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The Exciting Potential of OrthoBiologics

Companies

Anika Therapeutics (ANIK)
Biomet (private)
BioMimetic (BMTI)
MItek / DePuy (subsidiary of Johnson & Johnson ; JNJ)
Genzyme (subsidiary of Sanofi; SNY)
Kensey Nasy (KNSY)
Orthovita (VITA)
Smith & Nephew (SNN)
Zimmer (ZMH)

Expert

William J. Maloney, M.D. is Professor and Chairman of the Department of Orthopedic Surgery at the Stanford University School of Medicine and Stanford Medicine Outpatient Center. He is also Associate Editor of the *Journal of Orthopedic Research*.

Cartilage Repair Treatments:

- Speaking for the *in*Thought Expert Discussion Series, Dr. William Maloney described Autologous Chondrocyte Implantation (ACI) procedures, such as Genzyme's (SNY) Carticel, as expensive and technically challenging. Microfracture is inexpensive and simpler. ACI is unlikely to replace microfracture for the majority of cases.
- In the pipeline, Zimmer's (ZMH) DeNovo ET, Kensey Nash's (KNSY) CRD scaffold, and microfracture augmentations appear promising.
- *in*Thought estimates that the US ACI market will generate approximately $30 million this year, growing to $50 million by 2016.

Osteoarthritis (OA) Treatments:

- Injectable compounds in early development may change the way OA is treated. *in*Thought estimates the US viscosupplementation market at over $550 million in 2010, expanding to over $715 million by 2015. We expect Genzyme's SynviscOne and Anika's (ANIK) Monovisc to dominate this market, though this could change on data from early developmental compounds.
- One developmental injectable described by Dr. Maloney blocks pain signals rather than decreasing inflammation to treat the pain.

Other OrthoBiologics:

- Medtronic (MDT) will remain the giant in the bone morphogenic protein (BMP) space. As Medtronic's BMP-2 has come under scrutiny, FDA approval of these biologics has become more difficult.

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Expert Insight: Cartilage Repair

The majority of the cartilage repair market is focused on repair in the knee. Two types of cartilage in the knee can require treatment: the meniscus, which can be torn in sports injuries, and the hyaline or articular cartilage, which is the cartilage on the bone that has deteriorated in patients with osteoarthritis. Cartilage defects short of tears can also require treatment. A variety of different technologies are available to treat cartilage defects, though according to Dr. William Maloney, Professor and Chair at Stanford University in the Department of Orthopedic Surgery, none is clearly superior and all are inadequate.

The technology most commonly used to treat torn cartilage is a microfracture procedure, where the underlying bone of the knee joint is punctured repeatedly to encourage blood flow into the cartilage, promoting healing. The advantage of microfracture is that it is an inexpensive, single procedure that is relatively simple to perform. The downside is that results can take years to develop, and microfracture often does not work well on large defects.

Dr. Maloney estimates that 85% of patients with cartilage defects receive microfracture, 10% OATS, and less than 5% ACI.

At his institution, Dr. Maloney estimates that 85% of patients with cartilage defects get microfracture, 10% receive OATS (osteochondral autologous or autograft transplantation system), and 5% obtain ACI (autologous chondrocyte implantation) or other procedures.

With microfracture, there is no device or osteobiologic involved. The surgeon debrides the cartilage (cleans the damaged cartilage, removes devitalized tissue sometimes revealing healthy cartilage) and uses a little pick to perforate the bone, which allows blood entry, bringing in stem cells to regenerate fibrocartilage.

Beyond microfracture, the technological landscape is evolving towards regenerating cartilage. In the US, cartilage regeneration typically involves Carticel, an ACI procedure that Genzyme has been marketing since 1997. Dr. Maloney sees a lot of problems with Carticel from a practical standpoint, including the need for two separate procedures and a cost almost as high as knee replacement. Dr. Maloney believes Carticel is therefore unlikely to be a long-term solution.

Carticel is also technically challenging for the average surgeon. The first procedure is to harvest the patient's own cartilage from a "non-critical area." The cartilage is then sent to Genzyme, where the chondrocytes are isolated, purified, and sent back to the doctor. Then, in the second procedure, the cells are implanted into the defect and the patient's own tissue is sewn over the top of the defect.

In addition to Carticel, Genzyme markets an innovative ACI system called MACI, where the autologous chondrocytes are implanted into a matrix. MACI helps provide the patient with immediate relief, but is still a two-procedure prospect. Dr. Maloney sees MACI as an improvement on Carticel, but does not expect it to be the long-term solution favored by orthopedic surgeons.

Another procedure for cartilage repair involves an instrumentation system, which is commercialized as the osteochondral autologous (or autograft) transplant system (OATS). OATS uses a plug of bone or cartilage that is placed into the defect. This may be taken from a "non-critical part of the knee or ankle," and transplanted into the critical, weight-bearing defect. OATS is often used in larger defects where microfracture is not appropriate. According to Dr. Maloney, efficacy is less than desired; the better the study, the worse the outcome.

