

Research



Bayer, J&J clot-drug success lifts US prospects

A drug being developed by Bayer and Johnson & Johnson has again proved better than a standard treatment in preventing dangerous blood clots among patients undergoing orthopaedic surgery, boosting its chances for US approval

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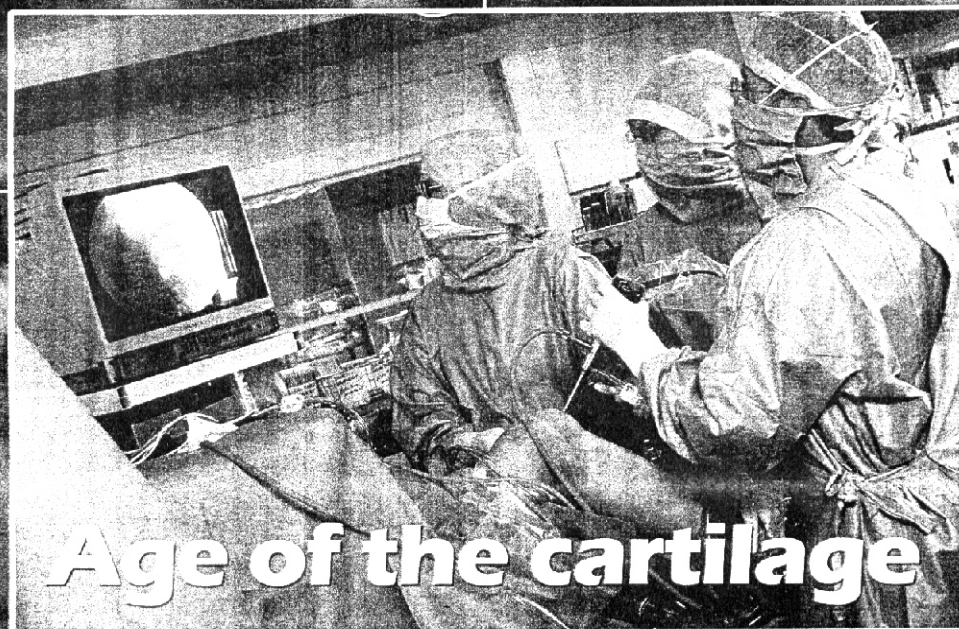
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Cartilage transplant has emerged as a strong alternative to many cartilage related deformities, especially knee replacement. **Sachin Jagdale** reports developments in this area.



Age of the cartilage

The well-known adage, no pain no gain, may have held true in the past millennium, but in this day and age, ease and comfort hold prime position, especially when it comes to suffering physical pain and having to rely on family members or caretakers for day-to-day existence and mobility. A car or bike that runs smoothly and a body that functions smoothly are the norms of today's fast paced world. And any thought of an illness cropping up and slowing you down is daunting, especially when it is a least thought about body part like cartilage that may malfunction and result in loss of mobility.

Cartilage is a dense connective tissue comprising cells called chondrocytes that produce vast quantity of extracellular matrix composed of collagen fibres, elastin fibres and a ground substance rich in proteoglycan. Cartilage is of three types—fibrocartilage, hyaline cartilage and elastic cartilage.

Cartilage is different from other connective tissues as it does not contain blood vessels. The pumping action generated by compression of the articular cartilage helps chondrocytes to feed by diffusion. This is why, compared to other connective tissues, the growth and repair of cartilage is slow. Cartilage is present in the rib cage, bones, nose, ear, bronchial tubes and intervertebral discs.

Another factor differentiating cartilage from other body tissues is that it is the only body tissue that never stops growing. Its continuous growth is evident from the longer ear lobes and bigger noses of elderly people. Cartilage in knees and elbows are probably the most important as it acts as a cushion between joints and prevents bones from rubbing against each other.

Not strong enough?

Cartilage is highly prone to diseases, osteoarthritis being one of the most common. In osteoarthritis, the cartilage tissue covering the bones becomes thin and subsequently wears out completely. This leads to friction between the joints and consequent pain and reduced mobility. Caused primarily due to high stress, osteoarthritis is more of a wear and tear problem rather than a proper disease. Costochondritis is another painful condition, where inflammation of rib cartilage, which holds the rib bones together, takes place.

