

**SUCCESS/FAILURE IN ORTHOPAEDIC CELL ENGINEERING**

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Science begins and ends with observation. Surgeons observe cell activity in normal healing, interfere with surgery, and increasingly move selected and culture expanded cells to injured areas. What observations can the clinician bring to the scientist? In orthopaedics, arthritis and fractures are our main problems. How can cell engineering help? Several groups have engineered new bone with MSCs, but skepticism remains over the ability to form cartilage with chondrocytes. Are the successes and failures due to biomechanical, biological or a 'choice of cells' issue? The main debate in the management of chondral defects is focused on the difference between adding cultured chondrocytes and techniques that enable and encourage natural healing. Clinical trials suffer from varied in-goes and fuzzy outcomes. The main debate in the management of chondral defects is focused on the difference between adding cultured chondrocytes and techniques that enable and encourage natural healing. Clinical trials suffer from varied in-goes and fuzzy outcomes.

The best test of the original ACI technique<sup>1</sup> to date remains the study by Knutsen<sup>2</sup>. This Norwegian randomized trial was run by surgeons who had never before performed ACI, and each surgeon only completed a few cases in the trial. The report at two years was of only a significant difference in one of 8 parameters measured, supporting microfracture over ACI<sup>3</sup>. A trend to better histology was noted in the ACI group, but there were difficulties in quantifying the histology. At 5 years the results (to be published in March 2008) are of equivalence in failure rates and symptoms. About 20% of patients have had further operations. The failures have been in those with poor histology. There are only 80 patients in that trial, but excellent follow-up is a tribute to the team and the patients involved.

A Belgian company Tigenix have developed a method of selecting the best cells in a patient's culture for the formation of cartilage, they believe. They have run a prospective randomised trial. Histology was assessed blindly using a newly developed score, and reports an improved histology for ACI over microfracture<sup>3</sup>. I place this as the most important report of recent years in this field. Taken with the observation from Norway that the histology predicts failure, this is evidence for ACI providing better outcomes.

ACTIVE is a prospective randomized trial, sponsored by Keele University, funded by MRC

and the NHS of UK, with a ten year follow-up. This trial is pragmatic: designed to be 'real world' and adapt to technique developments. The entry criteria are broad, setting ACI techniques against 'best alternative', and this allows generalization of the results following the trial. 210 patients are now enrolled. This makes it the largest randomised clinical trial that is testing the original autologous chondrocyte implantation (ACI) technique, and the plan is to continue recruitment up to 480 patients. Chondrocytes loaded in collagen are included in the cell culture arm, and recently AMIC as a 'best alternative'. Norway and 12 centres in the UK do the hard work of recruiting, with Stanmore in London recently joining.

Cost-effectiveness is an important measure in a health service where costs are rising. A study from Aberdeen reported that if ACI is just 10 to 20% better than an alternative at 10 years, then the extra costs of cell culture are cost-effective<sup>4</sup>. This sets the target for clinical trials as 10 year follow-up.

Are the failures of ACI due to failure to regenerate the underlying bone? Is this a problem of inappropriate cells being present? In non-union co-workers at Oswestry, and also in Kobe Japan and in Germany<sup>5</sup> have identified a 'non-union cell' present where bone fails to heal. Some patients with persisting pain have intense remodelling in the underlying bone. A technique of cell implantation over a large bone plug is giving good pain relief. This indicates that a biological joint replacement will need to replace both bone and cartilage.

Some preliminary work of the Myjoint EU programme will be presented where a new joint is planned to be formed in an 'endocultivation' bioreactor in the latissimus dorsi of the patient.

**References:**

- <sup>1</sup>. Peterson, et al., Autologous chondrocyte transplantation. Biomechanics and long-term durability. American Journal of Sports Medicine 2002; 30:2-12;
- <sup>2</sup>. Knutsen, et al., A Randomized Trial Comparing Autologous Chondrocyte Implantation with Microfracture. Findings at Five Years. J Bone Joint Surg Am 2007; 89: 2105-2112;
- <sup>3</sup>. Saris et al., Characterized Chondrocyte Implantation Results in Better Structural Repair When Treating Symptomatic Cartilage Defects of the Knee in a Randomized Controlled Trial Versus Microfracture Am J Sports Med 2008 36: 235-246;
- <sup>4</sup>. Clinical and cost-effectiveness of autologous chondrocyte implantation for cartilage defects in knee joints: systematic review and economic evaluation. Cummins, et al., Health Technol Assess 2005;9(47):1-98;
- <sup>5</sup>. Hofmann et al., Cell viability, osteoblast differentiation, and gene expression are altered in human osteoblasts from hypertrophic fracture non-unions. Bone. 2008 May;42(5):894-906.