniscal cartilage that protects the ends, and the surrounding bursa.



The Hopkins cartilage regeneration technology encompasses a number of separate components to replace damaged cartilage in the knee or in other joints or locations. **The technology provides a convenient and effective photopolymerization of a hydrogel that contains cells and growth factors necessary for the growth and integration of new cartilage in a damaged tissue.**

While cartilage is often considered a simple tissue with chondrocytes sparsely distributed throughout an extracellular matrix of type II collagen and aggrecan, it is a complex, heterogeneous tissue. On the cellular level chondrocytes are organized into superficial, proliferating, prehypertrophic and hypertrophic chondrocytes. These different types of chondrocytes have different cell morphology and gene expression. The extracellular matrix around the chondrocytes is also highly organized and changes depending on the where it is located. The cellular and extracellular matrix organization is controlled by mechanical and

["A Tissue-Engineered Conduit for Facial Nerve Repair"](#), Arch Otolaryngol Head Neck Surg, 124(10):1081-6, 1998

["Transdermally Photopolymerized Adhesive for Seroma Prevention"](#), Plastic and Reconstructive Surgery, 103:531-535, 1999

"In vitro prefabrication of human cartilage shapes using fibrin glue and human chondrocytes" Ann Plast Surg, 40(4):413-420, 1998

## Selected Abstracts

Transdermal Photopolymerization to Create an Injectable Tissue Engineered Cartilage", World Congress on Medical Physics and Biomedical Engineering, Nice, France, 1997

Interactions of light and skin for optimization of transdermal photopolymerization", 44th Annual ASAIO Meeting, Spring 1998

Transdermal Photopolymerization for Cartilage Tissue Engineering", Biomedical Engineering Society Annual Meeting, 1998

Meniscal Tissue Engineered by Suncutaneous Implantation of Fibrochondrocytes on Polymer Develops Biomechanical Compressive Properties Similar to Normal Meniscus", Orthopedic Research Society Meeting, Spring, 1997

Scaffold Materials to Engineer Cartilage", Biomedical Engineering Society Annual Meeting, 1998

Cationic Polymerization of Styrene in the Presence of Ethers and Sulfides", Polymer Preprints, 35(1):464, 1994

## Useful Link

[Cartilage \(chondral\) injuries of the knee - causes, diagnosis and treatment review](#)

## The Development Team

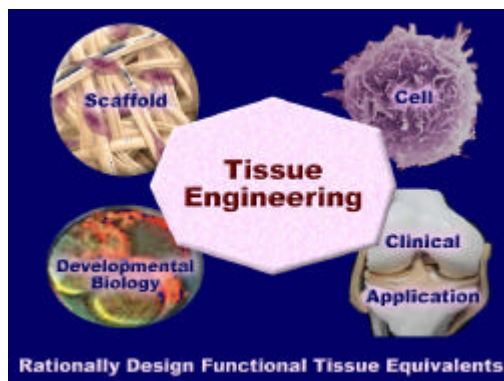
[Jennifer Elisseeff](#)  
Principal Investigator

- Christopher G. Williams, M.D. Surgical Fellow
- Tae Kyun Kim, M.D., Ph.D. Postdoctoral Fellow
- Dong-an Wang, Ph.D. Postdoctoral Fellow

of bones and cartilage from a separate area of the patient's joint and plug in into the area that's missing the cartilage. That can also be done in the ankle joint. A similar transplant procedure for articular cartilage involves removing cartilage and bone from a cadaveric donor and transplanting that into a patient's knee. There's minimal rejection problem because cartilage tends to be immunoprivileged, whereby the immune system has difficulty coming in direct contact with immunogenic cells.

