**Chester Knee Clinic**
**at the Grosvenor Nuffield Hospital**
Wrexham Road Chester Cheshire CH4 7QP UK
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# Autologous Chondrocyte Implantation (ACI)

## Patient and General Practitioner Information

Although articular cartilage is unable to repair itself, this advanced orthobiologic technology allows cartilage cells, known as chondrocytes, to be harvested from your knee, cultured and multiplied. The fresh chondrocytes are then implanted into your knee and cause hyaline-like cartilage to develop and repair the defect in the articulating surface. The technique of autologous cultured chondrocyte implantation was initially researched at the Hospital for Joint Diseases in New York and further developed at the University of Gothenburg and Sahlgrënska University Hospital, Gothenburg, Sweden, in an effort to provide a treatment option for people with articular cartilage damage.

**Indications:** ACI restores the articular surface with your own hyaline-like cartilage without compromising the integrity of healthy tissue or the subchondral bone. This technology has demonstrated significant benefits in patients with a femoral or patellar focal lesion, in terms of diminished pain and improved function. If you have this type of lesion, then ACI may be an appropriate treatment option. ACI treatment results in the development of a functional repair tissue and is particularly suited for larger defects. Suitable patients would be generally young and healthy individuals, who have had an injury to the knee, or a so-called osteochondral lesion, over the past few months or years, and have continued to have pain, swelling and mechanical problems. This is a new procedure (in clinical use since 1987) and although it has been performed on over 15000 patients internationally, especially in Sweden and the USA, not every patient is suitable and not every patient achieves a completely satisfactory functional outcome.

**Contraindications:** although cartilage damage is often associated with ligament and meniscal injuries, it is very important that the knee is stable and that there is no major meniscal deficiency or any alignment problems prior to cartilage repair. Other conditions in which treatment with ACI surgery is not indicated include some chronic viral infections (HIV and Hepatitis), osteonecrosis, chondrocalcinosis, advanced osteoarthritis (degenerative joint disease), rheumatoid arthritis and total meniscectomy.

**The Compassionate Use Programme:** our clinical experience with ACI surgery goes back to 1998. We have been using ChondroCelect™ ACI technology in Chester since November 2004. This tissue-engineered product is manufactured by TiGenix NV and licensed in Belgium. It is now available in the UK, for a limited number of patients, as an unlicensed medicinal product, under the MHRA (Medicines and Healthcare products Regulatory Agency, www.mhra.gov.uk) Specials Regulations. The MHRA is responsible for ensuring that medicines and medical devices work, are safe and of appropriate quality. An unlicensed medicinal product may only be placed on the market in order to meet the special needs (which a licensed product cannot meet) of an individual patient. This basically means that TiGenix NV provides ChondroCelect™ cultured chondrocytes free of charge in the UK, under the terms of the *Compassionate Use Programme* which is restricted to a limited number of individuals who need ACI surgery, as recommended by their doctor. *Children and adolescents under the age of 18 are not eligible for treatment with ChondroCelect™.*

**Surgical Procedure:** the procedure is initiated through a General Practitioner's or Orthopaedic Consultant's referral letter and followed by out-patient assessment and a high-resolution Magnetic Resonance Imaging (MRI) knee scan, optimised for imaging articulating surfaces and subchondral bone. If the damaged articular area is suitable for ACI repair, the planned surgical procedure will consist of two steps:

**1. The first step (ACI Stage 1)** is a day-case arthroscopic operation to assess the inside of the joint further and to obtain a small piece (a total weight of approximately 500mg) of healthy articular cartilage (chondral biopsy). This sample of articular cartilage is sent by courier service to TiGenix NV tissue engineering laboratory in Leuven, Belgium. The first laboratory step is an enzymatic process which separates the chondrocytes (cartilage forming cells) from their matrix. Cell culture over a period of about 4-6 weeks induces them to multiply to about 4-6 million stable chondrocytes. These are then placed into a special nutrient solution and sent back to arrive in time for the proposed date of implantation.

