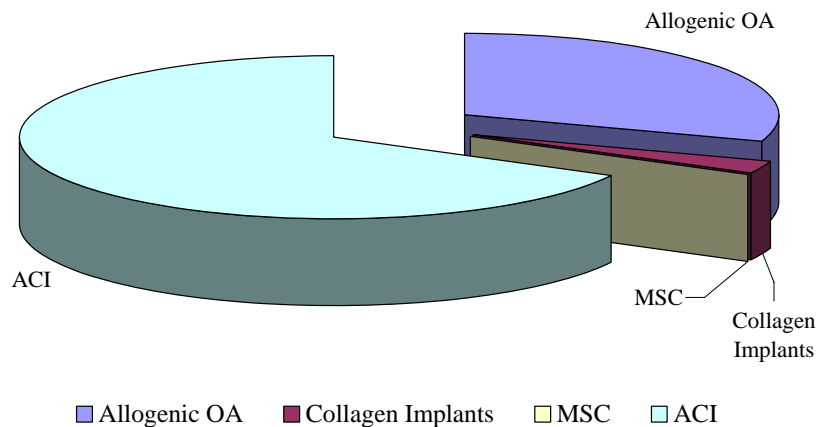


# Cartilage Repair – Selected Excerpts

## *Mesenchymal Stem Cells (MSCs) for Cartilage and Soft Tissue Repair*

Given the range of new cell-based technologies currently undergoing the FDA approval process, various new cell-based therapies will soon be available commercially for cartilage repair. MSCs are multi-potent cells that have the potential to differentiate into lineages of mesenchymal tissues, including bone, cartilage, tendon, fat, muscle, and marrow stroma. As MSCs divide and develop, they release several growth signaling proteins, cytokines and anti-inflammatory signals.

**2006 Cartilage Repair Market by Segment**  
**TOTAL SIZE \$40 Million**



Human clinical trials on utilizing bone marrow-derived MSCs to repair chondral defects have started in the United States. In November 2005, patients began enrolling in a randomized, double-blind, placebo-controlled Phase I/II clinical trial evaluating a pure MSC injection product called Chondrogen™ and produced by Osiris Therapeutics.

### *Next-Generation ACI (Autologous Chondrocyte Implant) Procedures*

ChondroCelect and Zimmer's DeNovo® are two examples of next-generation chondrocyte / ACI procedures that are attracting significant interest. ChondroCelect, specifically, has completed its Phase III clinical study with notably strong results.

ChondroCelect is roughly analogous to Genzyme's Carticel (in the sense that it uses the patient's own cells and cultures them up) but, according to its developer and supplier TiGenix, ChondroCelect produces a more durable, stable, hyaline-like cartilage than Carticel. In February 2007, TiGenix reported the results of a rigorous clinical study that compared ChondroCelect with microfracture for care of symptomatic cartilage defects of the knee (microfracture) in 118 patients at 13 orthopedic centers. This was a randomized, prospective, blinded control study.

Importantly, the end points were measured via biopsy and histomorphometry – which is difficult in terms of patient compliance but delivers solid measurement data.

ChondroCelect's primary end points were:

#### a) **Structural repair at 12 months**

- **Results:** ChondroCelect is superior to microfracture with debridement (assessment by independent histopathologists blinded to the treatment using (i) computerized histomorphometry and (ii) evaluation of overall histology of biopsies taken 12 months after treatment). This is a serious study.

b) **Symptomatic relief and improved functional outcome and quality of life at 12 and 18 months**

- **Results:** ChondroCelect delivered clinical improvement that was at least as good as microfracture as measured by KOOS (Knee Injury and Osteoarthritis Outcome Score).

**Bottom Line:** ChondroCelect regenerated tissue that was superior to the repair tissue formed following microfracture as assessed by histomorphometry ( $P=0.003$ ) and overall histology ( $P=0.012$ ) of biopsies taken 12 months after treatment. **The repair tissue in patients treated with ChondroCelect was found to be less fibrous and to display features indicative of more durable hyaline-like cartilage.**

This was a Phase III clinical trial for ChondroCelect. The Belgium-based TiGenix hopes to launch ChondroCelect in Europe in 2008 and in the U.S. after its FDA filings run their course. Call it three to four years.

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