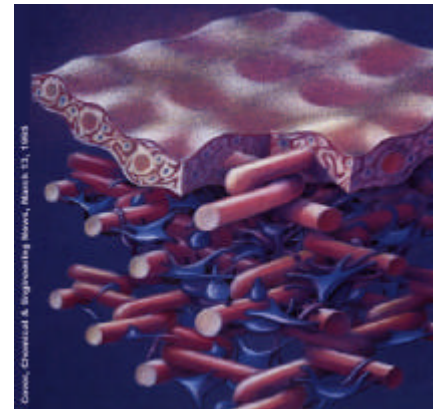
- The third type of transplant is analogous to patching an automobile tire; a patient's healthy cartilage cells are removed and sent to a laboratory that grows and duplicates them in tissue culture. Six weeks later they return the cells to the damaged joint. The damaged cartilage is then excised from the patient's knee and the test tube cells, called chondrocytes, are inserted. Placing a piece of lining of a bone and sewing it over the area will protect the cartilage cells so they can continue to grow and bond.

Tissue engineers today utilize a variety of approaches to regenerate tissues. These approaches can be broadly characterized into three major groups. First, biomaterials, without additional cells, are used to convey biological signals to surrounding tissues to recruit cells and promote inherent regeneration. Second, cells alone may be used, without a biomaterial, to form tissues. Finally, cells may be used with a biomaterial scaffold that acts as a framework for developing tissues. The technology focuses on the latter technique, developing and using biomaterial scaffolds for tissue engineering. The development of an effective cartilage regeneration system and future improvements rely on the merger of skills and knowledge as shown below:



The Elisseeff tissue engineering laboratory has applied rigorous basic science and engineering

biological signals during development and after. There is a large wealth of molecular and cell biology that has been applied to cartilage tissue engineering. This technology uses hydrogels for tissue engineering.



Hydrogels encapsulate cells and absorb a large volume of liquid for nutrient and waste transport. The poly(ethylene oxide)-based photopolymerizing polymers can incorporate, through physical interactions or covalent bonds, extracellular matrix derived gels and proteins. The composite hydrogel has a synthetic portion where physical properties can be easily manipulated and a biological portion where cell response and tissue development can be manipulated.

Integration of a biomaterial with surrounding tissue is critical to long term survival and function. Particularly in the case of hard tissues such as cartilage in the musculoskeletal system, integration of an implant is difficult due to the dense nature of the extracellular matrix and large mechanical forces to which these tissues are often subjected. We have designed a method to direct covalent attachment of (meth)acrylated polymers to collagen proteins. Collagen is ubiquitous so that this method for implantation may be applied throughout. Covalent integration of hydrogel biomaterials significantly improves the mechanical integrity of the tissue-biomaterial interface in challenging applications such as cartilage.

Photopolymerization is used as a method to encapsulate cells for drug delivery and tissue engineering applications in our minimally invasive <http://www.birchbob.com/jhu/indexJE.htm>

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- Leon Lum M.S. Student
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## Collaborators

[Dr. Kam Leong, Ph.D.](#)  
Biomedical Engineering - The Johns Hopkins University  
Synthetic and biological polymers applied to drug delivery, gene therapy, and tissue engineering.

[Dr. Christopher Chen, M.D., Ph.D.](#)  
Biomedical Engineering - The Johns Hopkins University  
Developing novel microfabrication and miniaturization tools for biological and medical research applications, understanding the mechanisms of tissue vascularization, the role of cell adhesion in cancer transformation, and the role of mechanical forces in cell function.

principles to the development and understanding of tissue engineering systems. They

- developed novel hydrogels with enhanced microstructure for tissue engineering;
- designed minimally invasive systems for biomaterial scaffold implantation;
- modeled mechanisms of cellular response and tissue development in tissue engineering scaffolds; and
- engineered tissues with the complex cellular and matrix organization found naturally in vivo using biomaterials, cell, and developmental biology to understand and control mechanisms of the developing tissue.