**2. The second step (ACI Stage 2)** is the re-implantation of the cultured chondrocytes. This procedure is done through an arthrotomy (open knee surgery): the surgeon debrides the cartilage defect down to the subchondral bone plate and prepares the recipient site. The defect area is covered with tissue-engineered bilayer collagen membrane (Chondro-Gide® which is a CE-registered product, constructed specifically for the treatment of articular cartilage defects), which is stitched in place and sealed with fibrin adhesive. The chondrocyte suspension is injected into this "bioactive chamber". Within this chamber the cells will undergo re-differentiation and will be stimulated by growth factors to proliferate and regenerate their specific articular cartilage matrix.

Following this operation the leg is placed in a hinged protective brace (for femoral lesions only), which will limit your knee flexion for the first 6 weeks. The main purpose of using the postoperative brace is to protect the repaired articular surface from too much compression and friction. We also use the Aircast® Cryo/Cuff device, which combines local compression with cooling to provide optimal control of swelling, oedema, haemarthrosis, and pain (www.aircast.com).

**Rehabilitation:** to get the maximum benefit from ACI, you should adhere to the ACI-specific rehabilitation programme (please see **Chester ACI Rehabilitation Guide** which can be downloaded from our website www.kneeclinic.info). This will include progressive weight-bearing, range of motion, and muscle strengthening exercises which commence as early as the day after surgery. When you successfully complete your rehabilitation, you should be able to resume normal activities, including sports.

**Chondrocyte Culture:** The chondrocyte culture product, ChondroCelect™, is provided by a biomedical company TiGenix NV, Leuven, Belgium (www.tigenix.com). ChondroCelect™ is an improved chondrocyte culture product that applies the company's proprietary molecular technology to improve the selection, characterisation and expansion of cartilage-forming cell populations. ChondroCelect™ is designed to increase the success rate of standard ACI procedures, as it is based on implanting only cell populations with a predictable and consistent hyaline cartilage forming ability. In rare cases it has occurred that insufficient numbers of cells or cells of insufficient quality have come out of the chondrocyte culture. In case this has happened to the cells, Mr Bobic will discuss the possible alternatives with you. The non-implanted cells may be used by TiGenix for testing to improve the production process. A reference sample of the cells is stored in the TiGenix laboratory for use in a Reference Cell Bank or quality assurance, as requested by regulatory authorities. After five years these cells will be destroyed according to Good Manufacturing Practices (GMP).

**Chondrocyte Cover:** Geistlich Pharma AG Biomaterials (Wolhusen, Switzerland, www.geistlich.com) manufactures and provides the Chondro-Gide® membrane which is used to cover and contain the implanted liquid chondrocyte suspension.

**Adverse Reactions:** ChondroCelect™ should not be used in patients with a known history of sensitivity to penicillin G, streptomycin sulphate, amphotericin B and fetal bovine serum (FBS) because these products are used during steps in the production process. The FBS, derived from calf foetuses, is used to make the cells grow consistently and predictably. Up to now no allergic reactions or illnesses have been reported due to the use of FBS. Since Chondro-Gide® is a collagen product of porcine origin, allergic reactions can not be totally excluded. This membrane should not be used in patients with known collagen allergies.

However, an alternative cover (your own periosteal membrane) can be used to cover the cartilage defect and to contain the chondrocyte suspension.

From November 2005, it is a mandatory requirement to electronically report serious suspected adverse drug reactions (ADRs) to the MHRA. However, we have not seen any adverse reactions to either ChondroCelect™ or Chondro-Gide® or any other drugs used during ACI surgery.

**Risks and Complications:** as with any other surgical procedure, there is a small risk of post-operative complications (bleeding, wound problems, skin and knee joint infection, deep venous thrombosis, etc). Complications specific to ACI surgery affect up to 10% of patients and include: persistent swelling, joint clicking, graft hypertrophy (which may require further arthroscopic surgery), and graft delamination (which may lead to the failure of the repair). There are no known untoward biological effects of this tissue engineering technology, including carcinogenic and teratogenic effects. The consequences of the treatment with ChondroCelect™ during pregnancy or breast-feeding are not known.