With significant limitations for microfracture, ACI, and OATS, opportunity for new orthobiologics exists. However, progress has been slow for the myriad developmental candidates in the cartilage injury pipeline.

TiGenix is a European company with an ACI process called ChrondroCelect. In that process, a patient's own cells are harvested and the most biologically active cells are isolated and implanted into the cartilage defect. The major issue with ChrondoCelect is that the cells are adult chondrocytes, which rarely provide a quality repair. Once cell donors are over the age of about 10 years, the biologic capacity to make a matrix / new cartilage is limited. TiGenix has had discussions with the FDA on approval, and the FDA has requested a new trial. Funding is an issue for the company, which has not announced a plan to pursue

a phase III trial in the US. Recently, TiGenix has agreed to merge with Cellerix, S.A.

Another potential combination is Histogenics and ProChon Biotech. Both Massachusetts-based companies are studying cartilage repair biologics. Dr. Maloney indicated that the companies are trying to combine the technologies of Histogenics' NeoCart with ProChon's BioCart. NeoCart initiated a phase III trial and has run out of money. The potential combination with ProChon may get the phase III trial up and running again. ProChon's expertise is in fibroblast growth factors. Combining this with Histogenics' scaffold could be interesting if there is no requirement for autologous cells that need to be cultured. As with other autologous procedures the problem with NeoCart is that it requires two procedures.

Another interesting solution for the cartilage repair market is a matrix / scaffold alone. If a scaffold is implanted into a microfracture bed, it protects that environment so that it is cell-supportive. The environment may actually direct the patient's own mesenchymal stem cells down the cartilage line. From a financial standpoint, a matrix would be an attractive product, potentially a single procedure that does not require the level of handling of other cell based procedures.

Any cartilage repair technology that requires two surgeries is unlikely to be the optimal solution.

Kensey Nash has developed a cartilage repair device / scaffold called CRD, currently in phase II trials in the US. The company describes CRD as a biphasic scaffold, a combination of collagen, a polymer, and a tricalcium phosphate plug. Other companies have studied biphasic scaffolds, but Kensey's CRD is most advanced.

Viscosupplementation and Osteoarthritis Treatments

The viscosupplementation market is interesting from a financial perspective and a clinical results perspective. The American Academy of Orthopedic Surgeons' guideline describes few efficacious therapies for treatment of OA. Weight loss is the most effective modality for decreasing the pain of OA. Clinical data have shown that viscosupplementation is only marginally better than placebo, as measured by analog pain scores.

Currently, anti-inflammatory drugs, both non-steroidal and cortisone, are the mainstays of treatment. Viscosupplementation products have a large market potential, and have already gained off-label support in some areas, especially in sports medicine.

The mechanism of action of viscosupplementation is poorly defined, but likely related to its lubrication effects. The therapeutic objective of viscosupplementation is pain control, not cartilage regeneration. Genzyme's SynviscOne is used most frequently. It is more convenient for patients than its competitors, as it is only one injection. SynviscOne has similar efficacy to its competitors.

In a normal orthopedic setting (not sports medicine), by the time doctors see a patient with a symptomatic knee from osteoarthritis, the patient has lost a significant percentage of the cartilage. At this point, the intervention is typically to control the pain and other symptoms, not to modify the disease. There are injectables under development for osteoarthritis that block pain signals. One such compound is Optimer's OPT 88, a disease modifying compound in preclinical development in the US that has demonstrated chondroprotective, anti-inflammatory and pain relief properties. The mechanism of action is undefined. Chugai and Denki Kagaku Kogyo are in preclinical development in Japan with an osteoarthritis injectable combining hyaluronic acid and methotrexate. The potent, anti-inflammatory effect of methotrexate and a viscoelasticity of hyaluronic acid are thought to better address osteoarthritis symptoms that hyaluronic acid alone.

*in*Thought estimates that US visco-supplementation products generated over $550 million in 2010. We expect this market to grow to over $715 million by 2015. Our model suggests that the 2010 market increased 17% from 2009, likely due to increased usage by sports medicine doctors in patients who have early OA. These doctors are treating patients with joint pain or minimal OA on imaging studies. In this area, the single injection is very popular.

Other Biologics

Growth factors are an attractive area. Cellular repair tends to be more efficacious than mechanical-based options. In the bone repair market, the biggest success is Medtronic's Infuse, a BMP-2 formulation. The next largest player is Stryker's OP-1.

Unfortunately, even the Medtronic product is coming under greater scrutiny, paradoxically because it works too well in some cases, causing excessive growth. It is commonly used off-label, which can also contribute to excess adversities. The FDA is therefore cracking down on use of Infuse and other growth factor formulations. Though there are interesting products in the pipeline, additional FDA scrutiny will lead to a tough approval process. Going forward, the FDA and / or payors may require demonstration of superiority, rather than just equivalency. Microfracture is a great example. If your product is not superior to microfracture, payors are not going to pay for it.