### Therapeutic Focus:

The Hopkins technology leverages the expertise of basic and clinical medicine, biomaterials, and engineering to provide an improved product with the following properties:

- **is conveniently injectable and flows to conform to the treated surface**
- **can strongly attach to the surrounding tissue**
- **promotes cell growth and integration with the surrounding tissue**
- **degrades/adsorbs slowly enough to allow stable tissue regeneration**



### Market Opportunity:

Over 15 million people worldwide suffer from knee-joint failure each year due to the breakdown of surrounding cartilage in the joint and the inability of this cartilage to repair itself through the natural regenerative processes of healing in the body. About 200,000 total knee replacements are performed each year at an average cost of \$25,000 each, in an attempt to treat this problem.

implantation systems. Most tissues in the body are complex, containing numerous cell types organized in specific extracellular matrix architecture. We have created multilayered photopolymerizing hydrogels in order to encapsulate numerous cell types or drug delivery vehicles. The tissue is comprised of layers of chondrocytes which contribute to the unique developmental and mechanical properties of the tissue. Furthermore, osteochondral implants, containing bone and cartilage are often used clinically to treat joint defects. Local factors released by the various cell types influence engineered tissue development and properties. Using the appropriate cell type, we have created both multilayered cartilage and osteochondral constructs to create engineered tissue with enhanced biochemical and functional properties.

A number of specialized hydrogels have also been optimized for specific cartilage regeneration applications. Proteoglycans are found throughout the body and serve numerous structural and functional roles. Chondroitin sulfate (CS) was modified to varying degrees with (meth)acrylate groups (CSMA) and polymerized to form a crosslinked hydrogel. Depending on the degree of modification, swelling, mechanical, and degradation properties of the CSMA hydrogels may be altered to fit a desired application. The CSMA gels are specifically degraded by chondroitinase and may be used as a diagnostic for the presence of chondroitinase, a degradative enzyme found in cartilage. Chondroitin sulfate is found naturally in other parts of the body including the intervertebral disc and may therefore be useful as a biomaterial in numerous applications.

The diagram below demonstrates the process of using the photopolymerizable hydrogel for cartilage repair. You can click on the diagram to see a larger version.

[Dr. Kristi Anseth, Ph.D.](#)  
 University of Colorado  
 Biomaterials and Tissue  
 Engineering  
 Developing strategies for  
 encapsulating cells in polymer  
 scaffolds for tissue  
 engineering and selectively  
 modifying these scaffolds to  
 control cellular

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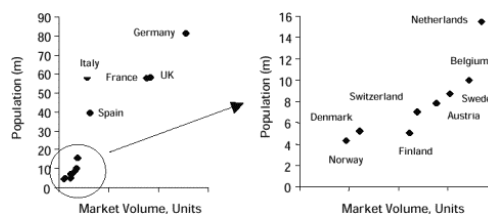
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According to industry estimates, more than 225,000 people worldwide underwent arthroscopic meniscal repair in 2002. The number of procedures is expected to have a compound annual growth rate of nearly 5% through 2007, according to a major company in the field. Chondrocyte transplantation is a relatively new procedure and is growing rapidly, in part due to improvements in cell harvesting and in vitro cell expansion. According to one industry player, more than 2,100 people in the United States have had cartilage cells harvested for grafting and implantation in hopes that these cultured cells will relieve the persistent pain and grinding in their knees. The current total cost of the procedure is about \$30,000, with the lab cultivation procedure costing \$10,000 and the hospital and surgical fees up around \$20,000. The primary markets for the Hopkins technology include North America, Europe, and some countries in Asia, such as Japan, Korea, and Singapore.



1998 Comparison of the European Knee Implant Market by Country  
 Source: Datamonitor Medical Equipment Division

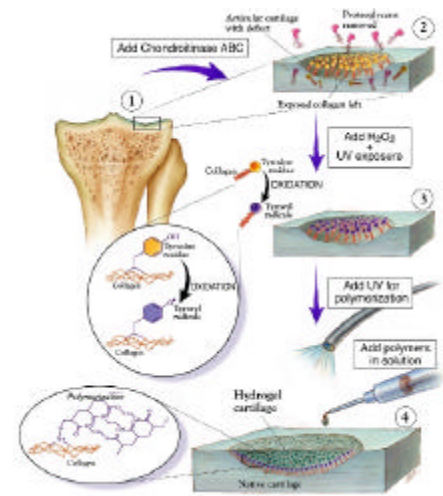
## Clinical Competitor Analysis:

