



### White Rose HIP Health Technology Bulletins

The White Rose Health Innovation Partnership (WRHIP) aims to accelerate new health-related technologies by facilitating interactions between academia, industry and the NHS using an *open innovation* approach.

The new projects funded as part of this initiative are built upon a foundation of excellence in health innovation by the Partnership's members. This series of Health Technology Bulletins offer an introduction to this research excellence and cover a broad range of clinical and technology areas.

Each bulletin is written to give a general introduction to the topic area along with short case studies of clinical applications of new knowledge. Information is also presented on where to learn more about these new technologies and health challenges, and how to access the network of health innovation professionals established by the Partnership.

## Clinical need for cartilage repair

Articular cartilage is a specialised avascular, connective tissue which covers the ends of articulating bones in synovial joints, such as the knee and is essential for smooth, painless movement of the skeleton. This weight-bearing tissue functions as a biological 'shock absorber' to decrease mechanical loading on the bones (developed during walking, running etc.) and provides a smooth, near frictionless surface for good joint mobility. These important functional properties are performed by the highly organised extracellular matrix and are entirely dependent on its structural integrity.

Articular cartilage is classified as a hyaline cartilage and is rich in an extracellular matrix which comprises over 90% of the dry weight. The two major components of the matrix are type II collagen and proteoglycans. The collagen forms an extensive, cross-linked, fibrillar meshwork which gives cartilage its tensile strength and rigidity. Whereas, the proteoglycans form large highly charged aggregates which swell as they attract water into the tissue and give cartilage compressibility and resilience during joint loading. The integrity of the matrix components is maintained by a sparse population of cartilage cells (chondrocytes) which are embedded throughout the tissue.

Articular cartilage has a limited capacity for self-repair. Therefore, cartilage injuries caused through trauma, mechanical overloading due to joint misalignment or instability, may lead to significant cartilage defects/lesions which do not heal spontaneously and can result in a progressive erosion of the cartilage and development of osteoarthritis. Cartilage damage or degeneration compromises the

integrity of the extracellular matrix initiating a progressive degeneration of the cartilage and loss of matrix components with concomitant decrease of the affected cartilage to withstand weight bearing. With time, further loss of matrix components may lead to full thickness cartilage lesions and pain, which in turn, can result in ensuing progressive loss of joint function and ultimately require replacement with a joint prosthesis to restore mobility. It has been estimated that in the UK, 10,000 patients each year suffer cartilage damage which needs repair. At present there are no effective pharmacological alternatives to orthopaedic surgery. Hence, effective treatments for repair of articular cartilage are of major interest to orthopaedic surgeons. The ideal therapy would be one which can fully regenerate the cartilage surface. Alternatively, a treatment would also have value if it provided a repair which would function well enough to increase the time period before joint failure and so delay the need for a joint prosthesis.



## Current UK treatment options supported by the National Institute for Health and Clinical Excellence (2005)

There is no uniform approach to managing hyaline cartilage lesions. Joint washout and debridement are employed to remove loose tissue debris and largely provide symptomatic relief. Interventions aimed to induce regeneration of repair tissue at the site of the lesion are abrasion arthroplasty and microfracture of the subchondral bone. The biological principal behind these techniques is that stem cells are released from the bone marrow into the defect and these will then become chondrogenic and make new cartilage. These techniques, however, result in the formation of a fibrocartilage repair tissue, not hyaline cartilage. Fibrocartilage is composed mainly of type I collagen and softer than hyaline cartilage with relatively poor mechanical/wear properties and so not as durable as hyaline cartilage and will fail.

A more recent technique is that of osteochondral autograft transplantation which can be used to treat small defects (less than 2cm<sup>2</sup>). Multiple small cylindrical grafts (approx 4.5mm diameter) of cartilage are harvested with a sample of underlying bone from non-weight bearing sites in the same knee as the cartilage lesion. The cartilage grafts are then transplanted into the cartilage lesions. While there is good evidence that the lesions heal, the patient is left with numerous small donor site lesions of which the long term consequences are not known.

## Developing approaches to cartilage repair

Developing regenerative cell-based methodologies and tissue engineering offer real potential to provide cartilage grafts to replace or regenerate the defective tissue. There are two main approaches to cartilage repair. The first is that of implanting a suspension of cartilage-forming (chondrogenic) cells directly into the cartilage lesion. This procedure is known as autologous chondrocyte implantation (ACI) with the first clinical study published in 1994. This study reported encouraging clinical outcomes for ACI in the knee and promoted further research into ACI. The second, more recent, tissue engineering approach firstly combines the cartilage cells with a biomaterial support or scaffold. The scaffold and cells are then transplanted either immediately into the cartilage defect (as in matrix assisted chondrocyte implantation, MACI) or cultured *in vitro* for a period of time before transplantation to initiate the development of the cartilage matrix. The ultimate goal of both of these approaches is to regenerate hyaline cartilage which will restore full tissue function.