Besides these diseases, asymmetrical compression of intervertebral disc leads to herniation of its

Results of a preclinical trial of Mesoblast's patented adult stem cell technology for repair and regeneration of the vertebral disc cartilage are expected soon. The cartilage trials signal Mesoblast's expansion of its line of products for spinal diseases and its strategic aim to build a robust franchise for the large global spinal disease market. Mesoblast is also conducting a Phase II trial in the US for spinal fusion, with a Phase III/pivotal trial planned for 2009.

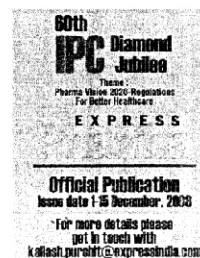
Also, after outstanding results in a pilot trial at the Royal Melbourne Hospital of 10 patients suffering from non-healing long bone fractures, the company is reviewing its options to embark on a Phase III clinical trial strategy that will ensure both the shortest time to market and product approval, for use of its specialist cells in the bone trauma market.



Cartilage transplant produces repair tissue with qualities very close to the articular cartilage we are born with. It can help relieve pain and stiffness and improve quality of life for patients. In properly selected patients it may even obviate the need for knee replacement

Dr Milind Sawant
Orthopaedic surgeon
Wockhardt Hospitals

soft content. The resultant compression of adjacent nerves causes back pain. There are also possibilities



of benign (chondroma) or malignant tumors (chondrosarcoma) of cartilage tissue.

Since cartilage has limited repairing capabilities, any disease affecting it is intimidating. Chondrocytes are bound in lacunae and so cannot migrate to the damaged area. The hyaline cartilage is devoid of blood supply and deposition of new matrix is slow. However, damaged cartilage can be replaced surgically through chondroplasty, but this comes with its limitations.

Cartilage transplant

Since the sixties, knee replacement was the most popular method to overcome severe wear and tear of the knee joint arising due to loss of cartilage. This complex invasive method involves implantation of

artificial joints. Scientific advances in the field of cartilage transplant have made it a viable, natural alternative to using artificial implants. And many orthopaedic surgeons now prefer this method.

Dr Norman Marcus of Virginia Cartilage Institute, a veteran of over a hundred cartilage transplants, says, "Cartilage transplantation, also called 'autologous chondrocyte implantation' (ACI) is done by performing a small biopsy of normal appearing cartilage. This tissue is sent to the lab and then cloned by tissue culture for several weeks to produce twelve million cells. In a second procedure, cells are implanted in the defective cartilage." However, Marcus cautions that even though ACI is not meant for patients with advanced degeneration, there is over 90 percent success rate in carefully selected patients.

Though research on cartilage transplant is still to catch on in India, orthopaedic surgeons have been quick to sense its benefits. Dr Milind Sawant, orthopaedic surgeon, Wockhardt Hospitals, Mumbai, gives it the thumbs up. "Cartilage transplant produces repair tissue with qualities very close to the articular cartilage we are born with. It can help relieve pain and stiffness and improve quality of life for patients. In properly selected patients, it may even obviate the need for knee replacement," he says. The indications and selection criteria for this surgery are still evolving and a clearer picture will take time to evolve, says Sawant, according to whom the biggest hurdle is the cost of surgery, which can run

► into a few lakhs.

A bright future

Cartilage regeneration is one of the most widely researched topics in the international arena today. Recently, scientists in Sydney conducted a successful trial of cartilage transplant on a sheep. A series of transplants were done by the researchers from the University of New South Wales and it was termed a success as there were no signs of transplanted cartilage rejection.

CyGenics, an Australian adult stem cell research company involved in developing new stem cell-based medical therapies has also come up with promising results in cartilage regeneration research using stem cells.

Promising results have also been published by a US drug company, Genzyme. The results of a multi-centre, observational study checked long term suitability of ACI in 72 patients with serious damages to the articular cartilage of the knees. They were monitored for ten years post ACI. The study, conducted after five years, showed significant improvement among 75 percent of the patients.