There are a number of competitors with products in the marketplace and under development. The distinguishing factors for market success will include efficacy, ease of use, cost, and long term benefits. The Hopkins technology is being optimized not only at the biomaterial's level, but also at the cellular level. Following are some of the major players in the field:

**Genzyme** Tissue Repair's Carticel® and its second generation products represent the market leader at present.

**Smith & Nephew** has introduced a new implant that applies the latest advances in medical technology to an established repair technique in the field of arthroscopic surgery. Called FasT-Fix AB Meniscal Repair System, the system was first launched in April 2001.

**OsteoBiologics, Inc.** is also focused on the research, development and manufacturing of bioabsorbable tissue-engineered scaffolds and instrumentation to identify and repair musculoskeletal tissue.



Creation of new cartilage will use controlled delivery of biological signals mentioned above in addition to physical signals provided by a scaffold to design anisotropic, organized cartilage tissue. In addition, chondrocytes with varying morphology and gene expression may be organized during the encapsulation process. Tissue engineered cartilage with an organized structure similar to native tissue will have functionality comparable to native tissue and may potentially integrate more easily into the heterogeneous host tissue where it is implanted. This three-dimensionality is expected to increase the speed and efficacy of tissue regeneration.

## Intellectual Property:

Multiple patent applications are currently pending and reviewable upon the execution of a confidentiality agreement

## Elisseeff Receives Award

[MIT's Technology Review](#) magazine recently recognized Jennifer Elisseeff, assistant professor of biomedical engineering at Johns Hopkins, as one of the World's Top 100 Young Innovators in technology and business.

The autologous cartilage transplant CaReS®-Cartilage Repair System - offered by **ARS ARTHRO AG®** is a 3D mechanically stable transplant based on patient specific autologous cartilage cells and a unique patent pending collagen matrix.

**BioTissue Technologies** has developed the Autologous Chondrocyte Graft BioSeed®-C for the treatment of defective joint cartilage.

**IsoTis** is developing tissue-engineered products, including skin, bone and cartilage for use in clinical settings.

**Isto Technologies** is involved in the development of engineered tissues and chemical compounds for the repair and regeneration of human tissue.

**Orquest** is involved in the development of orthobiologic products for bone and cartilage regeneration, using combined technology from tissue biology and biomaterial science.

**Osiris Therapeutics, Inc.** is a researcher and developer of regenerative human stem cell technologies for eventual use in therapeutic products.

**OsteoBiologics** is a developer and manufacturer of bioabsorbable tissue-engineering scaffolds (IMMIX) for the repair and replacement of musculoskeletal tissues.

**ReGen Biologics** designs, develops and manufactures minimally invasive implants and medical devices for the repair and regeneration of damaged or degenerating cartilage in the knee.

There are other therapies such as **Synvisc's** injectable rooster-derived extracellular proteins and also nonbiological implants, such as **Sulzer Orthopedics'** UniSpacer, designed to provide reduced friction between the joints.

## The Whitaker BME Institute at Johns Hopkins University

With the nationally recognized Department of Biomedical Engineering as its core the Whitaker Biomedical Engineering Institute has been established as a vital link between the School of Medicine and the Whiting School of Engineering. The vision of the Institute is of an integrative research and education enterprise that will provide leadership in moving biomedical engineering to the forefront of biomedical science and practice. The Institute will be housed in Biomedical Engineering facilities in the School of Medicine and in Clark Hall, a new facility on the Homewood Campus.

The Department currently has 17 primary faculty members, approximately 100 graduate students, and over 450 undergraduates. Ten new faculty members will be added to the Institute over the next six years, thanks to a Whitaker Foundation Leadership Award. The undergraduate program leading to the bachelor of science in engineering in biomedical engineering is now the largest program on the Homewood campus.



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