## Autologous chondrocyte implantation (ACI)

For ACI, patients must be between 15 and 55 years old and have symptomatic 2-10 cm<sup>2</sup> cartilage defects of the medial or lateral femoral condyle, femoral trochlea or patella with no radiographic evidence of osteoarthritis. Patient age is limited as there is evidence that the cartilage cells are more active in younger patients so the cartilage repair is more successful. The procedure is a two-step surgery. First a biopsy of healthy cartilage (total of 200-300mg, approx 2-3 x10<sup>5</sup> cells) is taken from the non-weight bearing areas of the affected knee. The cartilage is transferred to a cell culture laboratory where enzymes are used to release the chondrocytes. The cells are cultured under *in vitro* conditions for 3-5 weeks to expand the numbers of chondrocytes after which they are harvested for placement in the cartilage defect. In a second operative procedure, the cartilage lesion is debrided and a small patch of the patient's periosteum (the membrane lining the outer surface of the bone) is taken from the tibia and sutured over the defect. The chondrocytes are injected under the patch into the cartilage defect and fibrin glue applied to the patch edges to prevent leakage. In a modification of the technique, a type I/III collagen patch (prepared from porcine skin) is used instead of the periosteal patch. This modification avoids an incision to obtain the tissue and potential overgrowth problems encountered with a periosteum patch which necessitate further surgery to trim the tissue. In a further modification, the culture expanded chondrocytes are first allowed to adhere to the collagen membrane after which the membrane is placed in the cartilage defect and sutured in place. This modification makes handling and placing the cells much simpler than with the original procedure. After surgery, the patients undergo an extensive period of rehabilitation where full weight-bearing is not allowed until 12 weeks after the ACI procedure. Patients can expect to return to their pre-injury activities 6-12 months after ACI.

When accompanied by careful rehabilitation, ACI is reported to have a good clinical outcome in repair of focal lesions in 65-88% of patients, depending on the site and number of lesions. Outcomes are reported to be highest for lesions located in the femoral condyles and lowest for lesions of the patella. The technique has been used in various centres in the United States and Europe and clearly shows the feasibility of this type of approach to cartilage repair. More recently, trials have shown MACI to give similar results to ACI in the short term.

ACI has been performed for 14 years with more than 3900 patients treated. However, the procedure is complex and there remains much discussion about its long-term clinical efficacy, particularly in comparison with other procedures such as microfracture. It is reported that 74 -90% of patients with ACI scored as good to excellent clinical results in a 2-10 year follow-up study of 200 patients indicating durability of the cartilage repair is feasible. Currently, there are relatively few long term follow-up studies and robust randomised controlled trials

comparing ACI with other cartilage repair strategies such as microfracture.

There is also debate over the type of cartilage regenerated at the site of the lesion. Biopsies from the repair site show that on average, over several clinical trials, approximately 50% of patients had hyaline cartilage repair tissue with the remaining having either a mixture of hyaline and fibrocartilage or just fibrocartilage. The biopsies also showed lack of the typical hyaline cartilage architecture. However, it has become apparent that a period of 1-2 years is required to form a mature regenerated cartilage repair tissue.

Currently, ACI is not offered as a standard NHS therapy in the UK. The key issues leading to this decision are those of cost (£3000-£4000 alone for provision of cartilage cells in 2005 for implantation) and the lack of sufficient long-term follow-up studies in patients receiving ACI. Current guidelines issued by the National Centre for Health and Excellence (NICE) in 2005 on the clinical and cost-effectiveness of ACI state that,

*“ACI is not recommended for the treatment of articular cartilage defects of the knee except in the context of ongoing or new clinical studies that are designed to generate robust and relevant outcome data, including the measurement of health-related quality of life and long-term follow-up.”*

These recommendations are based on evidence from 4 randomised clinical trials involving 266 patients and further observational studies on a further 108 patients. The report by NICE concludes that there is insufficient evidence at present to say that ACI is cost-effective compared to microfracture but ACI is likely to yield a more durable repair tissue as it is more likely to produce hyaline cartilage in contrast to current microfracture procedures. The report also concludes that ‘more research is necessary’.

## Future perspectives for regenerative medicine in cartilage repair

Evidence from clinical studies clearly shows the feasibility of a cell-based approach for hyaline cartilage regeneration and research promoting the formation of hyaline cartilage is ongoing. One area of interest is in promoting the ability of transplanted chondrocytes to make the required matrix components. To ensure rapid expansion of cell numbers to achieve the number of cells needed for cartilage repair, the chondrocytes are grown in standard culture conditions using flat (2-dimensional) plastic culture dishes. It is well known that under such conditions chondrocytes proliferate well but lose their characteristic ability to make the components of hyaline cartilage and tend to make fibrocartilage instead. Hence, there is much research interest in investigating novel culture conditions and growth factors that promote the

retention or return of full chondrocyte properties (phenotype). A further issue is that of how many chondrocytes need to be implanted into a lesion to produce hyaline cartilage. Another area of interest is that of developing scaffold materials which can promote/direct the development and growth of cartilage cells to promote the formation of healthy cartilage. It would also be advantageous if the scaffold was weight bearing so that patients could return to full weight-bearing activity within a shorter time frame.