Another company that works towards the

Milestones in cartilage repair

- 1965: Smith first isolated and grew chondrocytes
- 1982: Experimental rabbit model HJD, NY
- 1984: First animal results. 80 percent defect fill
- 1987: First ACI in human. Goteborg, Sweden
- 1994: Pilot study reported in New England Journal of Medicine (NEJM). 16/23 patients with good or excellent results ACI availability
- 1997: Carticel by Genzyme approved by FDA for autologous chondrocyte implantation in knees.
- 2000: Dr Brian Sennet and Dr Gerald Williams use ACI for shoulder repair in a 37 year old male at Presbyterian Medical Center of University of Pennsylvania Health System.
- 2002: Dr Habermeyer and Dr Lichtenberg (ATOS-Klinik, Heidelberg, Germany) apply MACI for cartilage repair in shoulder.
- 2002: Miltek Worldwide (Johnson & Johnson) partnership with Verigen to begin MACI clinical trials in the United States.

(Web sources)

Cartilage regeneration is one of the most widely researched topics in the international arena today. Though research on cartilage transplant is still to catch on in India, orthopaedic surgeons have been quick to sense its benefits

► regeneration and protection of cartilage, is Mesoblast. Professor Silviu Itescu, Founder and Executive Director, Mesoblast, says, "We are developing an adult stem cell product aimed at regenerating and protecting the cartilage. Initially, we will target osteoarthritis of the knee. We recently announced the promising results of a 12-month preclinical study which showed that a single injection of its proprietary allogeneic or 'off the shelf' adult stem cells into the knee developing osteoarthritis after surgical meniscectomy, provided sustained protection against cartilage destruction and degeneration which lasted for up to nine months."

Now, based on these results, Mesoblast intends to present an Investigational New Drug (IND) submission to the US Food and Drug Administration (FDA) during the third quarter of 2008, to start off a blind, random phase II clinical trial of stem cell treatment to protect knee cartilage.

The primary endpoint of the trial will be to determine the safety of the cells injected into knee joints while the secondary endpoint will be pain score reduction along with improved joint mobility. An MRI assessment of cartilage thickness at six and 12 months after the direct injection of the cells into the knee is yet another step that will be used to decide the outcome of the trial.

In India, Reliance Life Sciences



Mesoblast is developing an adult stem cell product aimed at regenerating and protecting cartilage. Initially, we will target osteoarthritis of the knee, a degenerative disease that is characterised by the loss of cartilage and joint pain and disability

Professor Silviu Itescu
Founder and Executive Director
Mesoblast



The process of isolating cells from cartilage biopsies and culturing cells in a sterile environment is a challenging task. This, in addition to the high cost involved in setting up the facility, is a deterrent to pursuing research in this field

K V Subramaniam
President and CEO
Reliance Life Sciences

(RLS) is doing research on chondrocytes. "Reliance Life Sciences is developing cell culture techniques for expansion of chondrocytes *in vitro* and delivering the cells on a matrix," informs K V Subramaniam, President and CEO, RLS. He adds, "Cartilage from mesenchymal stem cells is also under study and is in phase III in the US. Autologous implantation although available in the West, is not yet performed in India."

European countries are way ahead of India in terms of research on cartilage. According to Subramaniam, this is because the process of isolating cells from cartilage biopsies and culturing cells in a sterile environment is a challenging task. This, in addition to the high cost involved in setting up the facility, is a deterrent to pursuing research in this field. Besides,

autologous therapy is a customised therapy and requires stringent manufacturing requirements. However, companies like RLS are changing this scenario and very soon India could be the key ally of European countries in the development of new ways of cartilage treatment. The ACI technique being developed at RLS would benefit several people suffering from cartilage diseases like osteoarthritis in India.

"Much new research is being done on improved methods, including implanting cells in a sponge or lattice-like scaffold, improving the quality of cells and exploring less expensive alternatives to cartilage regeneration," says Marcus. After all, as he aptly puts it, "biologic resurfacing" is the latest trend. ■

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Cartilage regeneration in the laboratory

Cartilage is a tissue made of chondrocytes. The thick matrix available between the chondrocytes prevents the cells from migrating to the damaged site and inducing regeneration. Local availability of the chondrocytes in the damaged area would induce regeneration.

A small biopsy of 1cm² is collected from the non-load bearing area of the normal cartilage. The biopsy is collected in a special medium, which ensures that the cells are kept nourished during transport to the clean rooms at Reliance Life Sciences (RLS). The cells are extracted from the biopsy and cultured in specialised nutrient media. During culture, the cells de-differentiate and lose their chondrogenic property. However, on culturing the cells in 3-D, the cells regain their chondrogenic potential and multiplication capability.

Source: Reliance Life Sciences