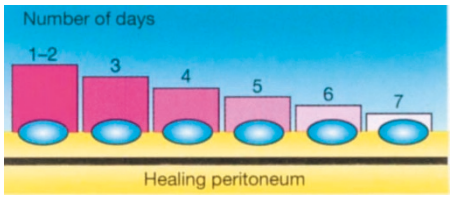
Genzyme's Seprafilm gets FDA marketing nod

The first biodegradable product to demonstrate clinical efficacy in reducing adhesion formation in general abdominal surgery—Genzyme's (Cambridge, MA) Seprafilm—was recommended and approved for marketing in the United States on March 25, 1996 by a panel of the US Food and Drug Administration's (FDA; Rockville, MD) Medical Devices Advisory Committee. Seprafilm contains glycosaminoglycan, which degrades to N-acetylglucosamine, glucuronic acid, and a urea derivative, all of which are innocuous. The product has shown no evidence of toxicity.

Seprafilm turns to viscous gel at 1–2 days, which slowly degrades over 3–7 days (potential adhesion formation period).



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The FDA panel's recommendation was conditional on Genzyme performing standard postmarketing studies to monitor adverse effects. It was also limited to uses in the indications for which Genzyme had generated clinical data—abdominal and gynecological surgery. Other uses will be contingent upon the company presenting additional safety and efficacy data.

Postoperative adhesions occur when tissues react to the trauma of surgery by attaching to other, normally separate, tissues. The adhesions can cause complications ranging from infertility to intestinal obstruction, and they may interfere with followup surgeries.

The two clinical trials that the review panel considered clearly demonstrated that Seprafilm reduces postoperative adhesion. An abdominal surgery trial demonstrated that, of the patients whose surgical incisions were treated with Seprafilm, 51% showed no signs of adhesion during a followup examination. Only 6% of untreated controls remained free of adhesions. A similar study of postsurgical uterine adhesions showed a 37% decrease in the number of adhesions in treated patients.

Genzyme is test-marketing Seprafilm in the Netherlands, the United Kingdom, and Sweden. The company has projected a US target marketing opportunity of about 1.3 million gynecological and 1.8 million general abdominal procedures per year. The FDA panel limited the promotion of Seprafilm to surgical procedures in locations studied in the clinical trials—including the uterus and structures near incisions into the abdominal wall. Genzyme hopes to eventually broaden the product's market to include a wider range of applications in the abdominal and pelvic cavity.

James Kling

Research answers critics of bionic knee technique

Recent research at Genzyme Tissue Repair (Cambridge, MA) may help diffuse some of the criticism of the company's autologous cartilage regeneration service, Carticel. "There is little scientific evidence of the cost-effectiveness of the procedure," Douglas Jackson, second vice president of the American Academy of Orthopedic Surgeons (AAOS, Rosemont, IL), said recently. But Genzyme has now countered by demonstrating that Carticel differs at the cellular level from other procedures. The essential finding is that effective regeneration of cartilage tissue requires that chondrocytes grown in vivo must be able to switch from production of fibrous type I collagen to the biomechanically superior type II collagen.

Genzyme licensed the Carticel process from Lars Peterson's group at Goteborg University (Goteborg, Sweden) and began offering its service to orthopedic specialists in March 1995. Damage to joint cartilage is often a debilitating injury because cartilage does not repair itself effectively, and this may lead to osteoarthritis and, sometimes, to the need for total joint replacement. Genzyme's process grows chondrocytes derived from tissue from a patient's cartilage in vitro and returns the expanded cells to the orthopedic surgeon, who reinjects them into the patient. (Chondrocytes are the living cells that produce the hyaluronic acid, collagens, and proteins that form the cartilage matrix.)

Genzyme has promoted the Carticel approach strongly through, among other activities, a two-day training course in the technique offered to surgeons. It is this "aggressive" approach—which, critics say, has raised "unrealistic expectations" from the public—combined with the absence of full regulatory oversight that has made the techniques controversial. In July last year, the US Food and Drug Administration (FDA, Rockville, MD) resolved the problems it seemed to be having in deciding which of its units had jurisdiction by indicating that it did not intend to regulate Carticel. The AAOS is concerned that, without regulation, appropriate standards for efficacy in cartilage replacement approached cannot emerge.

The new findings, presented by Genzyme's Leesa Barone at the American Chemical Society Meeting (March 24-28, New Orleans, LA) may, however, help reassure surgeons that Carticel has validity.

Previous chondrocyte culture methods have been ineffective because, once removed from their surrounding cartilage matrix and placed in a monolayer culture, chondrocytes tend to change their behavior and produce fibrous type I collagen almost exclusively. Genzyme's research shows that, with the correct culture techniques, cells in monolayer culture can begin expressing type II collagen within one to two weeks. After ten weeks, the cells produce type II exclusively.

"True committed articular chondrocytes must be able to maintain the gene switching ability; that is, from type I collagen expression to type II collagen expression," said Leesa Barone. "The reversibility of this [process] in monolayer culture is key to the successful repair of articular cartilage with cultured autologous chondrocytes. . ."

Genzyme's work also showed that monolayer culture cells do not produce type X collagen—a variant that is an indicator that cells may eventually form bone. Previous studies with primitive, undifferentiated stem cells and cells derived from periosteum have shown type X collagen expression. "This indicates that adult articular chondrocytes are committed cells that are not capable of differentiating further into bone," said Barone.

Genzyme's work may provide a cell-based baseline to which other researchers can compare alternative chondrocyte cell systems.

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