Another approach under investigation is that of using of adult mesenchymal stem cells (MSCs) and using appropriate biological growth factors to mature (differentiate) them into chondrocytes for use in repair strategies. MSCs are an attractive alternative as they have a high capacity for proliferation and, depending on their source, the ability to differentiate into several cell types. For most cartilage regeneration therapies, the research has been carried out using MSCs isolated from bone marrow biopsies. However, stem cells are found throughout the body and there is much interest in finding sources which require less invasive biopsy procedures, and mature more readily into cartilage forming cells. A disadvantage of using bone marrow derived MSCs is their tendency to mature down a bone forming rather than cartilage forming pathway. Full knowledge of the mechanisms by which MSCs differentiate into chondrocytes is not yet known. Therefore, there is still a need for basic science research into the genes and molecules that influence MSCs to become hyaline chondrocytes. With this information it may be possible to have more patients developing hyaline cartilage after microfracture. A further advantage of using stem cells is that it allows the possibility of taking the described regenerative cartilage therapies into an older population and those with early onset osteoarthritis. In aged patients, chondrocytes taken from a biopsy of articular cartilage frequently do not have good hyaline cartilage forming capacities.

Regenerative medicine is a multidisciplinary field requiring strong collaborations of scientists and clinicians across different specialisations including polymer chemistry, biomaterials, cell biology and medicine. However, progress in this field does hold promise to improve the quality of life in an aging population.

## ACI in the UK

ACI is a complex procedure and requires specialist training. Apart from the specialised surgical techniques, the patient's cells must be isolated and cultured to appropriate standards in licensed clean-room. There are commercial agencies (Genzyme Ltd UK and Ireland, BBraun/Te Tec AG, Geislich Biomaterials and Verigen UK Ltd) which provide support for ACI in the UK. These agencies provide training and culture of cartilage cells. In addition, in-house methods have been developed and in use at the Robert Jones and Agnes Hunt Orthopaedic and District NHS Trust in Oswestry.

## Founding partners in the Programme include:

University of Leeds  
University of Sheffield  
University of York  
University of Bradford  
Medipex  
Medilink Yorkshire & the Humber  
The Leeds Teaching Hospitals NHS Trust  
Sheffield Teaching Hospitals NHS Foundation Trust  
Bradford Teaching Hospitals NHS Foundation Trust  
Yorkshire Forward  
Health Technologies Knowledge Transfer Network  
New Jersey Biotechnology Life Science Coalition  
Rutgers, The State University of New Jersey  
University of Medicine and Dentistry of New Jersey  
New Jersey Institute of Technology  
Princeton University  
International ARI Institute, University of Toledo, Ohio  
Polymer Centre for Industrial Collaboration  
Biomaterials and Tissue Engineering Centre for Industrial Collaboration  
Pharmaceutical Innovation Centre for Industrial Collaboration  
Wireless Technologies Centre for Industrial Collaboration  
Particles Centre for Industrial Collaboration

## Case study: Tissue engineering of hyaline cartilage

Prosthetic and transplant surgeries improve the life span and quality of many thousands of people in the UK each year, but neither programme is without problems. Designing new materials, engineered tissues and cell therapies has the potential to overcome these problems but necessitates multidisciplinary collaboration between experts in a range of disciplines. The Centre for Biomaterials and Tissue Engineering at the University of Sheffield brings together scientists, engineers and clinicians to enable multidisciplinary collaboration. Current research is focussed in several areas of clinical need including developing *de novo* tissues of skin, cartilage, bone, cornea oral mucosa and blood vessels.

The focus of the cartilage tissue engineering group is developing *de novo* cartilage and bone tissues with therapeutic potential for maxillofacial reconstruction and repair of damaged joint tissues. To date no cell source has been identified as ideal for regenerative methodologies for cartilage repair. One area in which we are currently researching is that of investigating stem cells derived from the joint as potential chondrogenic cells for cartilage regeneration. This is a collaborative project carried out with Prof. D. McGonagle and Dr E. Jones of the Leeds Institute of Molecular Medicine and orthopaedic surgeon, Mr T. Chapman, of the Royal Calderdale Hospital and Smith and Nephew.

This project is part of ongoing research identifying potential chondrogenic cell sources for cartilage engineering. We are also investigating novel biomaterials which can be used as scaffolds in promoting tissue formation. This research is carried out in collaboration with scientists locally within the UK and through out Europe.

Author: Dr Aileen Crawford, Centre for Biomaterials & Tissue Engineering, University of Sheffield, School of Clinical Dentistry Email: [a.crawford@sheffield.ac.uk](mailto:a.crawford@sheffield.ac.uk)



White Rose Health Innovation Partnership  
Enterprise & Innovation Office  
Charles Thackrah Building  
101 Clarendon Road  
Leeds LS2 9LJ  
UK  
Tel: +44 (0)113 343 0923  
Fax: +44 (0)113 343 0949  
Email: [whiterosehip@adm.leeds.ac.uk](mailto:whiterosehip@adm.leeds.ac.uk)

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