**NICE Guidelines:** The National Institute for Health and Clinical Excellence (NICE) is part of the NHS. The treatment of your articular cartilage defect will be carried out *outside* of the NHS NICE guidelines on the use of ACI for articular cartilage defects in knee joints, but with full approval and support of Nuffield Hospitals and the Grosvenor Nuffield Hospital Medical Advisory Committee. We will ask you to sign a separate consent form which confirms that you are happy to proceed with ACI surgery outside of the NHS NICE ACI Guidance *(Technology Appraisal Guidance No. 89: The use of autologous chondrocyte implantation (ACI) for the treatment of cartilage defects in knee joints, May 2005).* Please see www.nice.org.uk/TA089 for more information. However, your ACI surgery will be carried out within NICE clinical trial requirements as Chester Knee Clinic is a registered participating centre in the Stanmore ACI vs. MACI clinical trial, with South East MREC (MREC/02/01/73) and South Cheshire LREC (No. M197/03) approval. NICE ACI clinical guidelines require a randomisation process and apply to NHS hospitals. They are produced to help healthcare professionals and patients make right decisions about healthcare in specific clinical circumstances. They sit alongside, but do not replace, the knowledge and skills of experienced health professionals. NICE guidance does not override the responsibility of health professionals to make appropriate decisions on the circumstances of individual patients.

**Consent Forms:** before you sign your operation consent and other forms, please make sure that you have read and understood this sheet, and information on Geistlich Biomaterials Chondro-Gide® and TiGenix ChondroCelect™ available from www.geistlich.com and www.tigenix.com websites. We will ask you to sign a separate consent form, which will allow us to test your blood for HIV and Hepatitis antibodies, before the cultivation of your chondrocytes begins in the laboratory, usually at ACI Stage 1 (arthroscopic chondral biopsy). These tests are legally required by TiGenix NV laboratories, for safety reasons.

**Questions:** please do not hesitate to ask questions about your ACI surgery and rehabilitation at any time.

**Questionnaires:** we will ask you to complete KOOS (Knee Outcome) and VAS (Visual Analog Score) questionnaires periodically, to assess your knee function and pain.

**Confidentiality:** your personal and clinical data, video-clips and digital clinical, arthroscopic and MR images will be stored and kept on a secure standalone computer, according to the Data Protection Act 1998 (www.dataprotection.gov.uk). This information will be available to Nuffield Hospitals and TiGenix NV but will not be shared with anybody else.
TiGenix NV will have access to relevant clinical data using your initials and the hospital number, but without revealing your name, address and date of birth etc.
TiGenix will analyse this data anonymously to determine the safety and efficacy of your treatment. TiGenix NV staff or auditors may request access your medical file at any time to verify the accuracy of the collected data.

TiGenix NV will share this information with the health authorities and the results may be used for scientific reports, publications or presentations.

Your ACI surgery may be recorded digitally and kept as a part of your record, and may be used for research, outcome studies, training and educational purposes. If we wish to publish any of your clinical data or images, which may identify you personally, we will ask for your written permission.

**Problems?** If you experience any postoperative problems please contact our Physiotherapy Department (01244 684314) or the Grosvenor Nuffield Hospital switchboard (01244 680 444). In an emergency please contact Mr Bobic directly (mobile phone 07774 981 481).

**What happens if something goes wrong?** If you want to make a comment or complaint please contact Mr Bobic directly, or the Hospital Manager. A full copy of Nuffield Hospitals' Complaints Policy can be provided to you on request.

**More Questions?** If you have any further questions or concerns please contact us by email: info@kneeclinic.info and give us your telephone number.

**Notes:**

Text and design: Vladimir Bobic, MD, FRCSEd
*Consultant Orthopaedic Knee Surgeon*

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